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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1147-US-P2C2DC
	Application Number	
Title of Invention	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Benjamin	Micah	Collman	

Residence Information (Select One) ● US Residency ○ Non US Residency ○ Active US Military Service

City	State/Province	Country of Residence
San Mateo	CA	US

Mailing Address of Inventor:

Address 1	39 N Humboldt Street
Address 2	

City	State/Province	Postal Code	Country
San Mateo	CA	94401	US

Inventor 2 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Lei		Hong	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	State/Province	Country of Residence
Cupertino	CA	US

Mailing Address of Inventor:

Address 1	1008 Cranberry Drive
Address 2	

City	State/Province	Postal Code	Country
Cupertino	CA	95014	US

Inventor 3 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Joanna	M.	Koziara	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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City	Foster City	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o Gilead Sciences, Inc.		
Address 2	333 Lakeside Drive		
City	Foster City	State/Province	CA
Postal Code	94404	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	25000		
Email Address	IPDocketing@gilead.com	Add Email	Remove Email

Application Information:

Title of the Invention	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS		
Attorney Docket Number	1147-US-P2C2DC	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	25000		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	16/987081	2020-08-06
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/987081	Continuation of	16/713380	2019-12-13
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/713380	Continuation of	15/346335	2016-11-08	10548846	2020-02-04

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/346335	Claims benefit of provisional	62/399999	2016-09-26
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/346335	Claims benefit of provisional	62/253042	2015-11-09

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

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Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[1] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Gilead Sciences, Inc.		
Mailing Address Information For Applicant:			
Address 1	333 Lakeside Drive		
Address 2			
City	Foster City	**State/Province**	CA
Country	US	Postal Code	94404
Phone Number	(650) 574-3000	Fax Number	(650) 522-5575
Email Address	IPDocketing@gilead.com		

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Donna Johnson Gressler/			Date (YYYY-MM-DD)	2022-05-06
First Name	Donna Johnson	Last Name	Gressler	Registration Number	45,544

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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

CROSS-REFERENCE TO THE RELATED APPLICATIONS

[0001] This patent application claims the benefit of priority of U.S. Application Serial No. 62/253,042, filed November 9, 2015 and of U.S. application serial No. 62/399,999, filed September 26, 2016. The content of each of these provisional applications is hereby incorporated herein in its entirety.

TECHNICAL FIELD

[0002] Pharmaceutical formulations suitable for treating viral infections such as HIV are provided, in particular solid oral dosage forms including the compound of Formula I, emtricitabine and tenofovir alafenamide.

BACKGROUND

[0003] Human immunodeficiency virus, type 1 (HIV-1) infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide (Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic, **2013**). Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and halt disease progression.

[0004] There is also a need for medications to serve populations with limited treatment options (e.g., children, women, and the elderly). In certain situations, these populations may have difficulty maintaining treatment because of pill burden (number of pills to take each day, as well as different combinations of pills) or the size of the pills themselves, once they are coformulated into a multidrug composition. For example, there is currently no fixed dose combination registered for once a day dosing (i.e., QD) for very young children (e.g., younger than age 12 years).

[0005] A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions (e.g., metformin, rifampin, HCV antivirals, hormonal contraceptives, etc.). Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug-drug interaction is a criterion for selection of

a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug-drug interactions (e.g., those that affect transporters (e.g., OCT-2) or activate receptors (e.g., PXR).

SUMMARY

[0006] All the compositions and oral dosage forms herein include a compound of Formula I, (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, having the following structure:

(I)



or a pharmaceutically acceptable salt thereof.

[0007] In certain embodiments, the pharmaceutically acceptable salt of the compound of Formula I is a compound of Formula II, sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure:

(II)



[0008] The inventors have successfully formulated an oral dosage form containing the compound of Formula I, tenofovir alafenamide and emtricitabine. This oral dosage form is suitable for use in medicine, and in particular in treating viral infections such as HIV.

[0009] In one aspect, a solid oral dosage form comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof is provided. In certain embodiments, the dosage form comprises 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine. For instance, in certain embodiments, the dosage form comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir

alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine. In certain embodiments, the dosage form comprises 52 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

[0010] In another aspect, a solid oral dosage form comprising 75 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine is provided. In certain embodiments, a solid oral dosage form comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine is provided. In certain embodiments, a solid oral dosage form comprising 78 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0011] The inventors have found that it is possible to formulate solid oral dosage forms that are pharmaceutically acceptable (*i.e.* pharmacologically efficacious and physically acceptable) while reducing the total amount of excipients necessary to achieve an acceptable pharmacokinetic profile. Accordingly, in one aspect a solid oral dosage form is provided, comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (*e.g.* less than 800 mg or less than 730 mg or less than 700 mg).

[0012] In another one aspect a solid oral dosage form is provided, comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (*e.g.* less than 800 mg or less than 700 mg).

[0013] In another aspect, a coated tablet comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0014] In another aspect, a coated tablet comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0015] In another aspect, a tablet comprising 52 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0016] In another aspect, a tablet comprising 78 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0017] In another aspect, a tablet comprising (a) 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g (*e.g.*, less than about 1 g). Typically, (a) and (b) are present within separate layers in a multilayer tablet.

[0018] In another aspect, a tablet comprising (a) 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g (*e.g.*, less than about 1 g). Typically, (a) and (b) are present within separate layers in a multilayer tablet.

[0019] In another aspect, a tablet comprising from 6.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the compound of Formula I is present as of the compound of Formula II and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate.

[0020] In another aspect, a tablet comprising from 9.5-11.5 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 2.5-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 26-33 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the compound of Formula I is present as of the compound of Formula II and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate.

[0021] The inventors have found that the use of a fixed dose combination may assist in achieving appropriate pharmacokinetic parameters and/or adequate tablet stability. In addition, the use of a multilayer tablet as a particular type of fixed dose combination may also provide pharmacokinetic and/or stability benefits. Accordingly, in another aspect a fixed dose combination tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided. Additionally, multilayer tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0022] In another aspect, a kit comprising (a) a tablet comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant (*e.g.* silica gel) is provided.

[0023] Methods of producing solid oral dosage forms such as tablets are also provided, as discussed in more detail below.

[0024] In addition, methods for treating patients are provided, which are also discussed in more detail below.

BRIEF DESCRIPTION OF DRAWINGS

[0025] Figure 1 shows the results of studies carried out on Formulations F1, F2, and F3 to assess the dissolution of 78 mg of the Compound of Formula II as a single agent compared to a bi-layer using fasted simulated intestinal fluid as a dissolution medium.

[0026] Figure 2 shows the results of studies carried out on Formulations F1 and F2 to assess the dissolution of 78 mg of the Compound of Formula II as a single agent compared to a bi-layer using fed simulated intestinal fluid as a dissolution medium.

[0027] Figure 3 shows the results of studies carried out on Formulations F1, F2, F4, F5, and F6 to assess the dissolution of 78 mg of the Compound of Formula II in tablets containing various excipients.

[0028] Figure 4 shows the results of studies carried out on Formulations F7 and F8 to assess the dissolution of 52 mg of the Compound of Formula II as a single agent compared to a bi-layer using fasted simulated intestinal fluid as a dissolution medium.

[0029] Figure 5 is a flow diagram illustrating the preparation of a tablet formulation containing the compound of Formula II.

[0030] Figure 6 is a flow diagram illustrating the preparation of a tablet formulation containing the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate.

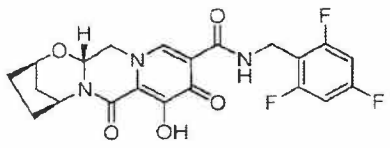
DETAILED DESCRIPTION

[0031] Typically, the oral dosage forms disclosed herein comprise three active pharmaceutical ingredients: the compound of Formula I (or a pharmaceutically acceptable salt thereof), tenofovir alafenamide (or a pharmaceutically acceptable salt thereof), and emtricitabine (or a pharmaceutically acceptable salt thereof).

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

[0032] (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I), is a potent HIV integrase inhibitor with *in vitro* activity against wild type HIV-1. It has the following formula (see WO2014/100323):

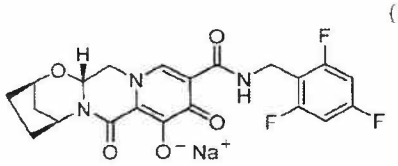
(I)



[0033] Its IUPAC name is (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. Its CAS name is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, (2R,5S,13aR). The compound of Formula I is a weak acid with pKa of 8.6. The aqueous solubility of the compound of Formula I free acid is pH-dependent, with solubility increasing with increasing pH, with a maximum at pH 10.5.The chemical stability of the compound of Formula I is also pH dependent, with maximum stability at pH 4. The compound of Formula I is considered a BCS Class 2 compound, with low solubility and high permeability.

[0034] Solid oral dosage forms disclosed herein include the compound of Formula I, usually in the form of a pharmaceutically acceptable salt. The compound of Formula I can be present within an oral dosage form in solvated or unsolvated form, and references to "Formula I" include both of these forms. Typically, the compound of Formula I is in the form of the compound of Formula II, having the formula below:

(II)

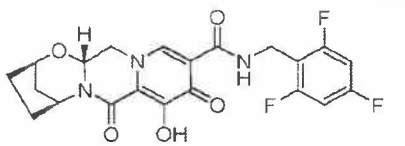


[0035] In certain specific embodiments, solid oral dosage forms containing 50 mg of the compound of Formula I, *e.g.* as about 52 mg of the compound of Formula II, are provided.

[0036] In certain specific embodiments, solid oral dosage forms containing 75 mg of the compound of Formula I, *e.g.* as about 78 mg of the compound of Formula II, are provided.

[0037] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of the compound of Formula I (*e.g.* Formula II), any dosages, whether expressed in *e.g.* milligrams or as a % by weight, should be taken as referring to the amount of the compound of Formula I free acid, *i.e.* the amount of:

(I)

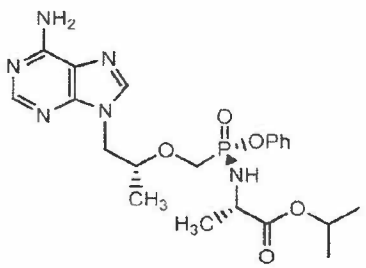


[0038] For example, therefore, a reference to "50 mg of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of the compound of Formula I as 50 mg of the compound of Formula I free acid.

[0039] For example, therefore, a reference to "75 mg of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of the compound of Formula I as 75 mg of the compound of Formula I free acid.

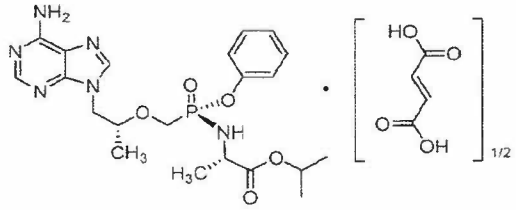
Tenofovir alafenamide

[0040] Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor having the formula below (see WO02/08241 A2):

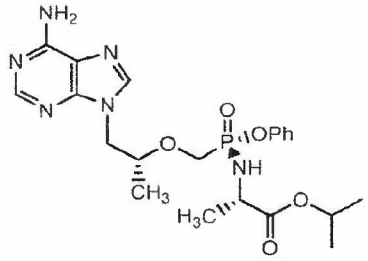


[0041] Its IUPAC name is (*S*)-isopropyl-2-(((*S*)-((((*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)(phenoxy)phosphoryl)amino)propanoate. It is also referred to as {9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl] amino]phenoxyphosphinyl]-methoxy]propyl]adenine}. Tenofovir alafenamide is a weak base, with a pKa of 3.9. Its solubility increases with decreasing pH, with a maximum solubility at about pH 3. Tenofovir alafenamide is considered a BCS Class 3 compound, with high equilibrium solubility and lower apparent permeability.

[0042] Solid oral dosage forms disclosed herein include tenofovir alafenamide, usually in the form of a pharmaceutically acceptable salt. Tenofovir alafenamide can be present within an oral dosage form in solvated or unsolvated form, and references to "tenofovir alafenamide" include both of these forms. In particular, tenofovir alafenamide may be associated with fumarate, such as monofumarate or hemifumarate. Typically, tenofovir alafenamide is in the form of tenofovir alafenamide hemifumarate having the formula below (see WO 2013/025788 A1):



[0043] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of tenofovir alafenamide, any dosages, whether expressed in *e.g.* milligrams or as a % by weight, should be taken as referring to the amount of tenofovir alafenamide, *i.e.* the amount of:

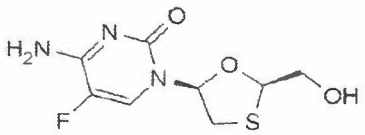


[0044] For example, therefore, a reference to "25 mg tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of tenofovir alafenamide as 25 mg of tenofovir alafenamide free base.

[0045] The amount of tenofovir alafenamide in a solid oral dosage form provided herein is generally between 10 mg and 30 mg, for instance within the range of 20 mg to 30 mg, and more typically between 24 mg and 28 mg. In certain specific embodiments, solid oral dosage forms containing 25 mg of tenofovir alafenamide *e.g.* as about 28 mg of tenofovir alafenamide hemifumarate, are provided.

Emtricitabine

[0046] Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor having the formula below:

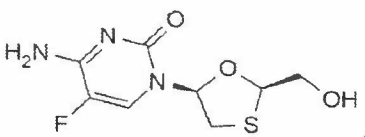


[0047] Its IUPAC name is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one. It is also referred to as 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. It is currently authorised as part of EMTRIVA® (emtricitabine 200 mg), TRUVADA® (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg), ATRIPLA® (emtricitabine 200 mg, efavirenz 600 mg, tenofovir disoproxil fumarate 300 mg) and STRIBILD® (emtricitabine 200 mg, cobicistat 150 mg, tenofovir disoproxil fumarate 300 mg, elvitegravir 150 mg) and COMPLERA®/EVIPLERA® (rilpivirine 25 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg).

[0048] Emtricitabine is a free base, exhibiting a pKa of 2.65. Solubility is enhanced under acidic conditions. It is considered a BCS Class 1 compound, with high solubility and high permeability.

[0049] Solid oral dosage forms disclosed herein include emtricitabine, optionally as a pharmaceutically acceptable salt. Emtricitabine can be present within an oral dosage form in solvated or unsolvated form, and references to "emtricitabine" include both of these forms. Typically, emtricitabine is present as a free base.

[0050] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of emtricitabine, any dosages, whether expressed in *e.g.* milligrams or as a % by weight, should be taken as referring to the amount of emtricitabine, *i.e.* the amount of:



[0051] For example, therefore, a reference to "200 mg emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of emtricitabine as 200 mg of emtricitabine free base.

[0052] The amount of emtricitabine in a solid oral dosage form provided herein is generally between 180 mg and 220 mg, for instance between 190 mg and 210 mg, and more typically between 195 mg and 205 mg. In certain specific embodiments, solid oral dosage forms containing 200 mg of emtricitabine are provided.

Solid oral dosage forms

[0053] The inventors have successfully formulated the compound of Formula I, emtricitabine and tenofovir alafenamide in a single, stable dosage form that is pharmacologically efficacious and physically acceptable. The solid oral dosage forms disclosed herein are intended for pharmaceutical use in human subjects. Accordingly, they must be of an appropriate size and weight for oral human administration (*e.g.* they should have a total weight of less than about 1.5 g, e.g., less than about 1.0 g), in addition to being therapeutically efficacious.

[0054] In certain embodiments, formulations of the three active ingredients into a solid oral dosage form which has a total weight of less than about 1.0 g are provided, for instance less than about 800 mg, or even less than about 750 mg, or even less than 700 mg. This is advantageous given that TRIUMEQ® (abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine) has a total weight of more than about 1000 mg, based on the weight of the active ingredients in each tablet (due to the amount of excipients that are required to produce a pharmaceutically acceptable tablet). The provision of a relatively small dosage form (in particular a tablet) represents a clinical advantage because it may be expected to increase patient convenience and thus compliance as compared to larger dosage forms which are more burdensome for patients to swallow. In specific embodiments, the solid oral dosage form disclosed herein has a total weight of between 700 and 750 mg. In certain embodiments, the solid oral dosage form disclosed herein has a total weight of between 700 and 725 mg, or about 700 mg. In specific embodiments, the solid oral dosage form disclosed herein has a total weight of between about 50 and about 750 mg, between about 100 and about 750 mg, between about 200 and about 750 mg, or between about 250 and about 750 mg. The presently disclosed dosage forms may comprise less than 600 mg of excipients, such as less than 500 mg of excipients, or less than 450 mg of excipients. For example, solid oral dosage forms disclosed herein may comprise between 300 and 600 mg of excipients, or between 350 mg and 500 mg of excipients, or between 400 mg and 500 mg of excipients. Most typically, solid oral dosage forms disclosed herein comprise between 425 mg and 450 mg of excipients. In such embodiments, the dosage forms comprise as active ingredients (a) 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms comprise as active ingredients (a) 52 mg of the compound of Formula II, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine. In some embodiments, the dosage forms comprise as active ingredients (a) 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms comprise as active ingredients (a) 78 mg of the compound of Formula II, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine.

[0055] The solid oral dosage forms disclosed herein will typically be in the form of a fixed dose combination tablet. This is because the inventors have found that the use of fixed dose combination tablets may assist in optimizing the pharmacokinetic properties of the active ingredients, particularly the total exposure of the compound of Formula I or a pharmaceutically acceptable salt thereof, as measured by area under the curve (AUC) and C_{max}. In particular embodiments, the solid oral dosage forms disclosed herein are in the form of a multilayer tablet. In certain embodiments, the use of a fixed dose combinations, e.g., multilayer tablets, may affect the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore lik,ly to have an impact on the *in vivo* pharmacokinetics of the dosage form. In particular, it has been observed that the dissolution of the compound of Formula I (e.g., as Formula II) varies depending on whether the tablet is in a fixed dose combination formulation with tenofovir alafenamide and emtricitabine and/or whether the tablet is a monolayer or multilayer tablet. It has also been observed that the presence of certain excipients in the multilayer tablet formulation (or absence of others) affects the dissolution profile of one or more of the active ingredients within the dosage form. The provision of a tablet with particular pharmacokinetic parameters, *e.g.* pharmacokinetic parameters is a particular advantage afforded by the present disclosure.

[0056] In one embodiment, a multilayer tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided. Typically, each layer contains at least one of (a), (b), and (c). For instance, in certain embodiments, the tablet comprises a first layer comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, and a second layer comprising (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and further comprises (c) emtricitabine or a pharmaceutically acceptable salt thereof. In such embodiments, typically the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.* the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof).

[0057] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, Formula II) and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and

emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein the first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0058] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, Formula II) and is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 52 mg of the compound of Formula II and is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing emtricitabine or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0059] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, Formula II) and is substantially free of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight each of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0060] In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 78 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.* the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 355 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch.

[0061] Unless otherwise specified, the terms "first layer", "second layer", "third layer" and so forth do not specify a particular order or orientation of the multilayer tablet formulations disclosed herein. Rather, these terms are used to distinguish the sections of the composition from each other and to specify the characteristics or components of each section or compartment. By way of example, in an

embodiment, a tablet is provided wherein a first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (*e.g.*, the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.*, the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. The first layer may be synthesized first or may be synthesized second. The first layer may be on the bottom or may be on the top or may be on a side. The term "first layer" is not limiting as to order and orientation.

[0062] The tablets disclosed herein are typically immediate release tablets. In one embodiment, a tablet is provided which releases at least 50% of the compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes, measured using USP apparatus II, in 333 mL of fasted state simulated intestinal fluid, pH 6.5, at 37 °C and paddle speed of 100 rpm. In certain embodiments, the tablets disclosed herein release at least 60% of the compound of Formula I or a pharmaceutically acceptable salt thereof in 20 minutes, measured using USP apparatus II, in 333 mL of 50 mM fasted state simulated intestinal fluid, at 37 °C and paddle speed of 100 rpm. In some embodiments, a tablet that releases at least 70% of the compound of Formula I in 60 minutes is provided, measured using USP Apparatus II, in 333 mL of fasted state simulated intestinal fluid at 37 °C and paddle speed of 100 rpm.

[0063] Tablets disclosed herein will generally have a hardness within the range 14-20 kP, and, in certain specific embodiments, have a hardness of 17 kP. Hardness can conveniently be assessed by driving an anvil to compress a tablet at a constant loading rate until it fractures, operating in accordance with USP <1217> (using *e.g.* a TBH 220, ERWEKA GmbH, Heusenstamm Germany hardness tester).

[0064] Tablets disclosed herein will generally have a friability of <1% by weight. Friability can be assessed according to USP <1216>.

[0065] The core of a tablet provided herein may have a hardness of between 14-20 kP, and a friability of <1% by weight.

[0066] Tablets will typically include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of tablet formulation and may be found *e.g.* in *Handbook of Pharmaceutical Excipients* (eds. Rowe, Sheskey & Quinn), 6th edition **2009**. As used herein the term "excipients" is intended to refer to *inter alia* basifying agents, solubilisers, glidants, fillers, binders, lubricant, diluents, preservatives, surface active agents,

dispersing agents and the like. The term also includes agents such as sweetening agents, flavoring agents, coloring agents, preserving agents, and coating agents. Such components will generally be present in admixture within the tablet.

[0067] Examples of solubilisers include, but are not limited to, ionic surfactants (including both ionic and non-ionic surfactants) such as sodium lauryl sulphate, cetyltrimethylammonium bromide, polysorbates (such as polysorbate 20 or 80), poloxamers (such as poloxamer 188 or 207), and macrogols. In a particular embodiment, a tablet that comprises the compound of Formula I or a pharmaceutically acceptable salt thereof, includes a polysorbate, in particular polysorbate 20. In certain specific embodiments, the amount of polysorbate 20 in a tablet disclosed herein is less than about 5 mg, such as less than about 1 mg, or about 0.5 mg.

[0068] Examples of lubricants, glidants and flow aids include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl behenate, sodium stearyl fumarate, colloidal silicon dioxide, and talc. The amount of lubricant in a tablet is generally between about 0.5-5% by weight. In certain embodiments, the amount of lubricant in a tablet is about 1.5% by weight. In certain specific embodiments, tablets disclosed herein include magnesium stearate. In certain other embodiments, the tablets disclosed herein do not include sodium stearyl fumarate. In certain embodiments, the tablet includes less than about 10 mg magnesium stearate, or less than about 7.5 mg magnesium stearate. In certain embodiments, the tablet includes less than about 9 mg magnesium stearate, or less than about 8.75 mg magnesium stearate. In certain embodiments, the tablet includes about 5 mg to about 10 mg magnesium stearate, or about 6 mg to about 9 mg magnesium stearate, or about 7 mg to about 9 mg magnesium stearate, or about 8 mg to about 9 mg magnesium stearate, or about 8.1 mg, about 8.2 mg, about 8.3 mg, about 8.4 mg, about 8.5 mg, about 8.6 mg, about 8.7 mg, about 8.8 mg or about 8.9 mg magnesium stearate.

[0069] Examples of disintegrants include, but are not limited to, starches, celluloses, cross-linked PVP (crospovidone), sodium starch glycolate, croscarmellose sodium, *etc*. In certain embodiments, the tablets disclosed herein include croscarmellose sodium. In certain other embodiments, the tablets disclosed herein do not include crospovidone. In certain embodiments, the tablet includes less than about 50 mg croscarmellose sodium, or less than about 25 mg croscarmellose sodium. In certain embodiments, the tablet includes about 30 mg to about 60 mg croscarmellose sodium, or about 40 mg to about 60 mg croscarmellose sodium, or about 45 mg to about 55 mg croscarmellose sodium, or about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg or about 53 mg, or about 54 mg, or about 55 mg croscarmellose sodium.

[0070] Examples of fillers (also known as bulking agents or diluents) include, but are not limited to, starches, maltodextrins, polyols (such as lactose), and celluloses. In certain embodiments, tablets provided herein may microcrystalline cellulose. In certain other embodiments, tablets provided herein do not contain lactose. In certain embodiments, tablets provided herein include less than about

300 mg microcrystalline cellulose, in particular less than about 250 mg microcrystalline cellulose, and/or less than about 225 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include less than about 500 mg microcrystalline cellulose, or less than about 450 mg microcrystalline cellulose, or less than about 400 mg microcrystalline cellulose, or less than about 375 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include about 250 mg to about 500 mg microcrystalline cellulose, or about 300 mg to about 450 mg microcrystalline cellulose, or about 300 mg to about 400 mg microcrystalline cellulose, or about 325 mg to about 375 mg microcrystalline cellulose, or about 350 mg to about 370 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include about 300 mg, or about 310 mg, or about 320 mg, or about 330 mg, or about 340 mg, or about 350 mg, or about 360 mg, or about 370 mg, or about 380 mg, or about 390 mg, or about 400 mg microcrystalline cellulose.

[0071] Examples of binders include, but are not limited to, cross-linked PVP, HPMC, sucrose, starches, *etc*.

[0072] In certain embodiments, tablets provided herein are uncoated. In certain other embodiments, tablets provided herein are coated (in which case they include a coating). Although uncoated tablets may be used, it is more usual in the clinical setting to provide a coated tablet, in which case a conventional non-enteric coating may be used. Film coatings are known in the art and can be composed of hydrophilic polymer materials, but are not limited to, polysaccharide materials, such as hydroxypropylmethyl cellulose (HPMC), methylcellulose, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), poly(vinylalcohol-co-ethylene glycol) and other water soluble polymers. Though in certain embodiments the water soluble material included in the film coating of the embodiments disclosed herein includes a single polymer material, in certain other embodiments it is formed using a mixture of more than one polymer. In certain embodiments, the coating is yellow or brown. Suitable coatings include, but are not limited to, polymeric film coatings such as those comprising polyvinyl alcohol *e.g.* 'Opadry® II' (which includes part-hydrolysed PVA, titanium dioxide, macrogol 3350 (PEG) and talc, with optional colouring such as iron oxide (e.g., iron oxide red or iron oxide black) or indigo carmine or iron oxide yellow or FD&C yellow #6). The amount of coating is generally between about 2-4% of the core's weight, and in certain specific embodiments, about 3%. Unless specifically stated otherwise, where the dosage form is coated, it is to be understood that a reference to % weight of the tablet means that of the total tablet, *i.e.* including the coating.

Pharmacokinetics

[0073] In certain embodiments, the pharmaceutical compositions disclosed herein result in increased systemic exposure (AUC_{inf}, C_{max}) for the compound of Formula I or a pharmaceutically acceptable salt thereof. In particular embodiments, the multilayer tablet formulations disclosed herein result in

increased systemic exposure for the compound of Formula I or a pharmaceutically acceptable salt thereof compared to a single agent tablet formulation of the compound of Formula I or a pharmaceutically acceptable salt thereof. In certain embodiments, the multilayer tablet formulation results in an increase of at least about 20% in the systemic exposure of the compound of Formula I or a pharmaceutically acceptable salt thereof compared to a single agent tablet formulation of the compound of Formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the increase in systemic exposure is at least about 25% or at least about 30%. In some embodiments, the increase in systemic exposure is about 30%.

C_{max}

[0074] C_{max} is the maximum observed plasma/serum concentration of drug.

[0075] In particular embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fasted patients of from about 5300 to about 8900 ng/mL, *e.g.* about 7100 ng/mL.

[0076] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fasted patients of from about 1700 to about 2800 ng/mL, *e.g.* about 2300 ng/mL.

[0077] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fasted patients of from about 190 to about 320 ng/mL, *e.g.* about 250 ng/mL.

[0078] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the Compound of Formula I of from about from about 4200 ng/mL to about 8000 ng/mL, regardless of whether the subject was fed or fasted.

[0079] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in

fasted patients of from about 4200 ng/mL to about 6500 ng/mL, or from about 4700 ng/mL to about 5300 ng/mL, or from about 4700 ng/mL to about 5800 ng/mL, or from about 5000 ng/mL to about 5500 ng/mL.

[0080] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fed patients of from about 4500 ng/mL to about 8000 ng/mL, or from about 4800 ng/mL to about 7900 ng/mL, or from about 5300 ng/mL to about 6900 ng/mL, or from about 5600 ng/mL to about 6600 ng/mL.

[0081] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine of from about from about 1770 ng/mL to about 2800 ng/mL, regardless of whether the subject was fed or fasted.

[0082] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fasted patients of from about 1770 ng/mL to about 2800 ng/mL, or from about 2000 ng/mL to about 2600 ng/mL, or from about 2000 ng/mL to about 2500 ng/mL, or from about 2100 ng/mL to about 2400 ng/mL.

[0083] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fed patients of from about 1000 ng/mL to about 3000 ng/mL, or from about 1500 ng/mL to about 2000 ng/m from about 1700 ng/mL to about 2200 ng/mL L, or from about 1800 ng/mL to about 2100 ng/mL.

[0084] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide of from about from about 185 ng/mL to about 315 ng/mL, regardless of whether the subject was fed or fasted.

[0085] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a

pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fasted patients of from about 185 ng/mL to about 315 ng/mL, or from about 200 ng/mL to about 300 ng/mL, or from about 210 ng/mL to about 290 ng/mL, or from about 220 ng/mL to about 275 ng/mL, or from about 230 ng/mL to about 265 ng/mL, or from about 240 ng/mL to about 260 ng/mL.

[0086] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fed patients of from about 150 ng/mL to about 350 ng/mL, or from about 185 ng/mL to about 300 ng/m from about 210 ng/mL to about 280 ng/mL L, or from about 250 ng/mL to about 265 ng/mL.

AUC_{inf}

[0087] AUC_{inf} is the area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$.

[0088] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fed patients of from about 117000 to about 196000 h•ng/mL, *e.g.* about 157000 h•ng/mL.

[0089] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 8700 to about 14500h•ng/mL, *e.g.* about 2300h•ng/mL.

[0090] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 150 and 260 h•ng/mL, *e.g.* about 210 h•ng/mL.

[0091] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the Compound of Formula I of from about from about 84450 h•ng/mL to about 141000 h•ng/mL, regardless of whether the subject was fed or fasted.

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[0092] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fasted patients of from about 84450 h•ng/mL to about 141000 h•ng/mL, or from about 90000 h•ng/mL to about 135000 h•ng/mL, or from about 95000 h•ng/mL to about 130000 h•ng/mL, or from about 100000 h•ng/mL to about 125000 h•ng/mL, or from about 110000 h•ng/mL to about 120000 h•ng/mL.

[0093] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fed patients of from about 100000 h•ng/mL to about 200000 ng/mL, or from about 112000 h•ng/mL to about 175000 ng/mL, or from about 126000 h•ng/mL to about 155000 ng/mL, or from about 133000 h•ng/mL to about 147000 ng/mL.

[0094] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine of from about from about 8100 h•ng/mL to about 13600 h•ng/mL, regardless of whether the subject was fed or fasted.

[0095] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fasted patients of from about 8100 h•ng/mL to about 13600 h•ng/mL, or from about 8700 h•ng/mL to about 13000 h•ng/mL, or from about 92000 h•ng/mL to about 12500 h•ng/mL, or from about 9700 h•ng/mL to about 12000 h•ng/mL, or from about 10000 h•ng/mL to about 11400 h•ng/mL.

[0096] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 7500 h•ng/mL to about 15000 ng/mL, or from about 8300 h•ng/mL to about 14000 ng/mL, or from about 9500 h•ng/mL to about 12000 ng/mL, or from about 9900 h•ng/mL to about 11600 ng/mL.

[0097] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide of from about from about 200 h•ng/mL to about 500 h•ng/mL, regardless of whether the subject was fed or fasted.

[0098] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fasted patients of from about 200 h•ng/mL to about 265 h•ng/mL, or from about 200 h•ng/mL to about 300 h•ng/mL, or from about 210 h•ng/mL to about 290 h•ng/mL, or from about 220 h•ng/mL to about 270 h•ng/mL, or from about 230 h•ng/mL to about 265 h•ng/mL.

[0099] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 200 h•ng/mL to about 500 ng/mL, or from about 230 h•ng/mL to about 400 ng/mL, or from about 260 h•ng/mL to about 350 ng/mL, or from about 275 h•ng/mL to about 370 ng/mL.

AUC_{last}

[0100] AUC_{last} is the area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration.

[0101] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fed patients of from about 114000 to about 190000 h•ng/mL, *e.g.* about 152000 h•ng/mL.

[0102] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine in fed patients of from about 8600 to about 14000 h•ng/mL, *e.g.* about 11000 h•ng/mL.

[0103] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof,

200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 150 and 260 h•ng/mL, *e.g.* about 210 h•ng/mL.

[0104] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I of from about from about 81700 h•ng/mL to about 140000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0105] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fasted patients of from about 81700 h•ng/mL to about 140000 h•ng/mL, from about 87000 h•ng/mL to about 131000 h•ng/mL, from about 92000 h•ng/mL to about 130000 h•ng/mL, from about 98100 h•ng/mL to about 120000 h•ng/mL, from about 104000 h•ng/mL to about 115000 h•ng/mL.

[0106] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fed patients of from about 100000 h•ng/mL to about 200000 ng/mL, or from about 108000 h•ng/mL to about 170000 ng/mL, or from about 122000 h•ng/mL to about 150000 ng/mL, or from about 128000 h•ng/mL to about 142000 ng/mL.

[0107] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine of from about from about 7500 h•ng/mL to about 15000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0108] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the emtricitabine in fasted patients of from about 8000 h•ng/mL to about 13400 h•ng/mL, from about 8500 h•ng/mL to about

12800 h•ng/mL, from about 9000 h•ng/mL to about 12300 h•ng/mL, from about 9500 h•ng/mL to about 11000 h•ng/mL, from about 10000 h•ng/mL to about 11200 h•ng/mL.

[0109] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine in fed patients of from about 7500 h•ng/mL to about 15000 ng/mL, or from about 8000 h•ng/mL to about 14000 ng/mL, or from about 9000 h•ng/mL to about 12000 ng/mL, or from about 9700 h•ng/mL to about 11300 ng/mL.

[0110] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide of from about from about 165 h•ng/mL to about 400 h•ng/mL, regardless of whether the subject was fed or fasted.

[0111] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the tenofovir alafenamide in fasted patients of from about 165 h•ng/mL to about 390 h•ng/mL, from about 186 h•ng/mL to about 227 h•ng/mL, from about 196 h•ng/mL to about 217 h•ng/mL.

[0112] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 200 h•ng/mL to about 400 ng/mL, or from about 230 h•ng/mL to about 390 ng/mL, or from about 260 h•ng/mL to about 345 ng/mL, or from about 275 h•ng/mL to about 330 ng/mL.

C_{last}

[0113] C_{last} is the last observed quantifiable plasma/serum concentration of the drug.

[0114] C_{max}, C_{last}, AUC_{inf}, and AUC_{last} are standard pharmacokinetic parameters that can be estimated manually or by using modelling software well known in the art, such as the Pharsight WinNonlin package using a non-compartmental model. The general basis for calculation of these quantities is well-known (*e.g.* see Rowland & Tozer (2010) *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications* ISBN 978-0781750097, or Jambhekar & Breen

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(2012) *Basic Pharmacokinetics* ISBN 978-0853699804). Typically the parameters will be assessed as the average (*e.g.* geometric or arithmetic mean) from within a group of at least 12 (and normally between 24 and 36) healthy human adults. Parameters should be measured in accordance with standards and practices which would be acceptable to a pharmaceutical regulatory agency such as FDA, EMA, MHLW, or WHO. The values may be based on measurements taken at appropriate intervals following the time of tablet ingestion, such as every hour, or at increasingly sparse sampling intervals, such as 1, 3, 5, 7, 9, 11, 13, 15, 20, and 24 hours after ingestion. They can be assessed either following a single-dose of drug or at steady state, but will typically be assessed following a single-dose.

[0115] It is well known in the bioavailability and bioequivalence arts how to determine whether any particular tablet meets regulatory requirements for equivalent bioavailability and pharmacokinetic bioequivalence *e.g.* see: Niazi (2014) *Handbook of Bioequivalence Testing*, 2nd Edition, ISBN 978-1482226379; *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations* FDA March 2003; and *Guideline On The Investigation Of Bioequivalence*, EMEA 2010 CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. To ensure statistical power a study to measure the C_{max}, AUC_{last} and AUC_{inf} values will be performed in multiple subjects *e.g.* in a group of at least 12 (and normally between 24 and 36) healthy human adults.

[0116] Because determining the C_{max}, AUC_{last} and AUC_{inf} values is necessarily destructive these parameters will not be determined directly for the dosage form (in particular the tablet) in question, but rather for a dosage form made by the same manufacturing process with the same components. Thus a batch of a dosage form (*e.g.* tablets) can be made by a particular process, and the 90% confidence interval of C_{max}, AUC_{last} and AUC_{inf} will be assessed on a sample of those tablets. If these values meet the 80-125% requirement noted above then tablets made by the manufacturing process in question are tablets of the present invention.

[0117] A fixed dose combination tablet is provided comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* Formula II), (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

[0118] In an embodiment, a multilayer tablet is provided, comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof (*e.g.* Formula II), (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

[0119] In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second

layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

[0120] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0121] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0122] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof and tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0123] In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer containing emtricitabine or a pharmaceutically acceptable salt thereof, and (c) further comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof.

[0124] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0125] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0126] In an embodiment of the multilayer tablet disclosed herein, the first layer is substantially free of emtricitabine.

[0127] In one embodiment, the multilayer tablet disclosed herein comprises 50 ± 6 mg of the compound of Formula I. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 25 ± 3 mg of tenofovir alafenamide.

[0128] In one embodiment, the multilayer tablet disclosed herein comprises 75 ± 6 mg of the compound of Formula I. In one embodiment, the multilayer tablet disclosed herein comprises

200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 25 ± 3 mg of tenofovir alafenamide.

[0129] In one embodiment, the multilayer tablet disclosed herein comprises 52 ± 6 mg of the compound of Formula II. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

[0130] In one embodiment, the multilayer tablet disclosed herein comprises 78 ± 6 mg of the compound of Formula II. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

[0131] In one embodiment, a first layer of the multilayer tablet disclosed herein comprises one or more excipients, for example one or more diluents, disintegrants, binders, or lubricants.

[0132] In one embodiment, a first layer of the multilayer tablet comprises croscarmellose sodium. In one embodiment, a first layer of the multilayer tablet comprises croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

[0133] In one embodiment a tablet is provided wherein less than about 25 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 20 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 16 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 5 to about 20 weight percent, or about 10 to about 18 weight percent, or about 14 to about 18 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 16 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0134] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 290 mg.

[0135] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 300 mg.

[0136] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 310 mg.

[0137] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg.

[0138] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg.

[0139] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 340 mg.

[0140] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg.

[0141] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 360 mg.

[0142] In one embodiment a tablet is provided wherein the first layer comprises 52± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 290 mg and is less than about 360 mg.

[0143] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 300 mg and is less than about 350 mg.

[0144] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 310 mg and is less than about 330 mg.

[0145] In one embodiment, the first layer of the multilayer tablet has a total weight of 323 ± 75 mg, or 323 ± 25 mg, or 323 ± 10 mg, or 323 mg.

[0146] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	**Mass (mg)**
The compound of Formula I or a salt thereof	40-60
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	1-10

[0147] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
the compound of Formula II	30-60
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	2-8

[0148] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
the compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5± 1.5

[0149] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52 ± 5.6
Microcrystalline cellulose	246 ± 10
Croscarmellose sodium	19 ± 2.5
Magnesium stearate	5 ± 0.75

[0150] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52 ± 2.8
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

[0151] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	**Mass (mg)**
the compound of Formula II	52.5
Microcrystalline cellulose	246.3
Croscarmellose sodium	19.4
Magnesium stearate	4.9

[0152] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	**Mass (mg)**
Intergranular	
the compound of Formula I or a pharmaceutically acceptable salt thereof	52.5 ± 1.6
Microcrystalline cellulose	214 ± 7.3
Croscarmellose sodium	19 ± 0.6
Magnesium stearate	2.4 ± 0.5
Extragranular	
Microcrystalline cellulose	32 ± 1
Magnesium stearate	2.4 ± 0.5
Total layer weight	*323*

[0153] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	**Mass (mg)**
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 7.3
Croscarmellose sodium	19 ± 0.6
Magnesium stearate	2.4 ± 0.5
Extragranular	
Microcrystalline cellulose	32 ± 1
Magnesium stearate	2.4 ± 0.5
Total layer weight	*323*

[0154] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	**Mass (mg)**
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.45 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.45 ± 0.5
Total layer weight	*323*

[0155] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	**Mass (mg)**
Intergranular	
the compound of Formula I, or a pharmaceutically acceptable salt therof	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.43 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.43 ± 0.5
Total layer weight	*323*

[0156] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.43 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.43 ± 0.5
Total layer weight	*323*

[0157] In one embodiment a tablet is provided wherein less than about 30 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 25 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 22 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 15 to about 27 weight percent, or about 17 to about 25 weight percent, or about 19 to about 23 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 21 weight percent of the first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0158] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg.

[0159] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg.

[0160] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 340 mg.

[0161] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg.

[0162] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 360 mg.

[0163] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 370 mg.

[0164] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 380 mg.

[0165] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 390 mg.

[0166] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg and is less than about 390 mg.

[0167] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg and is less than about 380 mg.

[0168] In one embodiment a tablet is provided wherein the first layer comprises 78 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg and is less than about 360 mg.

[0169] In one embodiment, the first layer of the multilayer tablet has a total weight of 353 ± 75 mg, or 353 ± 25 mg, or 353 ± 10 mg, or 353 mg.

[0170] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	**Mass (mg)**
The compound of Formula I or a salt thereof	40-85
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	1-10

[0171] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	**Mass (mg)**
The compound of Formula II	30-90
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	2-8

[0172] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5± 1.5

[0173] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
The compound of Formula II	78 ± 5.6
Microcrystalline cellulose	250 ± 10
Croscarmellose sodium	20 ± 2.5
Magnesium stearate	5 ± 0.75

[0174] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	78 ± 2.8
Microcrystalline cellulose	247 ± 5
Croscarmellose sodium	21 ± 1.75
Magnesium stearate	5 ± 0.5

[0175] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	78.7
Microcrystalline cellulose	247.8
Croscarmellose sodium	21.2
Magnesium stearate	5.3

[0176] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	

the compound of Formula II	78.7
Microcrystalline cellulose	212.5
Croscarmellose sodium	21.2
Magnesium stearate	2.65
Extragranular	
Microcrystalline cellulose	35.3
Magnesium stearate	2.65
Total layer weight	*353*

[0177] In one embodiment, the second layer of the multilayer tablet does not comprise lactose. In one embodiment, the second layer of the multilayer tablet does not comprise starch. In one embodiment, the second layer of the multilayer tablet comprises neither lactose nor starch.

[0178] In one embodiment, the second layer of the multilayer tablet comprises one or more excipients, for example, one or more diluents, disintegrants, binders, or lubricants.

[0179] In one embodiment, the second layer of the multilayer tablet comprises microcrystalline cellulose and croscarmellose sodium.

[0180] In one embodiment, the second layer of the multilayer tablet comprises microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

[0181] In one embodiment, the second layer of the multilayer tablet comprises 20-40 mg of croscarmellose sodium. In one embodiment, the second layer of the multilayer tablet comprises 105-125 mg of microcrystalline cellulose. In one embodiment, the second layer of the multilayer tablet comprises 1-8 mg of magnesium stearate.

[0182] In one embodiment, the second layer of the multilayer tablet does not comprise lactose. In one embodiment, the second layer of the multilayer tablet does not comprise starch. In one embodiment, the second layer of the multilayer tablet comprises neither lactose nor starch.

[0183] In one embodiment, the second layer of the multilayer tablet has a total weight of less than 600 mg, or less than 500 mg, or less than 400 mg, or less than 380 mg. In one embodiment, the second layer of the multilayer tablet has a total weight of 377 mg ± 50 mg or 377 mg ± 25 mg, or 377 mg ± 5 mg, or 377 mg.

[0184] In one embodiment, over 50 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 55 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In

one embodiment, about 55 % to about 65% by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate. In one embodiment, about 55 % to about 65% by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate.

[0185] In one embodiment, the second layer of the multilayer tablet contains less than 250 mg of excipients, for example less than 200 mg, or less than 150 mg.

[0186] In one embodiment, at least 50% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, at least 53% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 45% to about 65% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 50% to about 60% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment, about 51% to about 53% by weight of the second layer of the multilayer tablet is emtricitabine.

[0187] In one embodiment, at least 4% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 6% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 5% to about 10% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 6% to about 9% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 7% to about 8% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, about 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate.

[0188] In one embodiment, less than 20% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In one embodiment, less than 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In one embodiment, about 5% to about 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In certain embodiments, the use of about 5 to 7% (*e.g.* about 6%) croscarmellose sodium by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other disintegrants *e.g.* polyvinylpyrrolidone (crospovidone). In certain embodiments, the use of about 5 to 10% croscarmellose sodium by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other disintegrants *e.g.* polyvinylpyrrolidone (crospovidone).

[0189] In one embodiment, less than 50% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 40% by weight of the second layer of the

multilayer tablet is microcrystalline cellulose. In one embodiment, less than 31% by weight of the second layer of the multilayer tablet is microcrystalline cellulose.

[0190] In one embodiment, less than 5% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, less than 3% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, less than 2% by weight of the second layer of the multilayer tablet is magnesium stearate. In one embodiment, about 0.5% to about 1.5% by weight of the second layer of the multilayer tablet is magnesium stearate. In certain embodiments, the use of about 1% to about 2% (*e.g.* about 1.5%) magnesium stearate by weight of the second layer may provide enhanced dissolution of the compound of Formula I or a pharmaceutically acceptable salt thereof, relative to other lubricants *e.g.* sodium stearyl fumarate.

[0191] In one embodiment, the total weight of the second layer is less than 150% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 125% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 116% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 106% of the total weight of the first layer.

[0192] In one embodiment, the second layer of the multilayer tablet comprises:

Ingredient	**Mass (mg)**
Emtricitabine or a salt thereof	150-250
Tenofovir alafenamide or a salt thereof	20-35
Microcrystalline cellulose	90-130
Croscarmellose sodium	20-35
Magnesium stearate	1-7

[0193] In one embodiment, the second layer of the multilayer tablet comprises:

Ingredient	**Mass (mg)**
Emtricitabine	170-230
Tenofovir alafenamide hemifumarate	22-32
Microcrystalline cellulose	100-120
Croscarmellose sodium	20-35
Magnesium stearate	1-7

[0194] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	**Mass (mg)**
Emtricitabine	200 ±20

Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	5.6 ±1.1

[0195] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	**Mass (mg)**
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0196] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	**Mass (mg)**
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	5.7

[0197] In one embodiment, the second layer of the multilayer tablet consists of:

Ingredient	**Mass (mg)**
Intergranular	
Emtricitabine	200.00
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	2.85
Extragranular	
Magnesium stearate	2.85
Total layer weight	*377*

[0198] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide	25 ±3
Microcrystalline cellulose	115 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	3.8 ±1.1

[0199] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	115 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	3.8 ±1.1

[0200] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	115 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	3.8 ±0.5

[0201] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28.1
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	3.8

[0202] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	1.9
Extragranular	
Magnesium stearate	1.9
Total layer weight	*377*

[0203] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	5.7

[0204] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	**Mass (mg)**
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	115
Croscarmellose sodium	30.2
Magnesium stearate	3.8

[0205] In one embodiment, the second layer of the multilayer tablet includes:

Ingredient	**Mass (mg)**
Intergranular	
Emtricitabine	200
Tenofovir alafenamide hemifumarate	28
Microcrystalline cellulose	113.2
Croscarmellose sodium	30.2
Magnesium stearate	2.85
Extragranular	
Magnesium stearate	2.85
Total layer weight	*377*

[0206] In one embodiment of the multilayer tablet formulations disclosed herein, the first layer is in contact with the second layer.

[0207] In one embodiment, the first layer is produced first, followed be the second layer. That is, in one embodiment, the first layer is prepared and pressed into a first layer, followed by the second layer being prepared and being pressed with the first layer into a multilayer tablet. In one embodiment, the second layer is produced first, followed be the first layer. That is, in one embodiment, the second layer is prepared and pressed into a second layer, followed by the first layer being prepared and being pressed with the second layer into a multilayer tablet.

[0208] As used herein, when describing the multilayer tablets disclosed herein, the terms "first layer" and "second layer" are not intended to indicate the method by which the tablets are produced, in particular the order in which the layers are obtained.

[0209] In certain embodiments, the multilayer tablet further comprises additional layers. In certain embodiments, the additional layer or layers are located between the first and second layers. In certain

embodiments, the additional layer or layers are located on either side of the first and/or second layer, such that they are an outside layer of the table and/or are disposed between the first and/or second layer and a coating layer. In some embodiments, the additional layer or layers encapsulate the first and second layers.

[0210] In one embodiment, the multilayer tablet further comprises a third layer that is between and that separates the first layer and the second layer. In one embodiment, the third layer of the multilayer tablet comprises lactose monohydrate, or microcrystalline cellulose, or a mixture thereof.

[0211] In one embodiment, the multilayer tablet further comprises a film coating. In one embodiment, the multilayer tablet further comprises about 14 mg to about 28 mg of a film coating. In one embodiment, the multilayer tablet further comprises about 19 mg to about 23 mg of a film coating. In one embodiment, the multilayer tablet further comprises about 21 mg of a film coating.In one embodiment the film coating comprises polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and black iron oxide. In one embodiment the film coating consists of 21 ± 7 mg of Opadry II Brown 85F165072. In one embodiment the film coating consists of 21 ± 7 mg of Opadry II Yellow 85F92259.

[0212] In one embodiment, the multilayer tablet further includes a film coating. In one embodiment, the multilayer tablet further comprises about 1.9% to about 3.9% w/w of a film coating. In one embodiment, the multilayer tablet further comprises about 2.5% to about 3.5% w/w of a film coating. In one embodiment, the multilayer tablet further comprises about 3% of a film coating. In one embodiment the film coating includes polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, iron oxide red, and black iron oxide. In one embodiment the film coating includes 36%-40% polyvinyl alcohol, 18%-22% polyethylene glycol, 13%-16% talc, 20%-24% titanium dioxide, 2%-3% iron oxide red, and 0.5%-0.7% black iron oxide.

[0213] In one embodiment a tablet is provided comprising about 6.4-8.5% w/w of the compound of Formula II, about 25-32% w/w mg emtricitabine, about 3.5-4.5% w/w mg tenofovir alafenamide hemifumarate, about 46-57% w/w mg microcrystalline cellulose, about 5.9-8.5% w/w mg croscarmellose sodium, and about 1.0-2.0% w/w mg magnesium stearate.

[0214] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 10.5 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg.

[0215] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg tenofovir alafenamide hemifumarate, 360 ± 15 mg Microcrystalline cellulose, 50 ± 4 mg Croscarmellose sodium, and 10.5 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg and is less than about 715 mg.

[0216] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg Tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 8.6 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg.

[0217] In one embodiment a tablet is provided comprising 52 ± 6 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg Tenofovir alafenamide hemifumarate, 360 ± 15 mg Microcrystalline cellulose, 50 ± 4 mg Croscarmellose sodium, and 8.6 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 685 mg and is less than about 715 mg.

[0218] In one embodiment, the tablet has a total weight of 700 ± 75 mg, or 700 ± 25 mg, or 700 ± 10 mg, or 700 mg. In one embodiment, the tablet is uncoated and has a total weight of about 700 ± 75 mg, or about 700 ± 25 mg, or about 700 ± 10 mg, or about 700 mg. In one embodiment, the tablet has a total weight of about 720 ± 75 mg, or about 720 ± 25 mg, or about 720 ± 10 mg, or about 720 mg, or about 721 mg, or about 722 mg, or about 723 mg, or about 724 mg, or about 725 mg, or about 726 mg, or about 727 mg, or about 728 mg, or about 729 mg, or about 730 mg.

[0219] In one embodiment a tablet is provided comprising 80 ± 6 mg of the compound of Formula II, 200 ± 20 mg emtricitabine, 28 ± 3 mg Tenofovir alafenamide hemifumarate, 360 ± 30 mg Microcrystalline cellulose, 50 ± 8 mg Croscarmellose sodium, and 11 ± 3 mg magnesium stearate and wherein the total weight of the tablet is at least about 715 mg.

[0220] In one embodiment a tablet is provided comprising 78 ± 2.3 mg of the compound of Formula II, 200 ± 10 mg emtricitabine, 28 ± 1.5 mg Tenofovir alafenamide hemifumarate, 361 ± 15 mg Microcrystalline cellulose, 51 ± 4 mg Croscarmellose sodium, and 11 ± 1.5 mg magnesium stearate and wherein the total weight of the tablet is at least about 715 mg and is less than about 745 mg.

[0221] In one embodiment, the tablet has a total weight of 730 ± 75 mg, or 730 ± 25 mg, or 730 ± 10 mg, or 730 mg. In one embodiment, the tablet has a total weight of about 750 ± 75 mg, or about 750 ± 25 mg, or about 750 ± 10 mg, or about 750 mg, or about 751 mg, or about 752 mg, or about 753 mg, or about 754 mg, or about 755 mg.

[0222] In one embodiment, a tablet is provided comprising:

Ingredient	**Mass (mg)**
The compound of Formula II	52 ± 6
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	10.5 ± 3

[0223] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	52.5 ± 3
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28.1 ±1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	10.5 ± 1.5

[0224] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 5
Emtricitabine	200 ±20
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0225] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 2.5
Emtricitabine	200 ±10
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ±1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	8.6 ± 1.5

[0226] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	52 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0227] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	8.6 ± 3

[0228] In one embodiment, a tablet is provided including:

Ingredient	Mass (mg)
The compound of Formula II	52.5 ± 3
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28.1 ±1.5
Microcrystalline cellulose	360 ± 15
Croscarmellose sodium	50 ± 4
Magnesium stearate	8.6 ± 1.5

[0229] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	5.6 ±1.1

[0230] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	25 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	4 ±1.1

[0231] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt thereof	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	4 ±1.1

[0232] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	4 ±1.1

[0233] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 2.8

Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0234] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula I, or a pharmaceutically acceptable salt therof	50 ± 3
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide, or a pharmacetuically acceptable salt thereof	25 ±3
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	4 ±0.5

[0235] In one embodiment, a tablet is provided comprising a first layer including:

Ingredient	Mass (mg)
The compound of Formula II	52 ± 2.8
Microcrystalline cellulose	246 ± 5

Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer including:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	4 ±0.5

[0236] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	360 ± 30
Croscarmellose sodium	50 ± 8
Magnesium stearate	11 ± 3

[0237] In one embodiment, a tablet is provided comprising:

Ingredient	Mass (mg)
The compound of Formula II	78.6 ± 2.3
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28.1 ±1.5
Microcrystalline cellulose	361 ± 15
Croscarmellose sodium	51 ± 4
Magnesium stearate	11 ± 1.5

[0238] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	80 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5± 1.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±20
Tenofovir alafenamide hemifumarate	28 ±3
Microcrystalline cellulose	113 ±9
Croscarmellose sodium	30 ±3
Magnesium stearate	5.6 ±1.1

[0239] In one embodiment, a tablet is provided comprising a first layer consisting of:

Ingredient	Mass (mg)
The compound of Formula II	78 ± 2.8
Microcrystalline cellulose	247 ± 5
Croscarmellose sodium	21 ± 1.75
Magnesium stearate	5 ± 0.5

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ±10
Tenofovir alafenamide hemifumarate	28 ±1.4
Microcrystalline cellulose	113 ±4
Croscarmellose sodium	30 ±1.4
Magnesium stearate	5.6 ±0.5

[0240] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)

The compound of Formula I, or a pharmaceutically acceptable salt thereof	5-10
Microcrystalline cellulose	26-44
Croscarmellose sodium	2-4
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in tablet)
Emtricitabine	21-36
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	3-5
Microcrystalline cellulose	12-20
Croscarmellose sodium	3-6
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0241] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	5-10
Microcrystalline cellulose	26-44
Croscarmellose sodium	2-4
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in tablet)
Emtricitabine	21-36
Tenofovir alafenamide hemifumarate	3-5
Microcrystalline cellulose	12-20
Croscarmellose sodium	3-6
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0242] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)

The compound of Formula I, or a pharmaceutically acceptable salt thereof	6-9
Microcrystalline cellulose	30-40
Croscarmellose sodium	2.4-3.2
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	24-33
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	3.4-4.6
Microcrystalline cellulose	14-19
Croscarmellose sodium	3.6-4.9
Magnesium stearate	0.6-0.8

and optionally a film coating.

[0243] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	6-9
Microcrystalline cellulose	30-40
Croscarmellose sodium	2.4-3.2
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	24-33
Tenofovir alafenamide hemifumarate	3.4-4.6
Microcrystalline cellulose	14-19
Croscarmellose sodium	3.6-4.9
Magnesium stearate	0.6-0.8

and optionally a film coating.

[0244] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)

The compound of Formula II	7-8
Microcrystalline cellulose	32-37
Croscarmellose sodium	2.7-2.9
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	26-30
Tenofovir alafenamide hemifumarate	3.7-4.6
Microcrystalline cellulose	15-17
Croscarmellose sodium	4.0-4.5
Magnesium stearate	0.5-0.6

and optionally a film coating.

[0245] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7-8
Microcrystalline cellulose	33-36
Croscarmellose sodium	2.7-2.8
Magnesium stearate	0.7-0.8

and a second layer including:

	% w/w (in tablet)
Emtricitabine	27-29
Tenofovir alafenamide hemifumarate	3.8-4.2
Microcrystalline cellulose	16-17
Croscarmellose sodium	4.1-4.4
Magnesium stearate	0.5-0.8

and optionally a film coating.

[0246] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7.5
Microcrystalline cellulose	35.2

Croscarmellose sodium	2.8
Magnesium stearate	0.7

and a second layer including:

	% w/w (in tablet)
Emtricitabine	28.6
Tenofovir alafenamide hemifumarate	4.0
Microcrystalline cellulose	16.4
Croscarmellose sodium	4.3
Magnesium stearate	0.5

and optionally a film coating.

[0247] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in tablet)
The compound of Formula II	7.5
Microcrystalline cellulose	35.2
Croscarmellose sodium	2.8
Magnesium stearate	0.7

and a second layer including:

	% w/w (in tablet)
Emtricitabine	28.6
Tenofovir alafenamide hemifumarate	4.0
Microcrystalline cellulose	16.2
Croscarmellose sodium	4.3
Magnesium stearate	0.8

and optionally a film coating.

[0248] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically accpetable salt thereof	11-19
Microcrystalline cellulose	51-86

Croscarmellose sodium	4-7
Magnesium stearate	0.5-0.9
Extragranular	
Microcrystalline cellulose	7-12
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	39-67
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	5-10
Microcrystalline cellulose	22-38
Croscarmellose sodium	6-10
Magnesium stearate	0.3-0.7
Intergranular	
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0249] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	11 19
Microcrystalline cellulose	51-86
Croscarmellose sodium	4-7
Magnesium stearate	0.5-0.9
Extragranular	
Microcrystalline cellulose	7-12
Magnesium stearate	0.5-0.9

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	39-67
Tenofovir alafenamide hemifumarate	5-10
Microcrystalline cellulose	22-38
Croscarmellose sodium	6-10
Magnesium stearate	0.3-0.7
Intergranular	
Magnesium stearate	0.3-0.7

and optionally a film coating.

[0250] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	13-17
Microcrystalline cellulose	58-79
Croscarmellose sodium	4.6-6.3
Magnesium stearate	0.6-0.8
Extragranular	
Microcrystalline cellulose	5-11
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	45-61
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	6-9
Microcrystalline cellulose	25-35
Croscarmellose sodium	6.5-9.2
Magnesium stearate	0.4-0.5
Intergranular	
Magnesium stearate	0.4-0.5

and optionally a film coating.

[0251] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	13-17
Microcrystalline cellulose	58-79
Croscarmellose sodium	4.6-6.3
Magnesium stearate	0.6-0.8
Extragranular	
Microcrystalline cellulose	5-11
Magnesium stearate	0.6-0.8

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	45-61
Tenofovir alafenamide hemifumarate	6-9
Microcrystalline cellulose	25-35
Croscarmellose sodium	6.5-9.2
Magnesium stearate	0.4-0.5
Intergranular	
Magnesium stearate	0.4-0.5

and optionally a film coating.

[0252] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula I, or a pharmaceutically acceptable salt thereof	14-16
Microcrystalline cellulose	66-73
Croscarmellose sodium	5.2-5.8
Magnesium stearate	0.65-0.75
Extragranular	
Microcrystalline cellulose	8-10
Magnesium stearate	0.65-0.75

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	50-56
Tenofovir alafenamide, or a pharmaceutically acceptable salt thereof	7-8
Microcrystalline cellulose	28-32
Croscarmellose sodium	7.5-8.5
Magnesium stearate	0.45-0.55
Intergranular	
Magnesium stearate	0.45-0.55

and optionally a film coating.

[0253] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	14 16
Microcrystalline cellulose	66-73
Croscarmellose sodium	5.2-5.8
Magnesium stearate	0.65-0.75
Extragranular	
Microcrystalline cellulose	8-10
Magnesium stearate	0.65-0.75

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	50-56
Tenofovir alafenamide hemifumarate	7-8
Microcrystalline cellulose	28-32
Croscarmellose sodium	7.5-8.5
Magnesium stearate	0.45-0.55
Intergranular	
Magnesium stearate	0.45-0.55

and optionally a film coating.

[0254] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	15
Microcrystalline cellulose	69
Croscarmellose sodium	5.5
Magnesium stearate	0.7
Extragranular	
Microcrystalline cellulose	9
Magnesium stearate	0.7

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	53
Tenofovir alafenamide hemifumarate	7.5
Microcrystalline cellulose	30
Croscarmellose sodium	8
Magnesium stearate	0.5
Intergranular	
Magnesium stearate	0.5

and optionally a film coating.

[0255] In one embodiment, a tablet is provided comprising a first layer including:

	% w/w (in layer)
Intergranular	
The compound of Formula II	15
Microcrystalline cellulose	69
Croscarmellose sodium	5.5
Magnesium stearate	0.7
Extragranular	
Microcrystalline cellulose	9
Magnesium stearate	0.7

and a second layer including:

	% w/w (in layer)
Intergranular	
Emtricitabine	53
Tenofovir alafenamide hemifumarate	7.5
Microcrystalline cellulose	30
Croscarmellose sodium	8
Magnesium stearate	0.7
Intergranular	
Magnesium stearate	0.7

and optionally a film coating.

[0256] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in layer)
Intragranular		
The compound of Formula II	52.5	16.24
Microcrystalline cellulose	149.9-246.3	46.41-76.26
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	1.98-2.45	0.6-1.0

and a second layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	1.93-2.85	0.50-0.75
Extragranular		
Magnesium stearate	1.93-2.85	0.50-0.75

and optionally a film coating.

[0257] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	16.24
Microcrystalline cellulose	149.9-246.3	46.41-76.26
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	1.98-2.45	0.6-1.0

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	1.93-2.85	0.50-0.75
Extragranular		
Magnesium stearate	1.93-2.85	0.50-0.75

and optionally a film coating.

[0258] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	78.7	22.3
Microcrystalline cellulose	212.5	60.2
Croscarmellose sodium	21.2	6.00
Magnesium stearate	2.65	0.75
Extragranular		
Microcrystalline cellulose	35.30	10.0
Magnesium stearate	2.65	0.75

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.0	7.4
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.83	0.75
Extragranular		
Magnesium stearate	2.83	0.75

and optionally a film coating.

[0259] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	16.25
Microcrystalline cellulose	0-246.3	0-76.25
Croscarmellose sodium	19.4	8.00
Magnesium stearate	1.98-2.45	0.6-1.0
Extragranular		
Microcrystalline cellulose	0-97.0	0-30
Magnesium stearate	2.45	0.6-1.0

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.2	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.85	0.75
Extragranular		
Magnesium stearate	2.85	0.75

and a film coating consisting of 21 mg of Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0260] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
The compound of Formula II	52.5	13-21
Microcrystalline cellulose	0-246	0-59
Croscarmellose sodium	19	5-25
Magnesium stearate	2.0-2.5	0.5-3.2
Extragranular		
Microcrystalline cellulose	0-97	0-30
Magnesium stearate	2.0-2.5	0.5-3.2

and a second layer including:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200	35
Tenofovir alafenamide hemifumarate	28	4.9
Microcrystalline cellulose	113	20
Croscarmellose sodium	30	5.2
Magnesium stearate	2.9	0.5
Extragranular		
Magnesium stearate	2.9	0.5

and a film coating consisting of 21 mg of Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0261] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	% w/w (in tablet)
The compound of Formula II	47-58	6.75-8.25
Microcrystalline cellulose	222-271	32-59
Croscarmellose sodium	17-21	2.5-3.1
Magnesium stearate	4.4-5.4	0.6-0.8

and a second layer including:

	Mass (mg)	% w/w (in tablet)
Emtricitabine	180-220	26-31

Tenofovir alafenamide hemifumarate	25-31	3.6-4.4
Microcrystalline cellulose	104-127	15-18
Croscarmellose sodium	27-33	2.6-4.7
Magnesium stearate	3.4-6.0	0.4 1.0

and optionally a film coating (e.g., Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0262] In one embodiment, a tablet is provided comprising a first layer including:

	Mass (mg)	**% w/w (in tablet)**
The compound of Formula II	52.5	7.5
Microcrystalline cellulose	246	35
Croscarmellose sodium	19	2.8
Magnesium stearate	5	0.7

and a second layer including:

	Mass (mg)	**% w/w (in tablet)**
Emtricitabine	200	29
Tenofovir alafenamide hemifumarate	28	4
Microcrystalline cellulose	115	16
Croscarmellose sodium	30	4.3
Magnesium stearate	4	0.5

and optionally a film coating (e.g., Opadry II Brown 85F165072 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, iron oxide red, and iron oxide black).

[0263] In one embodiment, a tablet is provided comprising a first layer consisting of:

	Mass (mg)	**% w/w (in layer)**
Intergranular		
The compound of Formula II	78.6	22.3
Microcrystalline cellulose	212.5	60.2
Croscarmellose sodium	21.2	6.00
Magnesium stearate	2.65	0.75
Extragranular		
Microcrystalline cellulose	35.3	10.0
Magnesium stearate	2.65	0.75

and a second layer consisting of:

	Mass (mg)	% w/w (in layer)
Intergranular		
Emtricitabine	200.00	53.05
Tenofovir alafenamide hemifumarate	28.1	7.45
Microcrystalline cellulose	113.1	30
Croscarmellose sodium	30.2	8.00
Magnesium stearate	2.85	0.75 (0.5-0.75)
Extragranular		
Magnesium stearate	2.83	0.75 (0.5-7.5)

and a film coating consisting of 21.9 mg of Opadry II Yellow 85F92259 (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide and iron yellow).

[0264] In one embodiment, a composition is provided including about 75 mg of a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), about 25 mg tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and about 200 mg emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last} of each component following a single dose administered to a human is from about 81700 h-ng/mL to about 140000 h-ng/mL of the compound of Formula I, from about 7500 h-ng/mL to about 15000 h-ng/mL of emtricitabine, and from about 165 h-ng/mL to about 400 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer.

[0265] In one embodiment, a composition is provided including a compound of 50 mg Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), 25 mg tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last} of each component following a single dose is from about 87,000 h-ng/mL to about 131,000 h-ng/mL of the compound of Formula I, from about 8500 h-ng/mL to about 12,800 h-ng/mL of emtricitabine, and from about 186 h-ng/mL to about 227 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0266] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{inf} of each component following a single dose administered to a human is from about 84450 h-ng/mL to about 141000 h-ng/mL of the compound of Formula I, from about 8100 h-ng/mL to about 136000 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 500 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0267] In one embodiment, a composition is provided including a compound of Formula I (e.g., a compound of Formula II), tenofovir alafenamide, and emtricitabine, wherein the mean C_{max} of each component following a single dose is from about 90,000 h-ng/mL to about 135,000 h-ng/mL of the compound of Formula I, from about 8,700 h-ng/mL to about 13,000 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 300 h-ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0268] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean C_{max} of each component following a single dose administered to a human is from about 4200 ng/mL to about 8000 mg/mL of the compound of Formula I, from about 1770 ng/mL to about 2800 ng/mL of emtricitabine, and from about 185 ng/mL to about 315 ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0269] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean C_{max} of each component following a single dose is from about 4700 ng/mL

to about 5300 ng/mL of the compound of Formula I, from about 2000 ng/mL to about 2600 ng/mL of emtricitabine, and from about 200 ng/mL to about 300 ng/mL of tenofovir alafenamide. In certain embodiments, the composition is administered to the human in a fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0270] In one embodiment, a composition is provided including a compound of Formula I, or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula II), tenofovir alafenamide, or a pharmaceutically acceptable salt thereof, and emtricitabine, or a pharmaceutically acceptable salt thereof, wherein the mean AUC_{last}, AUC_{inf}, and/or C_{max} of each component following a single dose administered to a human in the fed state is 80-125%, 80-120%, 85-115%, 90-110%, or 95-105% of the mean AUC_{last}, AUC_{inf}, and/or C_{max} of each component following a single dose administered to a human in the fasted state. In certain embodiments, the composition is a tablet. In certain embodiments, the tablet is a bilayer tablet. In certain embodiments, the tablet is a bilayer tablet, with the Compound of Formula I in one layer and emtricitabine and tenofovir alafenamide in the other layer. In certain embodiments, the subject is fasted. In other embodiments, the subject is fed.

[0271] In certain embodiments, the pharmacokinetic profile of the compositions described herein is within acceptable ranges, regardless of whether the subject has eaten prior to taking the medication. Accordingly, in certain embodiments, the compositions described herein can be taken without regard to food intake by the subject. In certain embodiments, food intake is a low fat, moderate fat, or high fat meal.

[0272] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 160% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 145% of the mean AUC_{last} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 135% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 100% to about 125% of the mean AUC_{last} of a single dose following administration to fasted patients.

[0273] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 60% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 45% of the mean AUC_{last} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 35% of the mean AUC_{last} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{last} of a single dose following administration to fed patients is within 25% of the mean AUC_{last} of a single dose following administration to fasted patients.

[0274] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 160% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 150% of the mean AUC_{inf} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 135% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 100% to about 125% of the mean AUC_{inf} of a single dose following administration to fasted patients.

[0275] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 60% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 50% of the mean AUC_{inf} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir

alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 35% of the mean AUC_{inf} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within 25% of the mean AUC_{inf} of a single dose following administration to fasted patients.

[0276] In one embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 160% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 130% of the mean C_{max} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 120% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within about 100% to about 115% of the mean C_{max} of a single dose following administration to fasted patients.

[0277] In certain embodiments, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 60% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 30% of the mean C_{max} of a single dose following administration to fasted patients. In a further embodiment, a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 20% of the mean C_{max} of a single dose following administration to fasted patients. In another embodiments a composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine is provided, wherein the mean C_{max} of a single dose following administration to fed patients is within 15% of the mean C_{max} of a single dose following administration to fasted patients.

Manufacturing methods

[0278] Methods for producing the compositions and dosage forms (in particular tablets) disclosed herein are also provided. In some embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. For example, in some embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, followed by (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. In other embodiments, the method comprises (a) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof followed by (b) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as another layer. In other embodiments, the method comprises (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as one layer followed by (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as another layer. The first layer and second layer may be compressed separately and subsequently combined. However, more typically, a first layer is formed by compression and subsequently a second layer is compressed onto the first layer. In certain embodiments, the choice of layer order in the tableting of multilayer tablets may have an impact on the properties of the tablets (*e.g.* the adhesion of the layers within the tablet).

[0279] In some embodiments, a tablet is provided wherein the first layer is obtainable by a method of (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer. In other embodiments, a tablet is provided wherein the second layer is obtainable by a method of (a) compressing the compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a first layer.

[0280] In certain embodiments, the methods will include a step of coating the tablet cores after compression, *e.g.* with a film coating as described above.

[0281] In general, tableting methods are well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA), which is hereby incorporated by reference herein in its entirety.

[0282] A tablet can be made by compression or molding, optionally with one or more excipients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with excipients.

Therapeutic methods

[0283] The solid oral dosage forms (in particular tablets) disclosed herein are used for treatment of HIV infection (*e.g.* HIV-1 infection). In certain embodiments, the solid oral dosage forms (in particular tablets) disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

[0284] Accordingly, methods for treating a subject infected with HIV are provided, comprising administering a solid oral dosage form disclosed herein (in particular a tablet) to the subject. Similarly, a solid oral dosage form (in particular a tablet) is provided for use in such treatment methods. Also provided is the use of the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for treatment of HIV infection. In some embodiments, the invention provides the use of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for treatment of HIV infection.

[0285] In certain embodiments, the solid oral dosage forms (in particular tablets) disclosed herein are used for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1. Accordingly, methods for preventing infection in a subject at risk of infection with HIV are provided, comprising administering a solid oral dosage form disclosed herein (in particular a tablet) to the subject. Similarly, a solid oral dosage form disclosed herein (in particular a tablet) is provided for use in such treatment methods. The invention also provides the use of the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for prevention of HIV infection in a subject at risk for infection. In some embodiments, the invention provides the use of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form disclosed herein (in particular a tablet) for prevention of HIV infection.

[0286] In certain embodiments, a method of treating a subject with HIV with the compositions disclosed herein is provided, wherein the method does not increase the risk of a drug-drug interaction in the patient. In certain embodiments, a method of treating a subject with HIV with the compositions disclosed herein is provided, wherein the method decreases the risk of a drug-drug interaction in the patient. Exemplary drug-drug interactions include interactions between the compound of Formula I,

tenofovir alafenamide, or emtricitabine with rifampin, metformin, one or more hormonal contraceptives or an HCV antiviral agent (e.g., one or more of sofosbuvir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, boceprevir, elbasvir, dasabuvir, ombitasvir, paritaprevir, ABT-530, and ABT-493). In certain embodiments, a method of treating a subject with HIV is provided, wherein the subject is administered one or the compositions disclosed herein, wherein the subject is also being treated with rifampin, metformin, or an HCV antiviral agent (e.g., one or more of sofosbuvir, ledipasvir, velpatasvir, voxilaprevir, grazoprevir, boceprevir, elbasvir, dasabuvir, ombitasvir, paritaprevir, ABT-530, and ABT-493).

[0287] The methods involve administering an oral dosage form disclosed herein (in particular a tablet) to the subject, typically a human, and will generally involve repeated administrations, typically once daily. The treatment may be prophylactic or therapeutic treatment.

General

[0288] The term "fed" in relation to administration of a solid oral dosage form to a human subject means administration of the dosage form orally under fed conditions (moderate fat meal) *e.g.* administration within about 30 minutes of the human consuming a standardized meal of about 300 to 600 calories and about 10 to about 15 grams of fat. In some embodiments, "fed" refers to administration within about 30 minutes of the human consuming a high fat meal.

[0289] The term "substantially free" in relation to the presence of a given component within *e.g.* a composition means that less than 5% by weight of the composition (*e.g.* less than 1% by weight of the composition) is that given component. The word "substantially" does not exclude "completely" *e.g.* a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

[0290] The term "segregated" as used in relation to certain components (*e.g.* A and B) within a tablet means that those components are physically discrete such that the presence of one component (*e.g.* A) does not substantially affect the stability in storage of the other component(s) (*e.g.* B) from which it is segregated. Typically, when components are segregated in a tablet then they will be present in separate layers in a multilayer tablet. By way of example, components A and B may be present in separate layers in a multilayer tablet, wherein (a) the layer containing component A is substantially free of component B and (b) the layer containing component B is substantially free of component A. The separate layers may be in contact with each other or may be separated *e.g.* by one or more additional layers.

[0291] The term "comprise" and variations thereof, such as "comprises" and "comprising", are to be construed in an open, inclusive sense, that is as "including, but not limited to".

[0292] The term "between" with reference to two values includes those two values *e.g.* the range "between" 10 mg and 20 mg encompasses *e.g.* 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20 mg.

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[0293] The term "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity). For example, in certain nonlimiting example the term "about" in relation to a numerical value *x* refers to $x \pm 10\%$, $x \pm 5\%$, or $x \pm 1\%$.

[0294] "% w/w" means the weight of a component as a percentage of the total weight of *e.g.* a layer or dosage form in which the component is present. For example, a composition comprising "5% w/w X" refers to a composition in which the weight of component X is 5% of the total weight of the composition.

[0295] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment provided herein. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0296] The term "pharmaceutically acceptable" with respect to a substance refers to that substance which is generally regarded as safe and suitable for use without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio. "Pharmaceutically acceptable" with regard to excipients includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0297] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-napththalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19

(1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0298] As used herein, the term "salts" includes co-crystals. The term "co-crystal" refers to a crystalline compound comprising two or more molecular components, *e.g.* wherein proton transfer between the molecular components is partial or incomplete.

[0299] The term "solvate" means a molecular complex comprising a compound and one or more pharmaceutically acceptable solvent molecules. Examples of solvent molecules include water and C_{1-6} alcohols, *e.g.* ethanol. When the solvate is water, the term "hydrate" may be used.

[0300] "Treating" and "treatment" of a disease include the following.

(1) preventing or reducing the risk of developing the disease, *i.e.* causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, *i.e.* arresting or reducing the development of the disease or its clinical symptoms, and

(3) relieving the disease, *i.e.* causing regression of the disease or its clinical symptoms.

The term "effective amount" refers to an amount that may be effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The effective amount will vary depending on the compound, the disease and its severity and the age, weight, *etc.* of the subject to be treated. The effective amount can include a range of amounts.

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EXAMPLES

[0301] The following examples are provided for purposes of illustration, not limitation.

Example 1 – Compound of Formula II single agent tablets

[0302] A formulation (tablet F1) of the compound of Formula II was prepared by dry granulation. Figure 5 is a flow diagram illustrating the preparation of this formulation. The composition of the single agent formulation is shown in the table below:

	Tablet Formulation F1	
Component	**Mass (mg/tablet)**	**% w/w/ tablet**
Compound of Formula II	78.7*	26.2
Microcrystalline cellulose	120	40
Lactose monohydrate	75.8	25.3
Crospovidone	21	7
Sodium Stearyl Fumarate**	4.5	1.5
Total Weight	**300**	

*Equivalent to 75 mg of the Compound of Formula I

** Intergranular:2.25 mg (0.75%; Extragranular: 2.25 mg (0.75%)

[0303] In the pharmacokinetic studies of Example 3, the tablets of Formulation F1 were film coated with 12 mg Opadry II Yellow 85F92259. The total weight of the film coated tablets was 312 mg.

[0304] The Compound of Formula II was blended with intergranular excipients (lactose, microcrystalline cellulose, and crospovidone), further blended with the intergranular portion of the sodium stearyl fumarate), roller compacted, milled, and final blended with the sodium stearyl fumarate to yield a final powder blend for compression. The final powder blend had a mean particle size of 347 µm with a compressibility index of 21%. The final powder blend was compressed into tablet cores, which were film-coated as described above to a target weight gain of 4%.

Example 2 – Compound of Formula II / emtricitabine / tenofovir alafenamide bilayer tablets

[0305] A bilayer formulation (tablet F2) of the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate was prepared using the method described in Example 8. Figure 6 is a flow diagram illustrating the preparation of bilayer tablets. The composition of the formulation is summarized in the table below:

Ingredient	**Bilayer tablet F2 (mg/tablet)**	
	Compound of Formula II Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Compound of Formula II	78.7*	
Emtricitabine		200
Tenofovir alafenamide hemifumarate		28.1**
Microcrystalline cellulose	247.8***	113.1
Croscarmellose sodium	21.2	30.2
Magnesium Stearate	5.3†	5.7††
Layer Weight	353	377
Tablet Core Weight	**730**	

*Equivalent to 75 mg of the Compound of Formula I

**Equivalent to 25 mg tenofovir alafenamide

***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)

†Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)

††Intergranular: 2.83 mg (0.4%); Extragranular: 2.83 mg (0.4%)

[0306] In the pharmacokinetic studies of Example 3, the tablets of Formulation F2 were film coated with 21.9 mg Opadry II Yellow 85F92259 (represented 3% weight gain). The total weight of the film coated tablets was 752 mg.

[0307] The tablets were manufactured using a dry granulation by roller compaction process. An emtricitabine / tenofovir alafenamide final powder blend was manufactured by dry granulation of emtricitabine and tenofovir alafenamide with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate), followed by blending with extragranular lubricant (extragranular magnesium stearate). The final powder blend of the Compound of Formula I was manufactured by dry granulation of the active component with excipients (microcrystalline cellulose, croscarmellose sodium, intergranular magnesium stearate) followed by blending with the extragranular filler and lubricant (microcrystalline cellulose and extragranular magnesium stearate).

In this study, the emtricitabine/tenofovir alafenamide final powder blend was compressed as layer 1 and the final powder blend of the Compound of Formula I was compressed as layer 2 to give a final bilayer tablet core. The core was film coated as described above.

Example 2A Emtricitabine / tenofovir alafenamide tablets

[0308] The composition of the emtricitabine / tenofovir alafenamide (F/TAF) fixed dose combination tablets used in subsequent studies is shown in the following table:

Component	**Tablet Formulation F3 Emtricitabine/tenofovir alafenamide 200/25 mg (mg/tablet)**
Intergranular	
Emtricitabine	200
Tenofovir Alafenamide Hemifumarate	28.0
Microcrystalline Cellulose	88.7
Croscarmellose Sodium	28.0
Magnesium Stearate	2.6
Extragranular	
Magnesium Stearate	2.6
Total Tablet Core Weight	**350**
Film-Coating	
Opadry II Blue 85F105057	10.5

[0309] Emtricitabine and tenofovir alafenamide hemifumarate were co-blended with microcrystalline cellulose and croscarmellose sodium, followed by lubrication with magnesium stearate. The roller compaction pre-blend was then roller compacted and milled using an oscillating mill. The resultant granules were lubricated with magnesium stearate and compressed into 350 mg tablet cores which that were subsequently film coated.

Example 3 – Pharmacokinetic Studies

[0310] Studies were carried out to assess the pharmacokinetic profiles of the formulations F1, F2, and F3 of Examples 1, 2, and 2A. A randomized, open-label, multiple-period, fixed-sequence, crossover study was performed to evaluate the relative bioavailability of bilayer tablet formulation F2 compared with that of single agent tablet formulation F1 co-administered simultaneously with a

fixed-dose combination tablet containing emtricitabine and tenofovir alafenamide (tablet formulation F3). The bioavailability was evaluated in healthy subjects.

Study Design and Duration of Treatment

[0311] Three single doses of the following tablet formulations were administered orally during up to 21 days total study duration:

(a) a fixed dosed combination tablet containing emtricitabine and tenofovir alafenamide (200/25 mg – Tablet F3) and a single agent tablet containing the compound of Formula I (75 mg - Tablet F1) administered simultaneously, under fasted conditions (dosed on day 1; days 2-8 washout);

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (75/200/25 mg – Tablet F2) administered under fasted conditions (dosed on day 9; days 10-16 washout); and

(c) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (75/200/25 mg – Tablet F2) administered under fed conditions with a high-fat meal (dosed on day 17; day 21 discharge).

Criteria for Evaluation

[0312] The following plasma pharmacokinetic parameters were calculated: C_{max}, AUC_{last}, and AUC_{inf}.

Statistical Methods

[0313] Pharmacokinetics: Plasma concentrations and PK parameters were listed and summarized by analyte and treatment group using descriptive statistics. In addition, a parametric analysis of variance using a mixed-effects model appropriate for a crossover design was fitted to the natural logarithmic transformation of the PK parameters (AUC_{inf}, AUC_{last}, and C_{max}). Two-sided 90% confidence intervals (CIs) were constructed for the ratio of geometric least-squares means (GLSMs) of each PK parameter for the compound of Formula I, emtricitabine, and tenofovir alafenamide.

Results

[0314] Subject Disposition and Demographics

[0315] A total of 28 subjects were randomized and received at least 1 dose of study drug.

[0316] The results for the first cohort of the clinical study are summarized in the table below. This table presents the mean (%CV) values, Geometric Least Squares Mean (GLSM) ratios, and 90% CI values of the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} for each active ingredient, following administration of bilayer tablet formulation F2 or the single agent tablet formulation F1, co-

administered with a fixed dose combination of emtricitabine and tenofovir alafenamide under fasted conditions.

PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Compound of Formula I /F/TAF (75/200/25 mg) (Test) (N = 28)	Compound of Formula I (75 mg) + F/TAF (200/25 mg) (Reference) (N = 28)	
Compound of Formula I			
AUC_{last} (h•ng/mL)	151,844.0 (26.9)	119,619.4 (26.6)	126.76 (117.82, 136.37)
AUC_{inf} (h•ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87, 136.45)
C_{max} (ng/mL)	7123.9 (21.6)	5593.9 (31.0)	130.72 (119.95, 142.45)
FTC			
AUC_{last} (h•ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.50, 104.33)
AUC_{inf} (h•ng/mL)	11,642.8 (13.2)	11,436.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF			
AUC_{last} (h•ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (h•ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)

[0317] The total exposure of the compound of Formula I, under fasted conditions, was approximately 30% higher when dosed in the bilayer tablet formulation F2, containing two additional therapeutic agents (TAF and FTC), compared to single agent tablet formulation F1, co-dosed with a fixed dose combination tablet containing TAF and FTC (F3). Under fasted conditions, the AUC_{inf} and C_{max} of the compound of Formula I were 27% and 31% higher, respectively, following administration of bilayer tablet formulation F2 than following administration of single-agent tablet formulation F1 with the F/TAF fixed dose combination (F3, 200/25 mg). Emtricitabine and tenofovir alafenamide exposure was similar following administration of bilayer tablet formulation F2 or single-agent tablet formulation F1 with the F/TAF FDC (F3, 200/25 mg).

[0318] Based on the data from this study, a new fixed dose formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide was developed.

[0319] The effect of food on the pharmacokinetics of the compound of Formula I was also examined in a non-randomized, open label, crossover, 2 period, fixed sequence, and single dose cohort consisting of 8 unique subjects. In this study, a single dose of the compound of Formula I was

administered in two periods with fixed sequence under fasted and fed conditions respectively. A washout of at least five half-lives was required between fasted and fed sequences.

[0320] The compound of Formula I was prepared according to percent weight of the tablet formulation of Example 1, a dose equivalent to 100 mg of the compound of Formula I and excipient amounts adjusted accordingly to arrive at the designated weight percentages (100 mg/tablet). A single tablet containing the compound of Formula I (100 mg/tablet) was administered with approximately 240 mL water after an overnight fast (no food or drink, except water, for at least 10 hours) on Day 1. Subjects continued to fast until 4 hours post dose or until collection of the 4-hour postdose blood sample. On Day 9, A single tablet containing the compound of Formula I (100 mg/tablet) was administered with approximately 240 mL water after an overnight fast (no food or drink, except water, for at least 10 hours) and within 5 minutes of the subjects finishing a standard high-fat breakfast (approximately 800 calories with 50% of calories from fat).

[0321] The evaluation of the effect of food on compound of Formula I was obtained by comparing AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max} on Days 1 and 9 under fed and fasted conditions. The natural log-transformed PK parameters (i.e., AUC_{inf}, $AUC_{0\text{-last}}$, and C_{max}) were evaluated using a mixed-effects model with food as a fixed effect and subject as a random effect. The 90% CI for the geometric least square mean (GLSM) ratios for fast versus fed was constructed. The statistical comparison of the pharmacokinetic parameters of the compound of Formula I following single dose administration of this tablet formulation in fed and fasted states is presented in the table below.

	Mean (%CV)		
Compound of Formula I PK Parameter	**Test Compound of Formula I 100 mg Fed (n=8)**	**Reference Compound of Formula I 100 mg Fasted (n=8)**	**% GLSM Ratio (90% CI)**
AUC_{inf} (hr*ng/mL)	214,146.3 (15.9)	117,777.1 (23.3)	183.97 (152.05, 222.59)
AUC_{last} (hr*ng/mL)	209,259.9 (15.1)	115,681.7 (24.0)	183.58 (151.91, 221.86)
C_{max} (ng/mL)	11,268.8 (15.1)	5885.0 (34.9)	200.69 (165.93, 242.74)

[0322] The Table above presents the GLSM ratios and associated 90% confidence intervals (CIs) for the test (fed) versus reference (fasted) treatments for the primary plasma PK parameters of the compound of Formula I. Administration of a single dose of the compound of Formula I 100 mg with food (high-calorie/high-fat breakfast) increased the GLSM values of C_{max} and AUC_{inf} 101% (90% CI of GLSM ratio 165.93% to 242.74%) and 84% (90% CI of GLSM ratio 152.05% to 222.59%), respectively. There were no apparent changes in clearance and $t_{1/2}$ following administration with food, indicating that food enhanced the bioavailability of the compound of Formula I by improving its solubility and/or absorption.

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[0323] The effect of food on the PK of the compound of formula I, emtricitabine, and tenofovir alafenamide when administered as the tablet formulation F2 tablet was evaluated in the clinical study described above (The randomized, open-label, multiple-period, fixed-sequence, crossover study involving 28 subjects comparing bilayer tablet formulation F2 with that of single agent tablet formulation F1 co-administered simultaneously with a fixed-dose combination tablet containing emtricitabine and tenofovir alafenamide (tablet formulation F3).

[0324] The mean (%CV) values, GLSM ratios, and 90% CI values of the plasma for PK parameters AUC_{last}, AUC_{inf}, and C_{max} for the compound of Formula I, emtricitabine, and tenofovir alafenamide following administration of tablet formulation F1 under fasted conditions or with a high-fat meal are presented in the following table.

	Mean (%CV)		
PK Parameter	**Compound of Formula I /F/TAF (75/200/25 mg) (High-Fat Meal; Test) (N = 28)**	**Compound of Formula I /F/TAF (75/200/25 mg) (Fasted; Reference) (N = 28)**	**% GLSM Ratio (90% CI)**
Compound of Formula I			
AUC_{last} (h•ng/mL)	216,733.1 (23.4)	151,844.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (h•ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC			
AUC_{last} (h•ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.99, 102.75)
AUC_{inf} (h•ng/mL)	11,706.4 (15.6)	11,641.6 (13.2)	100.25 (97.96, 102.59)
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF			
AUC_{last} (h•ng/mL)	315.3 (44.0)	205.5 (45.5)	156.81 (140.57, 174.94)
AUC_{inf} (h•ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)

[0325] Compared with administration under fasted conditions, administration of the tablet formulation F2 with a high-fat meal resulted in a 46% higher AUC_{inf} and a 27% higher C_{max} for the compound of Formula I. The impact of food on emtricitabine and tenofovir alafenamide exposure was similar to that previously observed.

[0326] The data presented in the two tables above also demonstrate that the effect of food on the total exposure of the compound of Formula I is reduced in bilayer tablet formulation F2, relative to the single agent tablet formulation F1. The geometric mean ratio of AUC_{inf} for the compound of

Formula I in single agent tablet formulation F1 was 1.84, while the geometric mean ratio of AUC_{inf} for the compound of Formula I in bilayer tablet formulation F2 was 1.46. In comparison the geometric mean ratio of AUC_{inf} for emtricitabine in to 0.91 and 1.00 for emtricitabine and 1.75 and 1.58 for tenofovir alafenamide in each formulation respectively (comparing the emtricitabine and tenofovir alafenamide exposures of the tablet formulation F2 with that of tablet formulation F1 codosed with the tablet formulation F3). The geometric mean ratio of C_{max} for single agent tablet formulation F1 was 2.01, while the geometric mean ratio of C_{max} for bilayer tablet formulation F2 was 1.27. In comparison, the geometric mean ratios of C_{max} for emtricitabine and tenofovir alafenamide in tablet formulations F1 and F2 were 0.85 and 0.83, respectively. These data indicate that a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food.

Example 4 – Dissolution Studies

[0327] Studies were carried out to assess the dissolution profiles of tablets F1, F2, and F3-A. Dissolution of the compound of Formula II was measured using USP Apparatus II, in 250 mL of pH 6.5 fasted state simulated intestinal fluid (FaSSIF), at 37 °C and paddle speed of 100 rpm. FaSSIF was prepared by adding simulated intestinal fluid (SIF) powder (Biorelevant.com) to pH 6.5 phosphate buffer at approximately 4.48 g/L. Once the powder was dissolved, the volume of the resulting solution was doubled. In the case of the single agent tablet formulation F1, dissolution of the compound of Formula II was measured in the presence of the fixed dose combination tablet formulation F3 of Example 2A containing emtricitabine and tenofovir alafenamide hemifumarate. The results are shown in Figure 1. These data show that the bilayer formulation (tablet F2) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F1 codosed with F3). Tablet formulation F3-A was prepared as a single agent formulation according to the process described in Example 1 according to the table below.

Ingredient	Tablet F3-A (mg/tablet)
	Compound of Formula II Layer
Compound of Formula II	78.7*
Emtricitabine	
Tenofovir alafenamide hemifumarate	
Microcrystalline cellulose	247.8***
Croscarmellose sodium	21.2
Magnesium Stearate	5.3†
Tablet Core Weight	353

*Equivalent to 75 mg of the Compound of Formula I

***Intergranular: 212.5 mg (29.1%); Extragranular: 2.65 mg (0.4%)

†Intergranular: 2.65 mg (0.4%); Extragranular: 2.65 mg (0.4%)

[0328] As shown above, Tablet F3-A used the composition (excipient selection and quantities) of the Compound of Formula II Layer of Example 2 (F2). Figure 1 further demonstrates that Tablet formulation F2 exhibited enhanced dissolution of the compound of Formula II compared to Tablet formulations F1 and F3-A. The total percentage of the compound of Formula II dissolved from formulation F1 and F3-A was comparable at approximately 60%. The total amount of the compound of Formula II dissolved from formulation F2 was approximately 10% higher.

[0329] In a second study, dissolution of the compound of Formula II was measured using fed state simulated intestinal fluid (FeSSIF) as dissolution medium. FeSSIF was prepared by adding simulated intestinal fluid (SIF) powder (Biorelevant.com) to pH 5.0 phosphate buffer at approximately 22.405 g/L. Once the power was dissolved, the volume of the resulting solution was doubled. In this study, dissolution of the compound of Formula II was measured using USP Apparatus II, in 250 mL of pH 5.5 fed simulated intestinal fluid, at 37 °C and paddle speed of 100 rpm. As in the previous study using fasted simulated intestinal fluid, the single agent tablet formulation F1 was tested in the presence of a second tablet formulation containing emtricitabine and tenofovir alafenamide hemifumarate (tablet F3). The results are shown in Figure 2. These data also show that the bilayer formulation (tablet F2) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F1).

Example 5 – Excipient Studies

[0330] To further assess the effect of specific excipients on dissolution of the compound of Formula I, three additional bilayer tablet formulations were prepared, F4, F5, and F6. Tablet formulation F4 is similar to tablet formulation F2, with croscarmellose sodium being replaced with crospovidone. Likewise, tablet formulation F5 is similar to tablet formulation F2, with magnesium stearate being replaced with sodium stearyl fumarate. Finally, tablet formulation F6 is similar to tablet formulation F2, with both croscarmellose sodium and magnesium stearate being replaced with crospovidone and sodium stearyl fumarate, respectively. Tablets F4, F5, and F6 were prepared using the method described in Example 8.

Ingredient		**Bilayer tablet F4**	**Bilayer tablet F5**	**Bilayer tablet F6**
	Emtricitabine/ tenofovir alafenamide hemifumarate Layer (mg/tablet)	**Compound of Formula I Layer (mg/tablet)**		
Emtricitabine	200			
Tenofovir alafenamide hemifumarate	28.1			
Compound of Formula II		78.7	78.7	78.7
Microcrystalline cellulose	113	244	248	244
Croscarmellose sodium	30.2		21.2	
Crospovidone		24.7		24.7
Magnesium Stearate	5.7	5.3		
Sodium Stearyl Fumarate			5.3	5.3
Layer Weight	377	353	353	353
Tablet Core Weight		**730**	**730**	**730**

[0331] Figure 3 shows the results of dissolution studies performed on tablet formulations F4, F5, and F6, as well as tablet formulation F1 and F2. These data demonstrate that the substitution of each excipient enhances the dissolution of the compound of Formula I.

Example 6 – Compound of Formula I / emtricitabine / tenofovir alafenamide bilayer tablets – 50 mg dose

[0332] As a result of the higher *in vivo* exposure of the compound of Formula I that was observed in the pharmacokinetic studies, a bilayer formulation (tablet F7) of the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate was prepared incorporating a lower dose of the compound of Formula I. Tablet formulation F7 was prepared as described previously, *i.e.*, using the method described in Example 8. The composition of the formulation is summarized in the table below:

Ingredient	**Bilayer tablet F7 (mg/tablet)**	
	Compound of Formula II Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Compound of Formula II	52.5*	
Emtricitabine		200
Tenofovir alafenamide hemifumarate		28**
Microcrystalline cellulose	246.3	113.2
Croscarmellose sodium	19.4	30.2
Magnesium Stearate	4.9	5.7
Layer Weight	323	377
Tablet Core Weight	**700**	
Opadry II Brown 85F165072	21	
Film Coated Tablet	**721**	

*Equivalent to 50 mg of the Compound of Formula I

**Equivalent to 25 mg tenofovir alafenamide

Example 7 – Compound of Formula I single agent tablets (50 mg)

[0333] Dissolution studies were performed comparing the 50 mg dose bilayer tablet F7 with a 50 mg single agent tablet.

[0334] A 50 mg formulation (tablet F8) of the compound of Formula II was prepared in a similar manner as tablet formulation F1 of Example 1. The composition of the single agent formulation is shown in the table below.

	Tablet Formulation F8	
Component	**Mass (mg/tablet)**	**% w/w/ tablet**
Compound of Formula II	52.5	26.2
Microcrystalline cellulose	80	40
Lactose	50.5	25.3
Crospovidone	14	7
Sodium Stearyl Fumarate	3	1.5
Total Weight	**200**	

[0335] Figure 4 shows the dissolution of 50 mg bilayer tablet formulation (fixed dose combination) F7 and 50 mg single agent tablet formulation F8. Dissolution of the compound of Formula II was measured using USP Apparatus II, in 333 mL of pH 6.5 FaSSIF, at 37 °C and paddle speed of 100 rpm. Two tablets of each tablet formulation, F7 and F8 were tested. As in Example 3, in the case of the single agent tablet formulation F8, dissolution of the compound of Formula II was measured in the presence of the fixed dose combination tablet formulation of Example 2A containing emtricitabine and tenofovir alafenamide hemifumarate. These data show that the 50 mg bilayer formulation (tablet F7) exhibited enhanced dissolution of the compound of Formula II, compared to the single agent formulation (tablet F8).

Example 8 – manufacturing process

[0336] The manufacturing/packaging procedure for the compound of Formula II/emtricitabine/tenofovir alafenamide hemifumarate tablets is divided into five unit processes:

1. mixing of the compound of Formula II drug substance with intergranular excipients, roller compaction or slugging, milling, and blending with extragranular excipients to yield the final powder blend for the compound of Formula II;
2. mixing of emtricitabine and tenofovir alafenamide hemifumarate drug substances with intergranular excipients, dry granulation, milling, and blending with extragranular excipients to yield emtricitabine/tenofovir alafenamide hemifumarate final powder blend;

3. tablet compression to yield bilayer tablet cores;
4. tablet film-coating to yield film-coated tablets; and
5. packaging.

[0337] The manufacturing process steps to produce the final drug product are detailed below.

Final Powder Blend for the Compound of Formula II (Dispensing, Blending, Dry Granulation, Milling, Final Blending)

1. Weigh the compound of Formula II and the excipients (microcrystalline cellulose and croscarmellose sodium). Correct the weight of the compound of Formula II based on the drug content factor (DCF), with a concomitant reduction in the weight of microcrystalline cellulose.
2. Blend in intergranular portion of magnesium stearate to the tumble blender and blend.
3. Dry granulate the resulting blend using a roller compactor or slug the resulting blend and mill.
4. Add extragranular microcrystalline cellulose and magnesium stearate and blend.

Emtricitabine/tenofovir alafenamide hemifumarate Final Powder Blend (Dispensing, Blending, Dry Granulation, Milling, Final Blending)

5. Weigh emtricitabine and tenofovir alafenamide hemifumarate drug substances and excipients (microcrystalline cellulose and croscarmellose sodium). Adjust the weight of emtricitabine and tenofovir alafenamide hemifumarate drug substances based on their corresponding DCF, with a concomitant adjustment to the weight of microcrystalline cellulose.
6. Blend in emtricitabine and tenofovir alafenamide hemifumarate drug substance, microcrystalline cellulose, and croscarmellose sodium to a tumble blender and blend.
7. Blend in intergranular portion of magnesium stearate to the tumble blender and blend.
8. Dry granulate the resulting blend using a roller compactor or slug the resulting blend and mill.
9. Blend in the extragranular portion of magnesium stearate.

Tableting

10. Compress the final powder blend of the compound of Formula II as the first layer and the emtricitabine/tenofovir alafenamide hemifumarate final powder blend as the second layer, with an appropriate main compression force to achieve a target hardness of 17 kP (range: 14 to 20 kP). For tablet formulations containing 50 mg of the compound of Formula II, the final powder blend is compressed to a target layer weight of 323 mg using a target total tablet weight of 700 mg. For tablet formulations containing 75 mg of the compound of Formula II, the final powder blend is compressed to a target layer weight of 353 mg using a target total tablet weight of 730 mg.

Film-coating

11. Prepare a suspension of Opadry® II Brown 85F165072 (for tablets containing 50 mg compound of Formula I) or Opadry® II Yellow 85F92259 (for tablets containing 75 mg compound of Formula I). Film-coat the tablet cores to achieve the target tablet weight gain of 3% (range 2-4%). Dry film-coated tablets prior to cooling and discharge.

Example 9 – Pharmacokinetic Studies – Cohort 2

[0338] The pharmacokinetic study of Example 3 was continued with a second treatment group (cohort) to assess the pharmacokinetic profile of formulation F7 of Example 7 compared with that of formulation F2.

Study Design and Duration of Treatment

[0339] Four single doses of the following tablet formulations were administered once per day orally during 36 days total study duration:

(a) a fixed dosed combination tablet containing emtricitabine and tenofovir alafenamide (200/25 mg – Tablet F3) and a single agent tablet containing the compound of Formula I (75 mg - Tablet F1) administered simultaneously, under fasted conditions (Treatment A) (dosed on day 1; days 2-8 washout);

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg – Tablet F2) administered under fasted conditions (Treatment D) (dosed on day 9; days 10-16 washout); and

(b) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg – Tablet F2) administered under fed conditions with a high-fat meal (Treatment E) (dosed on day 17; days 18-24 washout);

(c) a fixed dose combination tablet containing the compound of Formula I, emtricitabine, and tenofovir alafenamide (50/200/25 mg – Tablet F2) administered under fed conditions with a moderate-fat meal (Treatment F) (dosed on day 25; day 29 discharge).

Criteria for Evaluation

[0340] The following plasma pharmacokinetic parameters were calculated: AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, C_{last}, T_{max}, T_{last}, CL/F, V_z/F, and $t_{1/2}$.

Statistical Methods

[0341] Pharmacokinetics: Individual subject concentration data and individual subject PK parameters for each analyte (compound of Formula 1, FTC, and TAF) were listed and summarized using descriptive statistics by treatment group (cohort) and treatment. Summary statistics were determined for both individual subject concentration data by time point, cohort, and treatment and individual subject PK parameters by cohort and treatment. Also, the geometric mean, 95% confidence interval (CI), and the mean, and standard deviation (SD) of the natural log-transformed values were presented for individual subject PK parameter data. The sample size for each time point was based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration below the level of quantitation (BLQ) was presented for each time point.

[0342] Statistical comparisons of the natural log-transformed PK parameters for each analyte and treatment comparison of interest were performed. The statistical modelling was based on the PK Analysis set for the analyte under evaluation. For each analyte, all subjects with available data for the PK parameter under evaluation were included in the modelling. The statistical comparisons using Treatment A as a reference only used data from this cohort, not from the earlier cohort of Example 3 (i.e., Treatment A was not pooled).

For each analyte and each PK parameter, a parametric (normal theory) mixed-effects ANOVA model was fitted to the natural log-transformed values of the PK parameter under evaluation. The statistical model included treatment as a fixed effect and subject as a random effect.

[0343] A total of 27 subjects completed the second treatement group of the study.

Results

[0344] Plasma pharmacokinetic parameters for each analyte are presented below. This table presents the mean (%CV) values, Geometric Least Squares Mean (GLSM) ratios, and 90% CI values of the plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} for each active ingredient, following administration of bilayer tablet formulation F7 and monolayer tablet formulation F1 coadministered with F/TAF formulation F3, under fasted conditions.

	Mean (%CV)		
	Formulation F7 Compound of Formula 1/F/TAF (50/200/25 mg), fasted (Test) (N = 27)	**Formulation F1 + F3** Compound of Formula (75 mg) + F/TAF (200/25 mg)), fasted (Reference) (N = 28)	**%GLSM Ratio (90% CI) (Test/Reference)**
Compound of Formula 1 PK Parameter			
AUC_{last} (hr*ng/mL)	109,061.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)

AUC_{inf} (hr•ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (hr•ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (hr•ng/mL)	208.8 (46.3)	238.3 (45.0)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

[0345] In particular, these data confirmed that the exposure of the compound of Formula I in Formulation F7 was proportionally lower than that observed in Formulation F2 and were consistent with predicted exposures for the revised dose. These data were consistent with the modelling of earlier clinical data confirming that these exposures provided anti-HIV antiviral efficacy. FTC and TAF exposure were similar between Formulation F7 and Formulation F2 coadministered with F3; TAF Cmax was slightly lower (by approximately 16%) for Formulation F7 than for the coadministration of F2 and F3.

[0346] The effect of food on the pharmacokinetics of the compound of Formula I, emtricitabine and tenofovir alafenamide when administered in formulation F7 was also examined in a further treatment group of the above described clinical study.

[0347] The mean (%CV) values, GLSM ratios, and 90% CI values of the plasma for PK parameters AUC_{last}, AUC_{inf}, and C_{max} for the compound of Formula I, emtricitabine, and tenofovir alafenamide following administration of tablet formulation F7 under fasted conditions or with a high-fat meal and with a moderate-fat meal are presented in the following table.

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Compound of Formula I/F/TAF (50/200/25 mg) high fat meal (Test) (N = 27)	Compound of Formula I/F/TAF (50/200/25 mg) fasted (Reference) (N = 27)	
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	140,632.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,213.0 (12.0)	10,652.9 (13.6)	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	318.4 (32.8)	208.8 (46.3)	166.55 (146.54, 189.29)
C_{max} (ng/mL)	236.6 (65.1)	249.2 (51.6)	91.71 (73.46, 114.49)

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Compound of Formula I/F/TAF (50/200/25 mg) moderate fat meal (Test) (N = 27)	Compound of Formula I/F/TAF (50/200/25 mg) fasted (Reference) (N = 27)	
Compound of Formula I PK Parameter			
AUC_{last} (hr•ng/mL)	135,217.3 (22.9)	109,061.4 (21.0)	123.56 (115.53, 132.14)
AUC_{inf} (hr•ng/mL)	140,197.7 (23.6)	112,619.6 (21.9)	124.06 (115.95, 132.74)
C_{max} (ng/mL)	6279.6 (18.3)	5228.1 (16.9)	119.90 (112.72, 127.55)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,738.3 (9.8)	10,652.9 (13.6)	101.17 (98.48, 103.94)
AUC_{inf} (hr•ng/mL)	10,973.3 (9.5)	10,873.9 (13.6)	101.33 (98.66, 104.06)
C_{max} (ng/mL)	1998.9 (18.4)	2220.4 (30.1)	91.84 (84.17, 100.21)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	290.6 (41.3)	207.1 (46.5)	148.20 (130.41, 168.41)
AUC_{inf} (hr•ng/mL)	293.1 (40.9)	208.8 (46.3)	148.23 (130.42, 168.47)
C_{max} (ng/mL)	251.1 (66.7)	249.2 (51.6)	99.04 (79.33, 123.65)

a N = 28 for the Reference group

[0348] Compared with administration under fasted conditions, administration of the tablet formulation F7 with a high-fat meal resulted in a 24% higher AUC_{inf} and a 13% higher C_{max} for the compound of Formula I. Administration of a moderate fat meal, resulted in a 24% higher AUC_{inf} and a 20% higher C_{max} for the compound of Formula I. The impact of food on emtricitabine and tenofovir alafenamide exposure was similar to that previously observed.

[0349] These data confirm that a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food.

Example 10 – Compression Studies

[0350] To further investigate the properties of the compositions, the following studies investigated blend compressibility and layer adhesion.

[0351] First, various final blend compositions including the Compound of Formula I (as a sodium salt, i.e., the Compound of Formula II) were prepared with varying levels of intergranular or extragranular lactose is shown in the table below.

Compound of Formula II: Final Powder Blends Containing Lactose

Components	Tablet Formulation					
	F9	F10	F11	F12	F13	F14
Intergranular % w/w						
Compound of Formula II	16.24	16.24	16.24	16.24	14.86	14.86
Microcrystalline Cellulose	46.25	56.25	56.25	56.25	69.12	60.63
Lactose	20.00	NA	NA	NA	0.00	8.50
Croscarmellose Sodium	6.00	6.00	6.00	6.00	5.49	5.49
Magnesium Stearate	0.75	0.75	0.75	0.75	0.69	0.69
Extragranular % w/w						
Microcrystalline Cellulose	10.00	10.00	5.00	15.00	9.15	9.15
Lactose	NA	10.00	15.00	5.00	NA	NA
Magnesium Stearate	0.75	0.75	0.75	0.75	0.69	0.69
Layer weight (mg)	323	323	323	323	353	353

[0352] Next, final blend compositions of the Compound of Formula II with varying amounts of magnesium stearate ranging from 0.75% to 0.5% were prepared as shown on the following table:

Compound of Formula I: Final Powder Blends with Varying Levels of Magnesium Stearate

Components	Tablet Formulation					
	F15	F16	F17	F18	F19	F20
Intergranular %w/w						
Compound of Formula II	16.24	16.24	16.24	16.24	16.24	16.24
Microcrystalline Cellulose	66.25	66.30	66.40	66.40	66.50	66.75
Croscarmellose Sodium	6.00	6.00	6.00	6.00	6.00	6.00
Magnesium Stearate	0.75	0.70	0.60	0.60	0.50	0.50
Extragranular %w/w						
Microcrystalline Cellulose	10.00	10.00	10.00	10.00	10.00	10.00
Magnesium Stearate	0.75	0.75	0.75	0.75	0.75	0.5
Layer weight (mg)	323	323	323	323	323	323

[0353] Finally, final blend compositions containing emtricitabine and tenofovir alafenamide were prepared with varying amounts of magnesium stearate ranging from 0.75% to 0.5% as shown in the table below:

Quantitative Compositions of F/TAF Final Powder Blends

Components	Tablet Formulation			
	F21	F22	F23	F24
Intergranular %w/w				
Tenofovir Alafenamide Hemifumarate	7.5	7.5	7.5	7.5
Emtricitabine	53.1	53.1	53.1	53.1
Microcrystalline Cellulose	29.9	30.4	30	30.2
Croscarmellose Sodium	8.0	8.0	8.0	8.0
Magnesium Stearate	0.75	0.50	0.70	0.60
Extragranular % w/w				
Magnesium Stearate	0.75	0.50	0.70	0.60
Layer Weight (mg)	377	377	377	377

[0354] Altering magnesium stearate content was studied to evaluate the impact on the compound of Formula I and emtricitabine / tenofovir alafenamide blend compressibility and layer adhesion. Formulations were also monitored for punch filming and sticking.

[0355] Fourteen combinations of the final powder blends described in the above tables were prepared as summarized in the table below. Critical tamp force was determined for all fourteen combinations.

Compression Study Critical Layer 1 Tamp Force Results

Formulation Combination	Tablet Formulation Layer 1	Tablet Formulation Layer 2	Critical Tamp Force (kN)	Observation
A*	F21	F15	1.0	Layers adhered
B*	F21	F9	<1.5	Delamination
C*	F21	F10	<1.5	Delamination
D*	F21	F11	<1.5	Delamination
E*	F21	F12	<1.5	Delamination
F*	F21	F13	<1.5	Delamination
G*	F21	F14	<1.5	Delamination
H	F15	F21	1.5	Delamination
I	F15	F22	2.0	Layers adhered
J	F16	F23	2.0	Layers adhered
K	F17	F24	1.5	Layers adhered
L	F18	F22	2.0	Layers adhered
M	F19	F22	2.5	Layers adhered, sticking
N	F20	F22	2.5	Layers adhered, sticking

* Note F/TAF as layer 1 and Compound of Formula I as layer 2

IG: Intergranular

EG: Extragranular

MgSt Magnesium Stearate

[0356] Combination A represents layer order and composition used as baseline for comparison of other compositions. The tablet formulation of each layer corresponds to the corresponding layer of tablet formulation F7.One objective was to investigate whether it was possible to improve on the critical tamp force of 1.0 kN observed for Combination A.

[0357] Combinations B – G represent studies in which lactose was included in the layer including the Compound of Formula I to investigate evaluate layer adhesion. Combination G included 20% lactose in the intergranular portion, with none in the extragranular portion. The ratio of lactose to microcrystalline cellulose ranged from 1:1, 3:1, 1:3 in Combinations C, D, and E, respectively. Combination G included 20 mg lactose in the intergranular portion. Delamination was observed at 1.5kN for Combinations B – G. As a result, lower tamp forces were not further investigated. When layer order was reversed (Combination H), delamination did not occur at 1.0 kN but was observed at 1.5 kN using the layer compositions of Combination A.

[0358] In Combinations I – N, varying the amount of magnesium stearate in each layer was investigated to determine the effect on compressibility and layer adhesion. Intergranular magnesium stearate was 0.75%, 0.70% and 0.60% in the Compound of Formula I layer of Combinations I, J, and K, respectively. Total magnesium stearate content in the F/TAF layer of each of Combinations I, J, and K was 1.0 %, 1.4% and 1.2%%, respectively. Intergranular magnesium stearate was 0.6% and 0.5% in the Compound of Formula I layer of Combinations L and M, respectively (with 0.75% extragranular magnesium stearate in each). Combination N has the lowest overall level of magnesium stearate in both layers (1.0% in each layer).

[0359] It was found that reducing magnesium stearate from 0.75% to 0.5% in each of the intergranular and extragranular portions the emtricitabine / tenofovir alafenamide layer increased critical tamp force to 2.0 kN (combination I). Critical tamp force could be further improved to 2.5 kN when magnesium stearate was reduced to 0.5% extragranular and/or intergranular in the layer containing the Compound of Formula I (combinations M and N). However, despite gaining an increase in critical tamp force, decreasing magnesium stearate to 0.5% in each component of the powder blend containing the Compound of Formula I had a negative effect on sticking. Intermediate changes in magnesium stearate (Combinations J – L) had no further improvement over combination I. As a result, magnesium stearate level was decreased in the emtricitabine/tenofovir alafenamide layer only (formulation combination I). A critical layer 1 tamp force of 1377 N was ultimately determined. The table below summarizes the composition of Formulation I.

[0360] Thus, the addition of intergranular or extragranular lactose to the layer containing the Compound of Formula I had little to ono effect on layer adhesion. Decreasing magnesium stearate from each of final powder blends improved compressibility.

Quantitative Composition of Combination Formulation I

Components	Quantity per Tablet (mg)	w/w (%)
Compound of Formula I Layer		
Compound of Formula II[a]	52.5[a, b]	7.5
Microcrystalline Cellulose	246.3	35.2
Croscarmellose Sodium	19.4	2.8
Magnesium Stearate	4.9	0.7
Subtotal	323	46.1
F/TAF Layer		
Emtricitabine[c]	200.0[c]	28.6
Tenofovir Alafenamide Fumarate[c]	28.0[c, d]	4.0
Microcrystalline Cellulose	115.0	16.4
Croscarmellose Sodium	30.2	4.3
Magnesium Stearate	3.8	0.5
Subtotal	377	53.9
Total Bilayer Tablet Core Weight	700	100
Film Coat		
Opadry II Brown 85F165072[e]	21[f]	3[f]
Purified Water[g]	---[g]	---[g]

a The quantity used is adjusted on the basis of the purity of each batch of Compound of Formula II with a concomitant adjustment of the quantity of microcrystalline cellulose.

b Equivalent to 50 mg of Compound of Formula I free acid.

c The quantity used is adjusted on the basis of the purity of each batch of emtricitabine and tenofovir alafenamide hemifumarate with a concomitant adjustment of the quantity of microcrystalline cellulose.

d Equivalent to 25 mg of tenofovir alafenamide free base.

e Opadry II Brown 85F165072 contains polyvinyl alcohol, USP (40.0% w/w); titanium dioxide, USP (22.0% w/w); polyethylene glycol, NF (20.2% w/w); talc, USP (14.8% w/w); iron oxide red, NF (2.4% w/w); iron oxide black, NF (0.6% w/w).

f Represents a theoretical weight gain of 3% w/w (range 2% to 4% w/w) onto the tablet core weight.

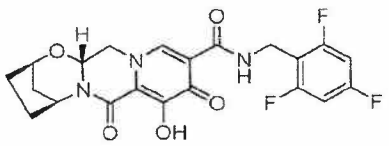
g Sufficient purified water is used for film coating and is removed during the process

[0361] All publications, patents and patent applications are incorporated by reference in their entirety, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

CLAIMS

1. A solid oral dosage form comprising the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.

2. The solid oral dosage form of claim 1, wherein the dosage form comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

3. The solid oral dosage form of claim 1 or 2, wherein the dosage form comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

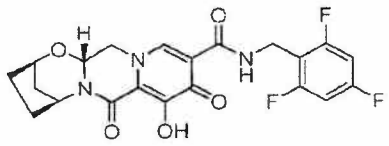
4. The solid oral dosage form of any preceding claim, wherein the dosage form has a total weight of less than about 800 mg.

5. The solid oral dosage form of any preceding claim, wherein the dosage form has a total weight of less than about 730 mg.

6. The solid oral dosage form of any preceding claim, wherein the dosage form is a tablet.

7. A coated tablet comprising 50 mg of a compound of Formula I:

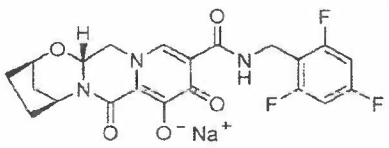
(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof and a coating.

8. A tablet comprising 52 mg of the compound of Formula II

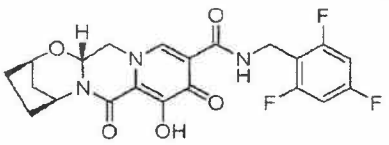
(II)



28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

9. A tablet comprising (a) 50 mg of the compound of Formula I:

(I)

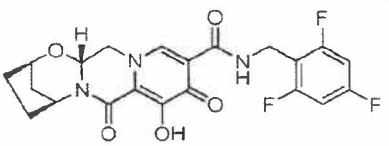


or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1 g.

10. The tablet of claim 9, wherein (a) and (b) are within separate layers in a multilayer tablet.

11. A tablet comprising from 6.5-11.0 % w/w of the compound of Formula I:

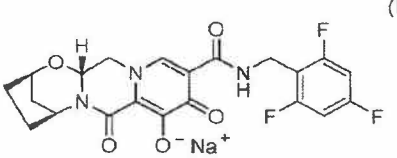
(I)



or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.

12. A tablet comprising from 7.0-11.0 % w/w of the compound of Formula II:

(II)



3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.

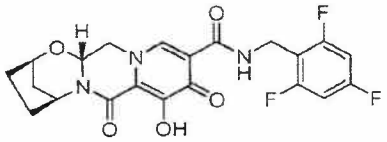
13. The tablet of any preceding claim, wherein the tablet does not contain lactose, crospovidone, and/or sodium stearyl fumarate.

14. The tablet of any preceding claim, wherein the tablet further comprises croscarmellose sodium and/or magnesium stearate.

15. The tablet of any preceding claim, wherein the tablet further comprises croscarmellose sodium, magnesium stearate, and/or microcrystalline cellulose.

16. A multilayer tablet comprising (a) a compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

17. The multilayer tablet of claim 16, wherein each layer contains at least one of (a), (b) and (c).

18. The tablet of claim 16 or 17, wherein the tablet comprises (a) a first layer comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

19. The tablet of claim 18, wherein (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of a compound of Formula I or a pharmaceutically acceptable salt thereof.

20. The tablet of claim 18 or 19, wherein (a) the first layer comprises a compound of Formula I or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of a compound of Formula I or a pharmaceutically acceptable salt thereof.

21. The tablet of any one of claims 16-20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone, and/or sodium stearyl fumarate.

22. The tablet of any one of claims 16-20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof comprises croscarmellose sodium and/or magnesium stearate.

23. The tablet of any one of claims 16-20, wherein the layer containing a compound of Formula I or a pharmaceutically acceptable salt thereof comprises croscarmellose sodium and/or magnesium stearate and/or microcrystalline cellulose.

24. The tablet of any one of claims 16-20, wherein the tablet comprises from 6.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.

25. The tablet of any one of claims 16-20, wherein the tablet comprises from 7.0-11.0 % w/w of a sodium salt of the compound of Formula I, 3.5-4.1 % w/w tenofovir alafenamide hemifumarate, and 25-30 % w/w emtricitabine, where the weight percentages denote a proportion of the whole tablet.

26. The solid oral dosage form or tablet of any preceding claim, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

27. The solid oral dosage form or tablet of any preceding claim, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

28. The solid oral dosage form or tablet of any preceding claim, wherein the tablet releases at least about 50% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes, measured using USP apparatus II, in 333 mL of fasted simulated intestinal fluid, pH 6.5, at 37 °C and paddle speed of 100 rpm.

29. The solid oral dosage form or tablet of claim 28, wherein the tablet releases at least about 60% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes.

30. The solid oral dosage form or tablet of any preceding claim, wherein the tablet releases at least about 70% of a compound of Formula I or a pharmaceutically acceptable salt thereof in about 60 minutes.

31. A method of producing a tablet of any one of the preceding claims, wherein the method comprises (a) compressing the a compound of Formula I or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer.

32. The method of claim 31, wherein the first layer and second layer are compressed separately and subsequently combined.

33. The method of claim 31, wherein the first layer is formed by compression and subsequently the second layer is compressed onto the first layer.

34. The first layer obtainable by the method of claim 31.

35. The second layer obtainable by the method of claim 31.

36. A kit comprising (a) a tablet comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant.

37. The kit of claim 36, wherein the desiccant is silica gel.

38. A solid oral dosage form or tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.

39. A method of therapeutic treatment of an HIV infection comprising administering to a subject a solid oral dosage form or tablet according to any one of the preceding claims.

40. A composition comprising about 40 mg to about 60 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, about 200 mg to about 400 mg microcrystalline cellulose, about 1 mg to about 40 mg croscarmellose sodium.

41. The composition of claim 40, wherein the composition is a first layer of a multilayer tablet.

42. The composition of claim 41, wherein the composition further comprises a second layer, wherein the second layer comprises about 150 mg to about 250 mg emtricitabine or a pharmaceutically salt thereof, about 20 mg to about 35 mg tenofovir alafenamide or a pharmaceutically salt thereof, about 90 mg to about 130 mg microcrystalline cellulose, about 20 mg to about 35 mg croscarmellose sodium, and about 1 mg to about 7 mg magnesium stearate.

43. A tablet comprising a first layer and a second layer, wherein
the first layer comprises about 5% to about 10% w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, about 26% to about 44% w/w microcrystalline cellulose, about 2% to about 4% w/w croscarmellose sodium, and about 0.5% to about 0.9% w/w magnesium stearate; and
the second layer comprises about w/w 21% to about 36% emtricitabine, about 3% to about 5% w/w tenofovir alafenamide, about 12% to about 20% w/w microcrystalline cellulose, about w/w 3% to about 6% croscarmellose sodium, and about w/w 0.3% to about 0.7% magnesium stearate.

44. A tablet composition comprising from about 6.4 w/w to about 8.5% w/w of the compound of Formula II, about 25% w/w to about 32% w/w emtricitabine, about 3.5% w/w to about 4.5% w/w tenofovir alafenamide hemifumarate, about 46% w/w to about 57% w/w microcrystalline cellulose, about 5.9% w/w to about 8.5% w/w croscarmellose sodium, and about 1.0-2.0% w/w magnesium stearate.

45. The composition of any one of claims 40 to 44, futher comprising a film coating.

46. A composition comprising 50 mg Compound of Formula I (e.g., a compound of Formula II), 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean AUC_{last} following administration of a single dose is from about 81700 h-ng/mL to about 140000 h-ng/mL of the compound of Formula I, from about 8100 h-ng/mL to about 13600 h-ng/mL of emtricitabine, and from about 165 h-ng/mL to about 400 h-ng/mL of tenofovir alafenamide.

47. The composition of claim 46, wherein the mean AUC_{inf} is from about 84,450 h-ng/mL to about 141,000 h-ng/mL of the compound of Formula I, from about 8,100 h-ng/mL to about 13,600 h-ng/mL of emtricitabine, and from about 200 h-ng/mL to about 500 h-ng/mL of tenofovir alafenamide.

48. The composition of claim 46 or 47, wherein the mean C_{max} is from about 4200 ng/mL to about 8000 ng/mL of the compound of Formula I, from about 1770 ng/mL to about 2800 ng/mL of emtricitabine, and from about 185 ng/mL to about 315 ng/mL of tenofovir alafenamide.

49. A composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean AUC_{last} of a single dose following administration to fed patients is within about 60% of the mean AUC_{last} of a single dose following administration to fasted patients.

50. A composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean AUC_{inf} of a single dose following administration to fed patients is within about 60% of the mean AUC_{inf} of a single dose following administration to fasted patients.

51. A composition comprising 50 mg Compound of Formula I, 25 mg tenofovir alafenamide, and 200 mg emtricitabine, wherein the mean C_{max} of a single dose following administration to fed patients is within about 60% of the mean C_{max} of a single dose following administration to fasted patients.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
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ABSTRACT

A solid oral dosage form is provided, comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1002**
113 of 1074

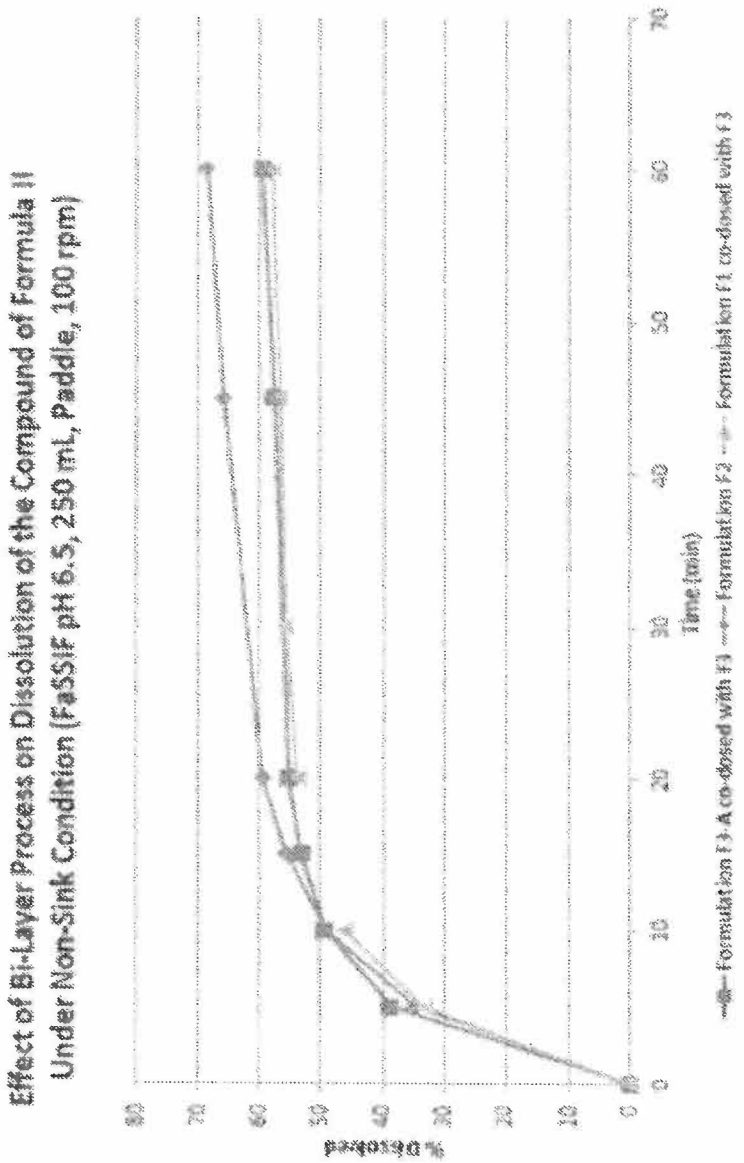

Effect of Bi-Layer Process on Dissolution of the Compound of Formula II
Under Non-Sink Condition (FaSSIF pH 6.5, 250 mL, Paddle, 100 rpm)
% Dissolved
Time (min)
Formulation F3-A co-dosed with F3
Formulation F2
Formulation F1 co-dosed with F3

FIGURE 1

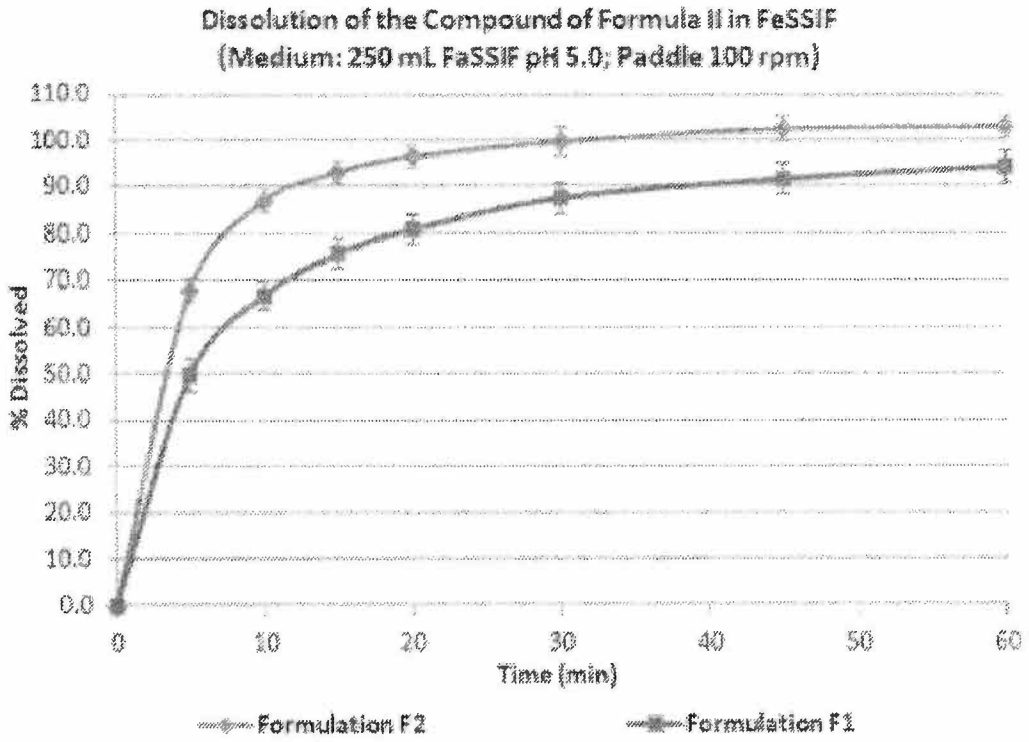

Dissolution of the Compound of Formula II in FeSSIF
(Medium: 250 mL FaSSIF pH 5.0; Paddle 100 rpm)
% Dissolved
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (min)
Formulation F2
Formulation F1

FIGURE 2

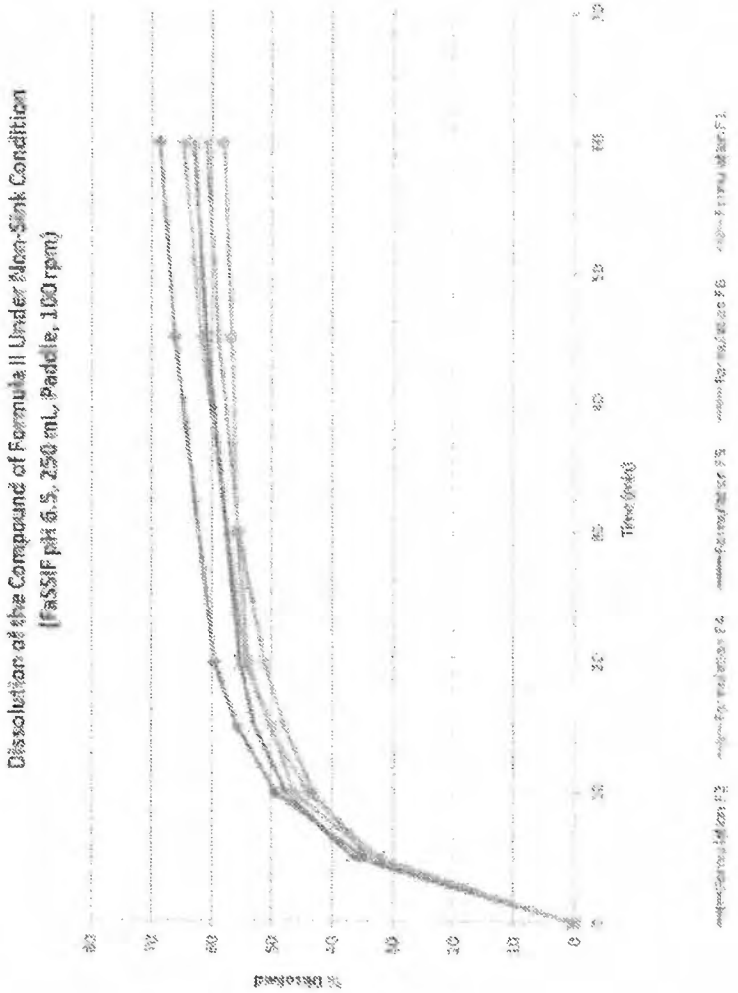

Dissolution of the Compound of Formula II Under Non-Sink Condition
(FaSSIF pH 6.5, 250 mL, Paddle, 100rpm)
% Dissolved
Time (min)

FIGURE 3

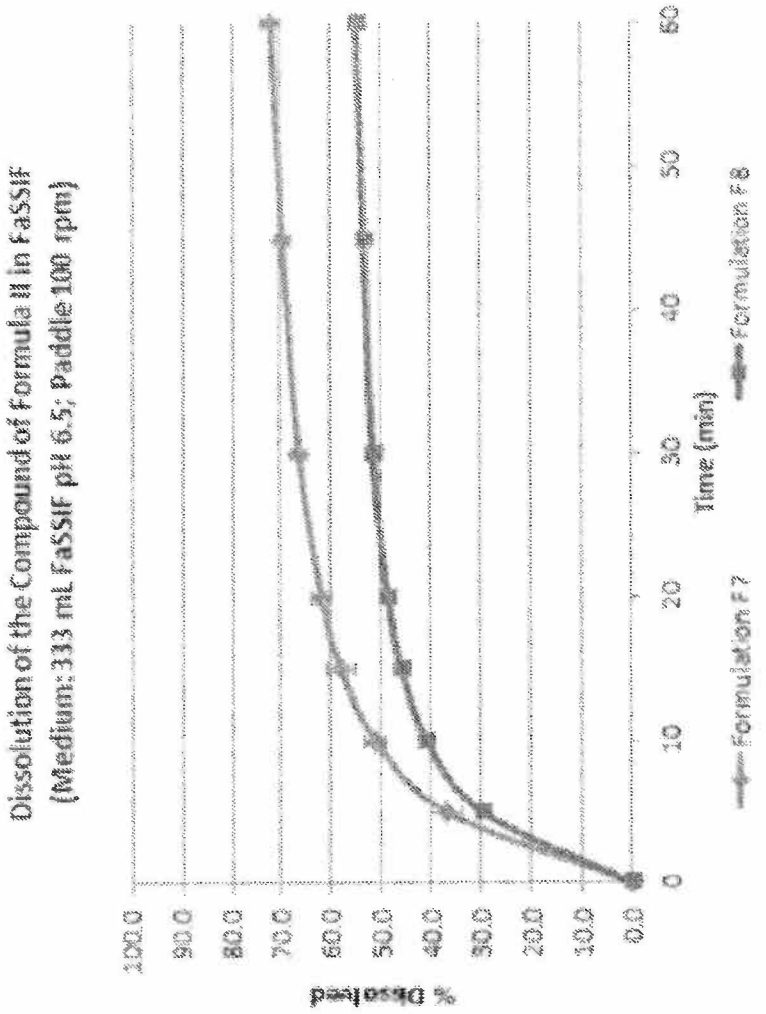

Dissolution of the Compound of Formula II in FaSSIF
(Medium: 333 mL FaSSIF pH 6.5; Paddle 100 rpm)
% Dissolved
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
10
20
30
40
50
60
Time (min)
Formulation F7
Formulation F8

FIGURE 4

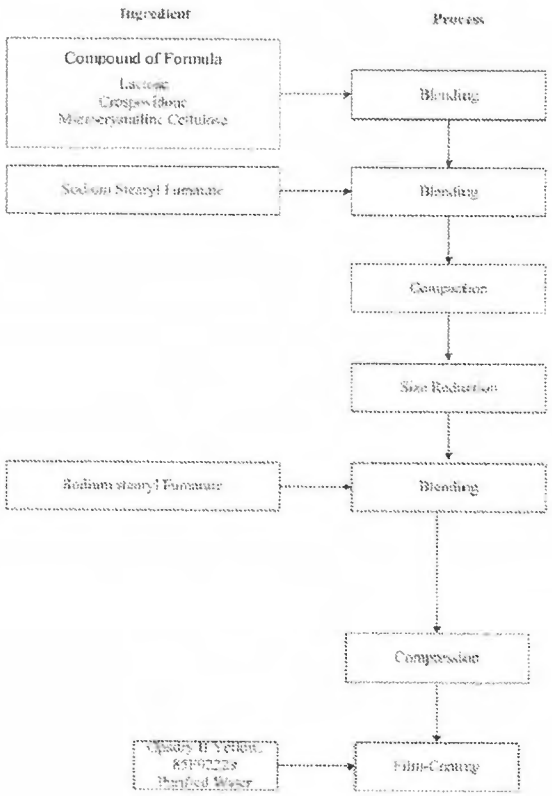

Ingredient
Process
Compound of Formula
Lactose
Crospovidone
Microcrystalline Cellulose
Blending
Sodium Stearyl Fumarate
Blending
Compaction
Size Reduction
Sodium stearyl Fumarate
Blending
Compression
Film-Coating

FIGURE 5

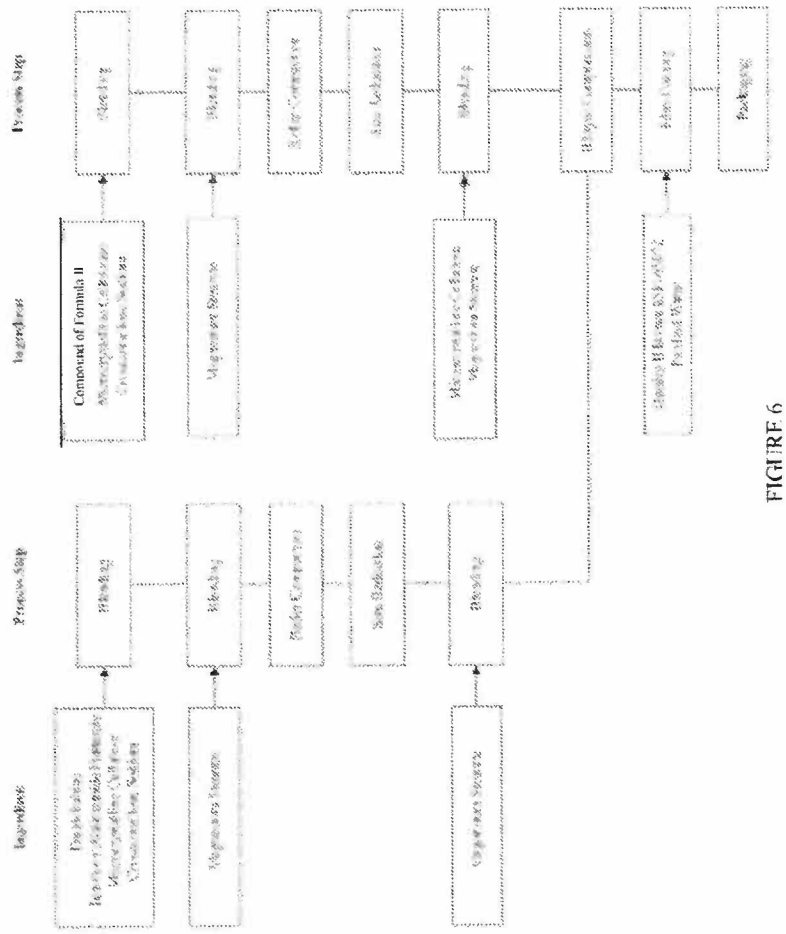


FIGURE 6

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	PHARMACEUTICAL FORMULATIONS

As the below named inventor, I hereby declare that:

This declaration is directed to:
- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Benjamin Micah Collman Date (Optional): 19 Oct 2016

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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[ ] United States application or PCT international application number _____ filed on _____

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LEGAL NAME OF INVENTOR

Inventor: Joanna M. Koziara Date (Optional): Oct 11, 2016

Signature: Joanna Koziara

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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As the below named inventor, I hereby declare that:

This declaration is directed to:
- [X] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Lei Hong Date (Optional): 12 Oct 2016

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt	
EFS ID:	45655350
Application Number:	17738803
International Application Number:	
Confirmation Number:	2232
Title of Invention:	THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Customer Number:	25000
Filer:	Donna Johnson Gressler/Trent Bastian
Filer Authorized By:	Donna Johnson Gressler
Attorney Docket Number:	1147-US-P2C2DC
Receipt Date:	06-MAY-2022
Filing Date:	
Time Stamp:	17:22:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	1147-US-P2C2DC_2022-05-06_ADS.pdf	2226215 0007dc5212a33f8d2d455de1af7a1e9c64f3661682	no	9

Warnings:

Information:					
2		1147-US-P2C2DC_2022-05-06_Application.pdf	1455799 f7d4727f9796855ea866978e14d1b4299aaf3b2c1	yes	110

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	97
	Claims	98	103
	Abstract	104	104
	Drawings-only black and white line drawings	105	110

Warnings:					
Information:					
3	Oath or Declaration filed	1147-US-P2C2DC_2022-05-06_Declarations.pdf	269222 00225374cc060691e736c0718a50ff3310d3e6f63e	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	3951236		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC

CONFIRMATION NO. 2232

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

FORMALITIES LETTER

OC000000133769738

Date Mailed: 05/11/2022

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 3, 6 are missing and/or blurry.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of $ **10520** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **320** basic filing fee.
- $ **160** surcharge.
- $ **700** search fee.
- $ **800** examination fee.
- $ **5760** for **12** independent claims over 3.
- $ **3900** for **39** total claims over 20.
- $ **860** for multiple dependent claim surcharge.
- $(**0**) previous unapplied payment amount.
- $ **12500** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ptnguyen/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/738,803

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	59 minus 20 =	* 39			OR	x 100 =	3900
INDEPENDENT CLAIMS (37 CFR 1.16(h))	15 minus 3 =	* 12				x 480 =	5760
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							860
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	12340

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/738,803	05/06/2022	1629	0.00	1147-US-P2C2DC	51	15

CONFIRMATION NO. 2232

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

FILING RECEIPT

OC000000133789737

Date Mailed: 05/11/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Benjamin Micah Collman, San Mateo, CA;
Lei Hong, Cupertino, CA;
Joanna M. Koziara, Foster City, CA;

Applicant(s)

Gilead Sciences, Inc., Foster City, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 16/987,081 08/06/2020
which is a CON of 16/713,380 12/13/2019 ABN
which is a CON of 15/346,335 11/08/2016 PAT 10548846
which claims benefit of 62/399,999 09/26/2016
and claims benefit of 62/253,042 11/09/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/10/2022
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/738,803**
Projected Publication Date: To Be Determined - pending completion of Missing Parts
Non-Publication Request: No
Early Publication Request: No
Title

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
131 of 1074

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 17738803	Filing Date
	Applicant(s) Benjamin Collman	
	* May be used for additional claims or amendments	

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		2				
4		(1)				
5		(1)				
6		(1)				
7	1					
8	1					
9	1					
10		1				
11	1					
12	1					
13		(1)				
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18		2				
19		2				
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45		5				
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Total Indep	15		0		0	
Total Depend	44	↵	0	↵	0	↵
Total Claims	59		0		0	

	Indep	Depend	Indep	Depend	Indep	Depend
51	1					
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To: IPDocketing@gilead.com,IPUS2@gilead.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 25000

May 11, 2022 04:23:00 AM

Dear PAIR Customer:

GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 25000 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
17738803	NTC.MISS.PRT	05/11/2022	1147-US-P2C2DC
	APP.FILE.REC	05/11/2022	1147-US-P2C2DC

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If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

CD Submission Review Results

Internal Worksheet Only - Do Not Scan

Application Number	17738803	Receipt Date	May 6, 2022

X	New Application		Response To Notice	Date Of Response

☐ Jumbo – Large tables are included on the CD

☒ **There are no problems with the CDs in the submission.**

Items checked below are to be selected in the PALM Pre-Exam CD problem list.

Omitted Items

	Files on compact disc are unreadable:
	Disc(s) of either set not readable:
	Disc(s) do not contain file names listed:
	Amended CD missing unamended files
	Missing compact discs

Missing Parts

	Disc(s) do not contain file names listed
	Discs contains files that are non-ASCII files:
	Only one copy of the CD, no duplicate:
	Wrong media type, e.g. CD-RW:
	The transmittal letter and specification do not list information:
	Both disc(s) contain unreadable files:
	One disc(s) contain unreadable files:
	Compact disc(s) contain viruses, but are still readable:
	EFS/Paper Submission:
	Table does not maintain data in proper alignment:
	Not proper subject matter for CD's:

Informality

	No statement in transmittal letter that CD's are the same:
	No incorporation by reference statement for the CD's:
	CD's not labeled "Copy 1" and "Copy 2":
	Deficient CD packaging:
	Deficient Labeling on CD's:
	The transmittal letter does not list information:
	The specification does not list information:
	Table less than 51 pages submitted on CD:

File Directory Attachment

	Copy of file directory listing is attached and should be mailed to applicant
	Copy of file directory listing is not attached
	Copy of file directory listing is not attached because it is over one page long

Additional Comments

Internal Worksheet Only - Do Not Scan

C:\Users\bmesfin1\Desktop\ScoreModule\20220518\17738803\1147-US-P2C2DC_2022-05-06_Application_QC.pdf

DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 17738803 Document Date: 05/06/2022

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: August 19, 2022
Electronic Signature for Kelsey Fajilan: /Kelsey Fajilan/

Docket No.: 1147-US-P2C2DC
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Benjamin Micah Collman et al.

Application No.: 17/738,803 | Confirmation No.: 2232

Filed: May 6, 2022 | Art Unit: 1629

For: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS | Examiner: Not yet assigned

RESPONSE TO MISSING PARTS AND PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Notice to File Missing Parts issued May 11, 2022 and prior to examination on the merits, please amend the above-identified U.S. patent application as follows. A request for a two-month extension of time is submitted herewith. Accordingly, this response is timely filed.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Amendments to the Drawings begin on page 5 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend the first paragraph of page 1 of the Specification as follows:

~~This patent application claims the benefit of priority of U.S. Application Serial No. 62/253,042, filed November 9, 2015 and of U.S. application serial No. 62/399,999, filed September 26, 2016. The content of each of these provisional applications is hereby incorporated herein in its entirety.~~

This application is a Continuation of Application No. 16/987,081, filed August 6, 2020, which is a Divisional of Application No. 16/713,380, filed December 13, 2019, which is a Continuation of Application No. 15/346,335, filed November 8, 2016. Application No. 15/346,335 claims the benefit of U.S. Provisional Application No. 62/253,042, filed November 9, 2015, and U.S. Provisional Application No. 62/399,999, filed September 26, 2016. The entire contents of these applications are incorporated herein by reference in their entirety.

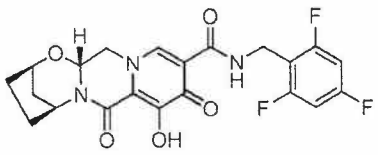
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of the claims in the application:

1-51. (Canceled)

52. (New) A tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

53. (New) The tablet of claim 52, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.

54. (New) The tablet of claim 52, wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.

55. (New) The tablet of claim 52, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

56. (New) The tablet of claim 52, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.

57. (New) The tablet of claim 52, wherein the tablet comprises 25 mg tenofovir alafenamide as tenofovir alafenamide fumarate.

58. (New) The tablet of claim 52, wherein the tablet comprises 28 mg tenofovir alafenamide hemifumarate.

59. (New) The tablet of claim 52, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

60. (New) The tablet of claim 52, wherein the tablet has a total weight of less than 1000 mg.

61. (New) The tablet of claim 60, wherein the tablet has a total weight of less than 800 mg.

62. (New) The tablet of claim 61, wherein the tablet has a total weight of less than 730 mg.

63. (New) The tablet of claim 52, wherein the tablet contains less than 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

64. (New) The tablet of claim 52, wherein the tablet contains less than 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
140 of 1074

UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/738,803	08/19/2022 02:48:29 PM ET	1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2232	FILED BY	Kelsey Fajilan
PATENT CENTER #	60890094	AUTHORIZED BY	Liuchun Yang
CUSTOMER #	25000	FILING DATE	05/06/2022
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Benjamin Micah Collman

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071250	E20228IE52224427	Kelsey Fajilan

PRE-AUTHORIZED ACCOUNT
071250

PRE-AUTHORIZED CATEGORY
37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
1051	SURCHARGE- LATE FILING FEE, SEARCH FEE, EXAMINATION FEE, INVENTOR'S OATH OR DECLARATION, OR APPLICATION FILED WITHOUT AT LEAST ONE CLAIM OR BY REFERENCE	160.00	1	160.00
1111	UTILITY PATENT APPL. SEARCH FEE	700.00	1	700.00
1011	BASIC FILING FEE - UTILITY (PAPER	320.00	1	320.00

	FILING ALSO REQUIRES NON-ELECTRONIC FILING FEE UNDER 1.16(T))			
1311	PATENT APPL. EXAMINATION FEE	800.00	1	800.00
1252	EXTENSION FOR RESPONSE WITHIN SECOND MONTH	640.00	1	640.00
			TOTAL AMOUNT:	$2,620.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

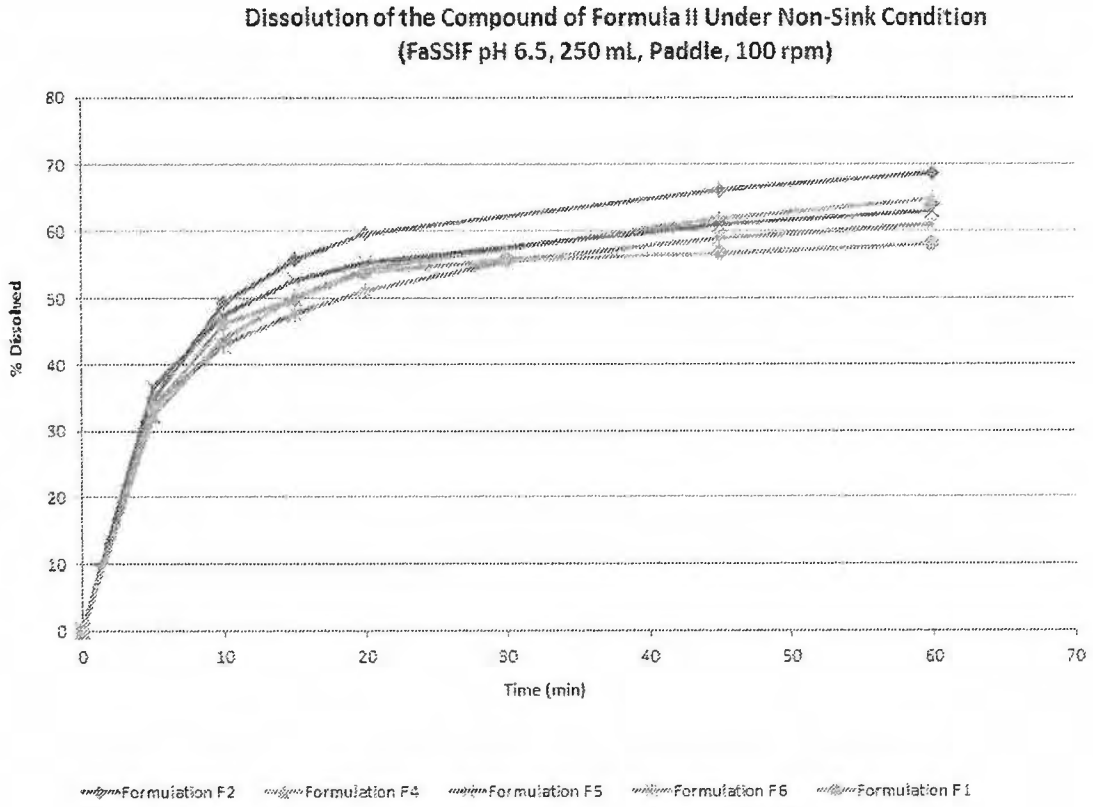

Dissolution of the Compound of Formula II Under Non-Sink Condition
(FaSSIF pH 6.5, 250 mL, Paddle, 100 rpm)
% Dissolved
Time (min)
0
10
20
30
40
50
60
70
80
Formulation F2
Formulation F4
Formulation F5
Formulation F6
Formulation F1

FIG. 3

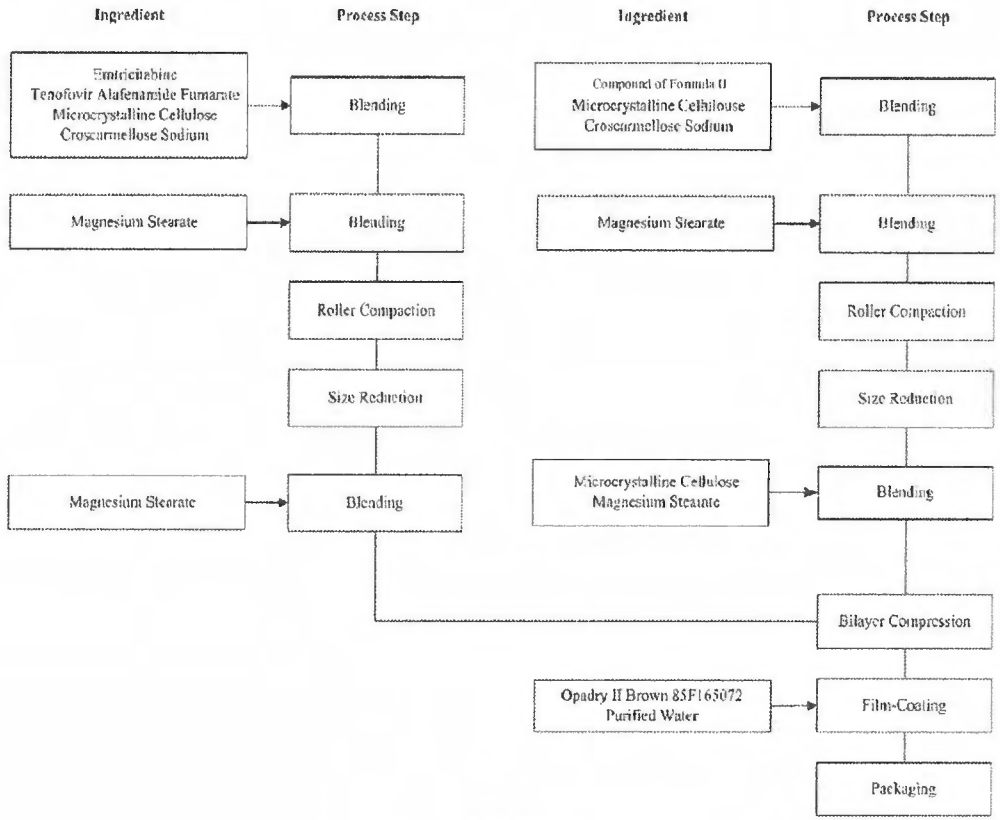

Ingredient
Process Step
Ingredient
Process Step
Emtricitabine
Tenofovir Alafenamide Fumarate
Microcrystalline Cellulose
Croscarmellose Sodium
Blending
Compound of Formula II
Microcrystalline Cellulose
Croscarmellose Sodium
Blending
Magnesium Stearate
Blending
Magnesium Stearate
Blending
Roller Compaction
Roller Compaction
Size Reduction
Size Reduction
Magnesium Stearate
Blending
Microcrystalline Cellulose
Magnesium Stearate
Blending
Bilayer Compression
Opadry II Brown 85F165072
Purified Water
Film-Coating
Packaging

FIG. 6

UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/738,803	08/19/2022 02:48:29 PM ET	1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

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PATENT CENTER #	60890094	FILING DATE	05/06/2022
CUSTOMER #	25000	FIRST NAMED INVENTOR	Benjamin Micah Collman
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Liuchun Yang

Documents

TOTAL DOCUMENTS: 6

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP.pdf		7	-	42 KB
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-A.PE.pdf	(1-1)	1	Preliminary Amendment	23 KB
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-SPEC.pdf	(2-2)	1	Specification	17 KB
1147-US-P2C2DC_2022-	(3-4)	2	Claims	27 KB

08-19_Preliminary_Amendment-MP-CLM.pdf				
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-DRW.pdf	(5-5)	1	Drawings-only black and white line drawings	16 KB
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-REM.pdf	(6-7)	2	Applicant Arguments/Remarks Made in an Amendment	20 KB
1147-US-P2C2DC_2022-08-19_Replacement_Drawings.pdf		2	Drawings-only black and white line drawings	798 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP.pdf	A9EBB72A6E3110BBC0245C95887489FBD188E815B9595D353129B5BE23610475D9904102303352A9E7398836ECE2331FA4FA1099E420127669B271B8E247BE26
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-A.PE.pdf	9A3E7774AEE1E372D6F36D576FE760751CBB6B3D7FA3FF22A826791F40C89F79B356BAF065EAAA9D5B7FBC6AB3CCAAB34435F3D8161D97B8403356321820D609
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-SPEC.pdf	01DE50ACEEAA0F14285B4E1EF853FCBE2A5BF45FC152091199DAC15738E2926B08255D60D735E55013964300DF3842C310B8FD528CED43F4904969B97E8C471A
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-CLM.pdf	7934DE8AECBF5BA2AC61901F3065D6A0B07C350B5CE3C3632ADBC862BFDE4E873C4026D6CEA4F2CFBCCE5BFCA558B40F32D22F5B2238A940873E8F3B0B3EEA17

1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-DRW.pdf	BE7A3F5999257CA3C5A2867A1EF9BA35B0E01165E067132AD25DFCA0FFE4B687DE1B0E4CDB2CCEDCC46B850529ED1A2738D9B3279592AAAACF3644BB9CC462ED
1147-US-P2C2DC_2022-08-19_Preliminary_Amendment-MP-REM.pdf	7CA57213E706BFAAEB705A6A94DA2466BC9FE62C10DEBA665CDC1A918E02004F2055ED5633FC35551FFD4C07C889EE68913B413B1A17F47E2A317F17D11AF422
1147-US-P2C2DC_2022-08-19_Replacement_Drawings.pdf	1F36B64E3CBC734E6AC621F4768061363968878CF59CF5D1663D7C7041667424A3C93D1F5F5B5C4231D4F320C3222EBF96FB926A8AC056159BDB8831C1BEB5983

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/738,803

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	13 minus 20 =	*			OR	x 100 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 480 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL			TOTAL	1820

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/738,803	05/06/2022	1629	1980	1147-US-P2C2DC	13	1

CONFIRMATION NO. 2232

UPDATED FILING RECEIPT

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

OC000000135970288

Date Mailed: 08/23/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Benjamin Micah Collman, San Mateo, CA;
Lei Hong, Cupertino, CA;
Joanna M. Koziara, Foster City, CA;

Applicant(s)

Gilead Sciences, Inc., Foster City, CA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 16/987,081 08/06/2020 ABN
which is a CON of 16/713,380 12/13/2019 ABN
which is a CON of 15/346,335 11/08/2016 PAT 10548846
which claims benefit of 62/399,999 09/26/2016
and claims benefit of 62/253,042 11/09/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/10/2022
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/738,803**
Projected Publication Date: 12/01/2022
Non-Publication Request: No
Early Publication Request: No
Title

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
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AMENDMENTS TO THE DRAWINGS

Please replace original drawing sheets 3 and 6 (Figures 3 and 6) with replacement drawing sheets 3 and 6, provided herewith.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1002**
153 of 1074

REMARKS

Amendments to the Claims

Claims 52-64 are currently pending. Claim 1-51 are canceled herein without prejudice or disclaimer. New claims 52-64 have been added. Applicant believes this amendment adds no new matter to the claims. Accordingly, with its entry, claims 52-64 are now pending before the Office.

Exemplary support for new claims 52-64 can be found in the originally filed application, as follows:

New claim	Exemplary support
52	Paragraphs [0009], [0021], and [0054]; and original claim 6;
53	Paragraphs [0034] and [0038];
54	Paragraphs [0042], [0043], [0044], and [0045];
55	Original claim 2;
56	Paragraphs [0034] and [0035];
57	Paragraphs [0042], and [0360];
58	Paragraphs [0042], [0043], [0044], and [0045];
59	Paragraphs [0015], and [0054]; original claims 3 and 8;
60	Paragraph [0054];
61	Original claim 4;
62	Original claim 5;
63	Original claim 26; and
64	Original claim 27.

Applicant expressly reserves the right to present claims drawn to any canceled subject matter in this or any other filed applications.

Amendments to the Drawings

The attached replacement drawing sheets 3 and 6 (Figures 3 and 6) are submitted in compliance with 37 C.F.R. §1.84 and §1.121(d). No new matter is added.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
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The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 07-1250, under Order No. 1147-US-P2C2DC from which the undersigned is authorized to draw.

Dated: August 19, 2022

Respectfully submitted,

Electronic signature: /Liuchun Yang/
Liuchun Yang
Registration No.: 69,330
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 574-3000
Attorney For Applicant

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1002**
155 of 1074

To: IPDocketing@gilead.com,IPUS2@gilead.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 25000

Aug 23, 2022 03:21:20 AM

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Application	Document	Mailroom Date	Attorney Docket No.
17738803	APP.FILE.REC	08/23/2022	1147-US-P2C2DC

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

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Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

CD Submission Review Results

Internal Worksheet Only - Do Not Scan

Application Number	17738803	Receipt Date	Aug 19, 2022

X	New Application		Response To Notice	Date Of Response

[ ] Jumbo – Large tables are included on the

[X] There are no problems with the CDs in the submission

Items checked below are to be selected in the PALM Pre-Exam CD problem

Omitted Items

	Files on compact disc are unreadable:
	Disc(s) of either set not readable:
	Disc(s) do not contain file names listed:
	Amended CD missing unamended files
	Missing compact discs

Missing Parts

	Disc(s) do not contain file names listed
	Discs contains files that are non-ASCII files:
	Only one copy of the CD, no duplicate:
	Wrong media type, e.g., CD-RW:
	The transmittal letter and specification do not list information:
	Both disc(s) contain unreadable files:
	One disc(s) contain unreadable files:
	Compact disc(s) contain viruses, but are still readable:
	EFS/Paper Submission:
	Table does not maintain data in proper alignment:
	Not proper subject matter for CD's:

Informality

	No statement in transmittal letter that CD's are the same:
	No incorporation by reference statement for the CD's:
	CD's not labeled "Copy 1" and "Copy 2":
	Deficient CD packaging:
	Deficient Labeling on CD's:
	The transmittal letter does not list information:
	The specification does not list information:
	Table less than 51 pages submitted on CD:

File Directory Attachment

	Copy of file directory listing is attached and should be mailed to applicant
	Copy of file directory listing is not attached
	Copy of file directory listing is not attached because it is over one page long

Additional Comments

Internal Worksheet Only - Do Not Scan

/scoredcm/OIPE/slsng@USPTO.GOV/S17738803202208300711107/disk1/1147-US-P2C2DC_2022-08-19_Replacement_Drawings.pdf

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 17738803 Document Date: 08/19/2022

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

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- Drawing

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Form Revision Date: March 1, 2019

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/738,803	05/06/2022	Benjamin Micah Coltman	1147-US-P2C2DC

CONFIRMATION NO. 2232

PUBLICATION NOTICE

25000
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

OC000000136945782

Title:THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Publication No.US-2022-0378798-A1
Publication Date:12/01/2022

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

25000 7590 12/06/2022
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER	
WORSHAM, JESSICA N	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
12/06/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDocketing@gilead.com
IPUS2@gilead.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 17/738,803	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 52-64 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 52-64 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Detailed Action

Status of Application

1. The instant application is a continuation of Application 16/987081 (currently abandoned) filed 6 August 2020, which is a continuation of Application 16/713380 (currently abandoned) filed 13 December 2019, which is a continuation of Application 15/346335 (now U.S. Patent No. 10,548,846) filed 8 November 2016. Claims 52-64 are currently pending. Claims 1-51 are cancelled. Claims 52-64 are examined on the merits within.

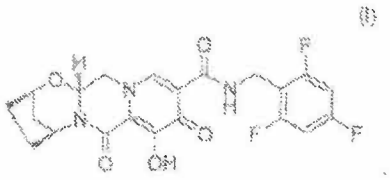
Claim Rejections – 35 U.S.C. 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

3. Claim(s) 52-59 is/are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Carra et al. (WO2015/196116).

Carra et al. disclose the compound of Formula 1:

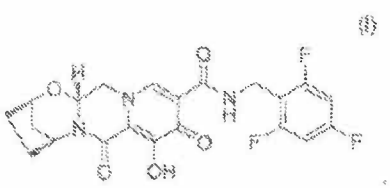


Carra et al. disclose the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0058]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0096]. Tenofovir alafenamide may be present as tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate. See paragraph [0082].

Thus the instant claims are anticipated by Carra et al.

4. Claim(s) 52-59 is/are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Carra et al. (U.S. Patent Application Publication No. 2016/0016973).

Carra et al. disclose the compound of Formula 1:



Carra et al. disclose the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0063]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0139]. Tenofovir alafenamide may be present as tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate. See paragraph [0087].

Thus the instant claims are anticipated by Carra et al.

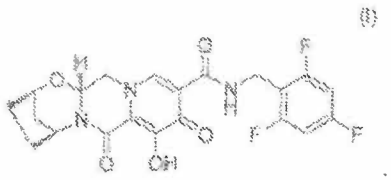
Claim Rejections – 35 U.S.C. 103

5. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 52-64 is/are rejected under 35 U.S.C. 103 as being unpatentable over Carra et al. (WO2015/196116) in view of Dahl et al. (U.S. Patent Application Publication No. 2007/0099902).

Carra et al. teach the compound of Formula 1:



Carra et al. teach the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula 1, is present in amounts of 25-100 mg. See paragraph [0058]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0096]. Tenofovir alafenamide may be present as tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate. See paragraph [0082]. Efavirenz is an HIV non-nucleoside or non-nucleotide inhibitor of reverse transcriptase that can be used as an additional therapeutic. See paragraph [0082]. The composition comprises surfactants to facilitate dissolution of the compound of the invention. See paragraph [0066]. Table 3 shows that the tablets comprise 30% active ingredient, 56% microcrystalline cellulose, 13% croscarmellose sodium, and 1% magnesium stearate.

Carra et al. do not teach the weight of the tablet or percentage of the compound of Formula 1.

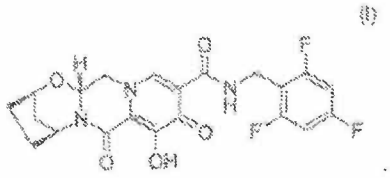
Dahl et al. teach a bilayer tablet of efavirenz, emtricitabine, and tenofovir. See paragraph [0050]. The unit dosage form comprises 1596.5 mg of ingredients per tablet. See Table 3. It is noted that efavirenz is present in 600 mg/tablet (see Table 1), emtricitabine is present in 200 mg/tablet and tenofovir is present in 300 mg/tablet (see Table 2). Typically the components of the dosage form are organized in multiple layers. See paragraph [0013]. The organization is so that

tenofovir is not placed in destabilizing contact with the surfactant of the efavirenz component. See paragraph [0016]. The bilayer tablet is film coated. See paragraph [0050]. Dahl et al. teach 38.71% efavirenz combined with 11.52% microcrystalline cellulose, 2.48% hydroxypropylcellulose, 0.77% sodium lauryl sulfate, 3.87% croscarmellose sodium and 0.58% magnesium stearate in a first layer with 12.9% emtricitabine, 19.35% tenofovir, 5.77% microcrystalline cellulose, 3.1% crsocarmellose sodium and 0.94% magnesium stearate in a second layer. See tables 1 and 2.

It would have been well within the purview of the skilled artisan to modify the amounts of ingredients, percentages of ingredients and weight of the tablet to optimize the formulation to achieve the desired result, especially since the combination of ingredients are commonly known in similar formulations.

7. Claim(s) 52-64 is/are rejected under 35 U.S.C. 103 as being unpatentable over Carra et al. (U.S. Patent Application Publication No. 2016/0016973) in view of Dahl et al. (U.S. Patent Application Publication No. 2007/0099902).

Carra et al. teach the compound of Formula 1:



Carra et al. teach the compound of Formula 1 in a composition comprising one to three additional therapeutic agents wherein these agents are anti-HIV drugs. See claim 14. The composition further comprises tenofovir alafenamide and emtricitabine. See claim 18. The composition is in

the form of a tablet. See claim 21. The compound of Formula II, which is the sodium salt of the compound of Formula I, is present in amounts of 25-100 mg. See paragraph [0063]. Tenofovir alafenamide is present in 5-30 mg and emtricitabine is present in 200 mg. See paragraph [0139]. Tenofovir alafenamide may be present as tenofovir alafenamide fumarate or tenofovir alafenamide hemifumarate. See paragraph [0087]. Efavirenz is an HIV non-nucleoside or non-nucleotide inhibitor of reverse transcriptase that can be used as an additional therapeutic. See paragraph [0087]. The composition comprises surfactants to facilitate dissolution of the compound of the invention. See paragraph [0071]. Table 3 shows that the tablets comprise 30% active ingredient, 56% microcrystalline cellulose, 13% croscarmellose sodium, and 1% magnesium stearate.

Carra et al. do not teach the weight of the tablet.

Dahl et al. teach a bilayer tablet of efavirenz, emtricitabine, and tenofovir. See paragraph [0050]. The unit dosage form comprises 1596.5 mg of ingredients per tablet. See Table 3. It is noted that efavirenz is present in 600 mg/tablet (see Table 1), emtricitabine is present in 200 mg/tablet and tenofovir is present in 300 mg/tablet (see Table 2). Typically the components of the dosage form are organized in multiple layers. See paragraph [0013]. The organization is so that tenofovir is not placed in destabilizing contact with the surfactant of the efavirenz component. See paragraph [0016]. The bilayer tablet is film coated. See paragraph [0050]. Dahl et al. teach 38.71% efavirenz combined with 11.52% microcrystalline cellulose, 2.48% hydroxypropylcellulose, 0.77% sodium lauryl sulfate, 3.87% croscarmellose sodium and 0.58% magnesium stearate in a first layer with 12.9% emtricitabine, 19.35% tenofovir, 5.77% microcrystalline cellulose, 3.1% croscarmellose sodium and 0.94% magnesium stearate in a second layer. See tables 1 and 2.

It would have been well within the purview of the skilled artisan to modify the amounts of ingredients, percentages of ingredients, and weight of the tablet to optimize the formulation to achieve the desired result, especially since the combination of ingredients are commonly known in similar formulations.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §

2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

9. Claims 52-64 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,548,846.

Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant application and U.S. Patent No. 10,548,846 are directed to a tablet comprising the compound of Formula 1, tenofovir alafenamide and emtricitabine. The only difference lies in the fact that U.S. Patent No. 10,548,846 describes the tablet as a multilayer tablet. The invention of the patent is in effect a "species of the "generic" invention of the instant application. It has been held that the generic invention is "anticipated" by the "species". See In re Goodman, 29 USPQ2d 2010 (Fed. Cir. 1993). Thus the two are not patentably distinct.

Conclusion

10. No claims are allowed at this time.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JESSICA WORSHAM whose telephone number is (571)270-7434. The examiner can normally be reached Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Notice of References Cited	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20070099902-A1	05-2007	Dahl; Terrence C.	A61K9/2054	514/269
*	B	US-20160016973-A1	01-2016	Carra; Ernest A.	C07D498/18	544/95
	C					
	D					
	E					
	F					
	G					
	H					
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	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO-2015196116-A1	12-2015	WO	CARRA E	A61K31/513
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1002**
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/738,803	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor Search: PE2E, PALM	12/01/2022	JW
PE2E: See attached	12/01/2022	JW
SciFinder: See attached	12/01/2022	JW

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	

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(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

(72) Inventors: **CARRA, Ernest, A.**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **CHEN, Irene**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US). **ZIA, Vahid**; c/o Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(74) Agents: **EDWARDS, Mary, J.** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Forster City, CA 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: SODIUM (2R, 5S, 13AR) -7, 9-DIOXO-10- ((2,4,6-TRIFLUOROBENZYL) CARBAMOYL) -2, 3, 4, 5, 7, 9, 13, 13A-OCTAHYDRO-2, 5-METHANOPYRIDO [1',2' : 4,5] PYRAZINO [2, 1-B] OXAZEPIN-8-OLATE

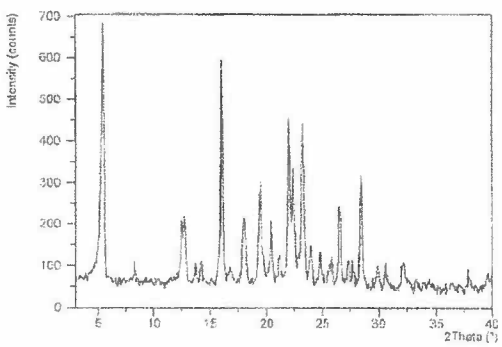


Figure 1

(57) Abstract: The present Invention relates to sodium (2R,5S,13aR)-7,9-dioxo-10 -((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

WO 2015/196116 A1

SODIUM (2R,5S,13AR)-7,9-DIOXO-10-((2,4,6-TRIFLUOROBENZYL)CARBAMOYL)-2,3,4,5,7,9,13,13A-OCTAHYDRO-2,5-METHANOPYRIDO[1',2':4,5]PYRAZINO[2,1-B][1,3]OXAZEPIN-8-OLATE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit under 35 U.S.C. 119(e) of U.S. Provisional Patent Application Serial No. 62/015,245, filed June 20, 2014, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD

[0002] The present invention relates to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, the crystalline forms, the pharmaceutical formulations, and the therapeutic uses thereof.

BACKGROUND

[0003] Human immunodeficiency virus infection and related diseases are a major public health problem worldwide. Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al. *N. Engl. J Med.* (1998) 338:853--860; Richman, D. D. *Nature* (2001) 410:995--1001).

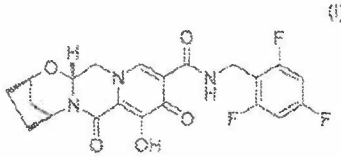
[0004] A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions. Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for

drug interactions.

[0005] As discussed in co-pending application United States Serial No. 14/133,855, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE", (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide demonstrates anti-viral activity. As discussed in co-pending application PCT Serial No. US2013/076367, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE", (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide demonstrates anti-viral activity.

[0006] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, (Formula I), has the following structure:

(I)

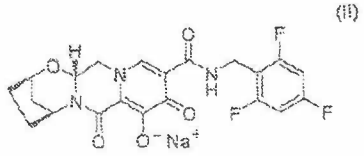


[0007] It is desired to have physically stable forms of the compound that are suitable for the therapeutic use and the manufacturing process.

BRIEF SUMMARY

[0008] In certain embodiments, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula II):

(II)



[0009] In a still further embodiment, the present invention is directed to crystalline sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0010] In a still further embodiment, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0011] In a certain embodiment, the present invention is directed to pharmaceutical formulations comprising sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0012] In another embodiment, the present invention is directed to methods of treating or prophylactically preventing an HIV infection by administering sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0013] In another embodiment, the present invention is directed to sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate for use in methods of treating or prophylactically preventing an HIV infection.

[0014] In another embodiment, the present invention is directed to the use of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate in the manufacture of a medicament for treating or prophylactically preventing an HIV infection.

DESCRIPTION OF THE FIGURES

[0015] **Figure 1:** XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

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trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0016] **Figure 2:** DSC for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0017] **Figure 3:** TGA for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0018] **Figure 4:** DVS for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0019] **Figure 5:** Dissolution profiles of Formula I Form I, Formula I Form III, and Formula II Form I.

[0020] **Figure 6:** Solubility profiles of Formula I Form III and Formula II Form I in Fasted-State Simulated Gastric Fluid (FaSSGF).

[0021] **Figure 7:** Solubility profiles of Formula I Form III and Formula II Form I in Fed-State Simulated Intestinal Fluid (FeSSIF) and Fasted-State Simulated Intestinal Fluid (FaSSIF).

[0022] **Figure 8:** Calculated and Experimental XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

DETAILED DESCRIPTION

[0023] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details. The description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the appended claims to the specific embodiments illustrated. The

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headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Definitions

[0024] Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is as "including, but not limited to".

[0025] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0026] The invention disclosed herein is also meant to encompass all pharmaceutically acceptable compounds of Formulas (I) and (II) being isotopically-labeled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labeled compounds of Formulas (I) and (II), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0027] Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability. For example, *in vivo* half-life may increase or dosage requirements may be reduced. Thus, heavier isotopes may be preferred in some circumstances.

[0028] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formulas (I) and (II) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0029] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0030] "Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0031] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0032] A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

[0033] "Effective amount" or "therapeutically effective amount" refers to an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of

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administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

[0034] The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. In certain embodiments, the term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. In certain embodiments, the term "treatment" as used herein is further or alternatively intended to mean the administration of a compound or composition according to the present invention to maintain a reduced viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease; and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life. In certain embodiments, the term "treatment" as used herein is further or alternatively intended to mean the administration of a compound or composition according to the present invention post-exposure of the individual to the virus as a subsequent or additional therapy to a first-line therapy (e.g., for maintenance of low viral load).

[0035] "Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. The term "prevention" also encompasses the administration of a compound or composition according to the present invention pre-exposure of the individual to the virus (e.g., pre-exposure prophylaxis), to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood.

[0036] The terms "Subject" or "patient" refer to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal (or the patient). In some embodiments the subject (or the patient) is human, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), and/or laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys). In one embodiment, the subject (or the patient) is a human. "Human (or patient) in need thereof" refers to a human who may have or is suspect to have diseases or conditions that would benefit from certain treatment; for example, being treated with the compounds disclosed herein according to the present application.

[0037] The term "antiviral agent" as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being.

[0038] The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro*, *ex vivo* or *in vivo*.

[0039] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

[0040] Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X". Also, the singular forms "a" and "the" include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay"

includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[0041] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0042] "Unit dosage forms" are physically discrete units suitable as unitary dosages for subjects (*e.g.*, human subjects and other mammals), each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

Crystalline Form

Formula II

[0043] It is desirable to develop a crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate that may be useful in the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be an intermediate to the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may be the final product in the synthesis of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. A polymorphic form or polymorph or cocrystal may have properties such as bioavailability and stability at certain conditions that may be suitable for medical or pharmaceutical uses.

[0044] A crystalline form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. In certain embodiments, a crystalline form sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate provides an advantage of improved bioavailability (Table 3) and/or stability (Table 4). Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ability to consistently prepare doses of known strength) and stability (*e.g.*, thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage form including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0045] The use of certain solvents has been found to produce different polymorphic forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, including polymorphic Form I, which may exhibit one or more favorable characteristics described above. In certain embodiments, Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate provides an advantage of improved bioavailability (Table 3) and/or stability (Table 4). The processes for the preparation of the polymorphs described herein and characterization of these polymorphs are described in greater detail below.

[0046] The compound name provided above is named using ChemBioDraw Ultra and

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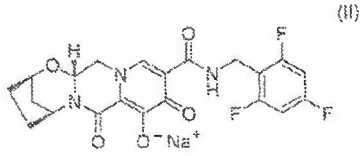
one skilled in the art understands that the compound structure may be named or identified using other commonly recognized nomenclature systems and symbols. By way of example, the compound may be named or identified with common names, systematic or non-systematic names. The nomenclature systems and symbols that are commonly recognized in the art of chemistry including but not limited to Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Accordingly, the compound structure provided above may be named or identified as sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate under IUPAC.

[0047] In particular embodiments, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

Formula II, Form I

[0048] In a certain embodiment, novel forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure (Formula II) are disclosed:

(II)



[0049] In a further embodiment, crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are disclosed.

[0050] In a certain embodiment, sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is disclosed.

[0051] In one embodiment, provided is polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the polymorph exhibits an X-ray powder diffraction (XRPD) pattern substantially as shown in FIG. 1 and/or FIG. 8. Polymorphic sodium Form I may exhibit a differential scanning calorimetry (DSC) thermogram substantially as shown in FIG. 2. Polymorphic sodium Form I may exhibit a thermographic analysis (TGA) graph substantially as shown in FIG. 3. Polymorphic sodium Form I may exhibit dynamic vapour sorption (DVS) graphs substantially as shown in FIG. 4.

[0052] The term "substantially as shown in" when referring, for example, to an XRPD pattern, a DSC thermogram, or a TGA graph includes a pattern, thermogram or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0053] Polymorphic sodium Form I may have a unit cell as determined by crystal X-ray crystallography of the following dimensions: a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °.

[0054] In some embodiments of polymorphic sodium Form I, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or all of the following (a)-(j) apply: (a) polymorphic Form I has an XRPD pattern substantially as shown in FIG. 1 and/or FIG. 8; (b) polymorphic sodium Form I has a DSC thermogram substantially as shown in FIG 2; (c) polymorphic sodium Form I has a TGA graph substantially as shown in FIG. 3; (d) polymorphic sodium Form I has DVS graphs substantially as shown in FIG. 4; (e) polymorphic sodium Form I has a unit cell, as determined by crystal X-ray crystallography, of the following dimensions: a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °; (f) polymorphic sodium Form I has an orthorhombic crystal system; (g) polymorphic sodium Form I has a P212121 space group; (h) polymorphic sodium Form I has a volume of 3879.2(7) $Å^3$; (i) polymorphic Form I has a Z value of 4; and (j) polymorphic Form I has a density of 1.614 Mg/m^3.

[0055] In some embodiments, polymorphic sodium Form I has at least one, at least two, at least three, at least four, or all of the following properties:

a. an XRPD pattern substantially as shown in FIG. 1 and/or FIG. 8;

b. a DSC thermogram substantially as shown in FIG 2;

c. TGA graphs substantially as shown in FIG 3;

d. DVS graphs substantially as shown in FIG 4; and

e. a unit cell, as determined by crystal X-ray crystallography, of the following dimensions a = 8.9561 (10) Å; b = 13.9202 (14) Å; c = 31.115 (3) Å; α = 90 °; β = 90 °; and γ = 90 °;

[0056] In some embodiments, polymorphic sodium Form I has an XRPD pattern displaying at least two, at least three, at least four, at least five, or at least six of the degree 2θ-reflections with the greatest intensity as the XRPD pattern substantially as shown in FIG 1 and/or FIG. 8.

[0057] In certain embodiments, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and one or more of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and one of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and two of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, and 23.3 and three of the degree 2θ-reflections (+/- 0.2 degrees 2θ) at 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, 23.3, 22.1, 28.5, and 22.5. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising degree 2θ-reflections (+/- 0.2 degrees 2θ) at 5.5, 16.1, 23.3, 22.1, 28.5, 22.5, 19.5, and 26.6. In one embodiment, polymorphic sodium Form I has an XRPD pattern comprising any three degree 2θ-reflections (+/- 0.2 degrees 2θ) selected from the group consisting of 5.5, 16.1, 23.3, 22.1, 28.5, 22.5, 19.5, 26.6, and 17.9.

Pharmaceutical Compositions

[0058] For the purposes of administration, in certain embodiments, the compounds described herein are administered as a raw chemical or are formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a compound of Formula (II), including forms and co-crystals thereof, and a pharmaceutically acceptable carrier, diluent or excipient. The compound of Formula (II) is present in the composition in an amount which is effective to treat a particular disease or condition of interest. The activity of compounds of Formula (II) can be determined by one skilled in the art, for example, as described in co-pending application Serial No. 14/133,855, filed December 19, 2013 entitled "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE". The activity of compounds of Formula (II) can also be determined by one skilled on the art, for example, as described in co-pending PCT Serial No. US2013/076367, filed December 19, 2013 entitled, "POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE." Appropriate concentrations and dosages can be readily determined by one skilled in the art. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount from about 25 mg to about 500 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 100 mg to about 300 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 5 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 25 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 50 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 5 mg to about 100 mg. In certain embodiments, a compound of Formula (II) is present in the pharmaceutical composition in an amount of about 5 mg, 25 mg, 50 mg, 75, mg, 100 mg, 200 mg, 300 mg, 400 mg or about 500 mg.

Formula II

[0059] Provided are also compositions comprising at least one polymorph (e.g., any one or more of Formula II polymorphic Forms I) as described herein. In a particular embodiment, a composition comprising Formula II polymorphic Form I, described herein is

provided. In other embodiments, the compositions described herein may comprise substantially pure polymorphic forms, or may be substantially free of other polymorphs and/or impurities.

[0060] In some embodiments, the composition comprises a polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments are provided compositions comprising a polymorphic form as described herein, wherein the sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate within the composition is substantially pure (*i.e.*, substantially pure Form I). In particular embodiments of compositions comprising a polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition is Formula II, Form I, disclosed herein. In certain embodiments, the composition includes at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% of Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0061] In other embodiments of compositions comprising a polymorphic form disclosed herein, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate present in the composition are other polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate and/or impurities.

[0062] In yet other embodiments of compositions comprising the polymorphic forms disclosed herein, impurities make up less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the total mass relative to the mass of the polymorphic forms present. Impurities may, for example, include by-products from synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, amorphous form, water, and solvents. In certain embodiments, impurities include by-products from the process of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include contaminants from the process of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include degradation products of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include other polymorphic forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate. In certain embodiments, impurities include water or solvent. In certain embodiments of compositions comprising a polymorphic form disclosed herein, impurities are selected from the group consisting of by-products from synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, contaminants, degradation products, other polymorphic forms, water, solvents and combinations thereof.

[0063] In yet other embodiments, the composition comprising Formula II, Form I disclosed herein has less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about 1% by weight of amorphous or non-crystalline sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0064] In some embodiments, the term "substantially pure" or "substantially free" with respect to a particular polymorphic form of a compound means that the composition

comprising the polymorphic form contains less than 95%, less than 90%, less than 80%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, or less than 1% by weight of other substances, including other polymorphic forms and/or impurities. In certain embodiments, "substantially pure" or "substantially free of" refers to a substance free of other substances, including other polymorphic forms and/or impurities. Impurities may, for example, include by-products or left over reagents from chemical reactions, contaminants, degradation products, other polymorphic forms, water, and solvents.

Administration

[0065] Administration of the compounds disclosed herein in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration of agents for serving similar utilities. The pharmaceutical compositions described herein can be prepared by combining a compound disclosed herein with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as solid dispersions and solid solutions. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, transdermal, inhalation, parenteral, sublingual, buccal, rectal, vaginal, and intranasal. In one embodiment, the pharmaceutical compositions is prepared for oral administration. In a specific embodiment, the pharmaceutical compositions is a tablet. Pharmaceutical compositions of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a subject or patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 20th Edition (Philadelphia College of Pharmacy and Science, 2000). The composition to be administered will, in any

event, contain a therapeutically effective amount of a compound of the invention for treatment of a disease or condition of interest in accordance with the teachings of this disclosure.

[0066] The pharmaceutical compositions disclosed herein may be prepared by methodology well known in the pharmaceutical art. For example, a pharmaceutical composition intended to be administered by injection can be prepared by combining a compound of the invention with sterile, distilled water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the compound of the invention so as to facilitate dissolution or homogeneous suspension of the compound in the aqueous delivery system.

[0067] For example, a solid pharmaceutical composition intended for oral administration can be prepared by mixing a compound of the invention with at least one suitable pharmaceutical excipient to form a solid preformulation composition, which then may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. Accordingly, in one embodiment, a pharmaceutical composition is provided, which includes a compound of Formula (II) and a pharmaceutical excipient.

[0068] The compounds disclosed herein are administered in a therapeutically effective amount, which will vary depending upon a variety of factors including the activity of the specific compound employed; the metabolic stability and length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; the severity of the particular disorder or condition; and the subject undergoing therapy. In some embodiments, the compounds of the invention can be administered alone or in combination with other antiviral agents once or twice daily for as long as the patient is infected, latently infected, or to prevent infection (e.g. for multiple years, months, weeks, or days).

Combination Therapy

[0069] In one embodiment, a method for treating or preventing an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or

one to three) additional therapeutic agents. In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0070] In one embodiment, a method for treating an HIV infection in a human having or at risk of having the infection is provided, comprising administering to the human a therapeutically effective amount of a compound or composition disclosed herein in combination with a therapeutically effective amount of one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents.

[0071] In certain embodiments, the present invention provides a method for treating an HIV infection, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition disclosed herein in combination with a therapeutically effective amount of one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0072] One embodiment provides a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents for use in a method for treating or preventing an HIV infection in a human having or at risk of having the infection. One embodiment provides a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents for use in a method for treating an HIV infection in a human having or at risk of having the infection. One embodiment provides a compound disclosed herein for use in a method for treating or preventing an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. One embodiment provides a compound disclosed herein for use in a method for treating an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In certain embodiments, the present invention provides a compound disclosed herein in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection, for use in a method for treating an HIV infection. In certain embodiments, the present invention provides a compound disclosed herein for use in a

method for treating an HIV infection, wherein the compound is administered in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0073] One embodiment provides the use of a compound disclosed herein thereof, in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents in the manufacture of a medicament for treating or preventing an HIV infection in a human having or at risk of having the infection. One embodiment provides the use of a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection. One embodiment provides the use of a compound disclosed herein in the manufacture of a medicament for treating or preventing an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. One embodiment provides the use of a compound disclosed herein thereof, in the manufacture of a medicament for treating an HIV infection in a human having or at risk of having the infection, wherein the compound is administered in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents. In certain embodiments, the present invention provides the use of a compound disclosed herein thereof, in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection, in treating an HIV infection. In certain embodiments, the present invention provides the use of a compound disclosed herein thereof for treating an HIV infection, wherein the compound is administered in combination with one or more additional therapeutic agents which are suitable for treating an HIV infection.

[0074] A compound as disclosed herein (e.g., any compound of Formula (II)) may be combined with one or more additional therapeutic agents in any dosage amount of the compound of Formula II (e.g., from 50 mg to 1000 mg of compound).

[0075] In one embodiment, pharmaceutical compositions comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

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[0076] In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[0077] In one embodiment, kits comprising a compound disclosed herein in combination with one or more (e.g., one, two, three, one or two, or one to three) additional therapeutic agents are provided.

[0078] In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), and WO 2013/006792 (Pharma Resources), pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

[0079] In other embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, HIV entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, HIV vaccines, HIV maturation inhibitors, latency reversing agents (e.g., histone deacetylase inhibitors, proteasome inhibitors, protein kinase C (PKC) activators, and BRD4 inhibitors), compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds, HIV nucleocapsid p7 (NCp7) inhibitors, HIV p24 capsid protein inhibitors), pharmacokinetic enhancers, immune-based therapies (e.g., Pd-1 modulators, Pd-L1 modulators, toll like receptors modulators,, IL-15 agonists,), HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins

(e.g., DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives) including those targeting HIV gp120 or gp41, combination drugs for HIV, HIV p17 matrix protein inhibitors, IL-13 antagonists, Peptidyl-prolyl cis-trans isomerase A modulators, Protein disulfide isomerase inhibitors, Complement C5a receptor antagonists, DNA methyltransferase inhibitor, HIV vif gene modulators, Vif dimerization antagonists, HIV-1 viral infectivity factor inhibitors, TAT protein inhibitors, HIV-1 Nef modulators, Hck tyrosine kinase modulators, mixed lineage kinase-3 (MLK-3) inhibitors, HIV-1 splicing inhibitors, Rev protein inhibitors, Integrin antagonists, Nucleoprotein inhibitors, Splicing factor modulators, COMM domain containing protein 1 modulators, HIV Ribonuclease H inhibitors, Retrocyclin modulators, CDK-9 inhibitors, Dendritic ICAM-3 grabbing nonintegrin 1 inhibitors, HIV GAG protein inhibitors, HIV POL protein inhibitors, Complement Factor H modulators, Ubiquitin ligase inhibitors, Deoxycytidine kinase inhibitors, Cyclin dependent kinase inhibitors Proprotein convertase PC9 stimulators, ATP dependent RNA helicase DDX3X inhibitors, reverse transcriptase priming complex inhibitors, HIV gene therapy, PI3K inhibitors, compounds such as those disclosed in WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), WO 2013/091096A1 (Boehringer Ingelheim), WO 2009/062285 (Boehringer Ingelheim), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO2012/003497 (Gilead Sciences), WO2014/100323 (Gilead Sciences), WO2012/145728 (Gilead Sciences), WO2013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences) and WO 2013/006792 (Pharma Resources), and other drugs for treating HIV, and combinations thereof.

[0080] In certain embodiments, the additional therapeutic is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof.

[0081] In certain embodiments a compound of Formula (II) is formulated as a tablet, which may optionally contain one or more other compounds useful for treating HIV. In certain embodiments, the tablet can contain another active ingredient for treating HIV, such as HIV protease inhibitors, HIV non-nucleoside or non-nucleotide inhibitors of reverse

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transcriptase, HIV nucleoside or nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, pharmacokinetic enhancers, and combinations thereof. In certain embodiments, the tablet can contain one or more active ingredients for treating HIV, such as HIV nucleoside or nucleotide inhibitors of reverse transcriptase. In certain embodiments, such tablets are suitable for once daily dosing.

[0082] In further embodiments, the additional therapeutic agent is selected from one or more of:

(1) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, rilpivirine, BILR 355 BS, VRX 840773, lersivirine (UK-453061), RDEA806, KM023 and MK-1439;

(3) HIV nucleoside or nucleotide inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, MIV-210, ß-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), KP-1461, GS-9131 (Gilead Sciences), fosalvudine tidoxil (formerly HDP 99.0003), tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, tenofovir alafenamide fumarate (Gilead Sciences), GS-7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) and CMX-157 (Chimerix);

(4) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin,

derivatives of quercetin, S-1360, AR-177, L-870812, and L-870810, raltegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, elvitegravir, dolutegravir, dolutegravir sodium, and GSK-744;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) including, but not limited to, BI-224436, CX0516, CX05045, CX14442, compounds disclosed in WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO 2012/003497 (Gilead Sciences), WO 2012/003498 (Gilead Sciences) each of which is incorporated by references in its entirety herein;

(7) gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide, albuvirtide, FB006M, and TRI-1144;

(8) the CXCR4 inhibitor AMD-070;

(9) the entry inhibitor SP01A;

(10) the gp120 inhibitor BMS-488043;

(11) the G6PD and NADH-oxidase inhibitor immunitin;

(12) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(13) CD4 attachment inhibitors selected from the group consisting of ibalizumab (TMB-355) and BMS-068 (BMS-663068);

(14) pharmacokinetic enhancers selected from the group consisting of cobicistat and SPI-452; and

(15) other drugs for treating HIV selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), HRG214, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040),

and combinations thereof.

[0083] In certain embodiments, the additional therapeutic agent is selected from one or more of:

(1) Combination drugs selected from the group consisting of ATRIPLA® (efavirenz+tenofovir disoproxil fumarate +emtricitabine), COMPLERA® or EVIPLERA® (rilpivirine+tenofovir disoproxil fumarate +emtricitabine), STRIBILD® (elvitegravir+cobicistat+tenofovir disoproxil fumarate +emtricitabine), dolutegravir + abacavir sulfate +lamivudine, TRIUMEQ® (dolutegravir + abacavir + lamivudine) , lamivudine + nevirapine + zidovudine, dolutegravir+rilpivirine, dolutegravir+rilpivirine hydrochloride, atazanavir sulfate + cobicistat, atazanavir + cobicistat, darunavir + cobicistat, efavirenz + lamivudine + tenofovir disoproxil fumarate, tenofovir alafenamide hemifumarate + emtricitabine + cobicistat + elvitegravir, tenofovir alafenamide hemifumarate + emtricitabine, tenofovir alafenamide + emtricitabine, tenofovir alafenamide hemifumarate + emtricitabine + rilpivirine, tenofovir alafenamide + emtricitabine + rilpivirine , Vacc-4x + romidepsin, darunavir + tenofovir alafenamide hemifumarate+ emtricitabine + cobicistat, APH-0812, raltegravir + lamivudine, KALETRA® (ALUVIA®, lopinavir+ritonavir), atazanavir sulfate + ritonavir, COMBIVIR® (zidovudine+lamivudine, AZT+3TC), EPZICOM® (Kivexa®, abacavir sulfate +lamivudine, ABC+3TC), TRIZIVIR® (abacavir sulfate+zidovudine+lamivudine, ABC+AZT+3TC), TRUVADA® (tenofovir disoproxil fumarate +emtricitabine, TDF+FTC), doravirine + lamivudine + tenofovir disoproxil fumarate, doravirine + lamivudine + tenofovir disoproxil, tenofovir + lamivudine and lamivudine + tenofovir disoproxil fumarate;

(2) HIV protease inhibitors selected from the group consisting of amprenavir, atazanavir, fosamprenavir, fosamprenavir calcium, indinavir, indinavir sulfate, lopinavir, ritonavir, nelfinavir, nelfinavir mesylate, saquinavir, saquinavir mesylate, tipranavir, brecanavir, darunavir, DG-17, TMB-657 (PPL-100) and TMC-310911;

(3) HIV non-nucleoside or non-nucleotide inhibitors of reverse transcriptase selected from the group consisting of delavirdine, delavirdine mesylate, nevirapine, etravirine, dapivirine, doravirine, rilpivirine, efavirenz, KM-023, VM-1500, lentinan and AIC-

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(4) HIV nucleoside or nucleotide inhibitors of reverse transcriptase selected from the group consisting of VIDEX® and VIDEX® EC (didanosine, ddI), zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, censavudine, abacavir, abacavir sulfate, amdoxovir, elvucitabine, alovudine, phosphazid, fozivudine tidoxil, apricitabine, amdoxovir , KP-1461, fosalvudine tidoxil, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide, tenofovir alafenamide hemifumarate, tenofovir alafenamide fumarate, adefovir, adefovir dipivoxil, and festinavir;

(5) HIV integrase inhibitors selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, raltegravir, elvitegravir, dolutegravir and cabotegravir;

(6) HIV non-catalytic site, or allosteric, integrase inhibitors (NCINI) selected from the group consisting of CX-05168, CX-05045 and CX-14442;

(7) HIV gp41 inhibitors selected from the group consisting of enfuvirtide, sifuvirtide and albuvirtide;

(8) HIV entry inhibitors selected from the group consisting of cenicriviroc;

(9) HIV gp120 inhibitors selected from the group consisting of Radha-108 (Receptol) and BMS-663068;

(10) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, cenicriviroc, PRO-140, Adaptavir (RAP-101), nifeviroc (TD-0232), TD-0680, and vMIP (Haimipu);

(11) CD4 attachment inhibitors selected from the group consisting of ibalizumab;

(12) CXCR4 inhibitors selected from the group consisting of plerixafor, ALT-1188, vMIP and Haimipu;

(13) Pharmacokinetic enhancers selected from the group consisting of cobicistat and ritonavir;

(14) Immune-based therapies selected from the group consisting of dermaVir, interleukin-7, plaquenil (hydroxychloroquine), proleukin (aldesleukin, IL-2), interferon alfa, interferon alfa-2b, interferon alfa-n3, pegylated interferon alfa, interferon gamma, hydroxyurea, mycophenolate mofetil (MPA) and its ester derivative mycophenolate mofetil (MMF), WF-10, ribavirin, IL-2, IL-12, polymer polyethyleneimine (PEI), Gepon, VGV-1, MOR-22, BMS-936559, toll-like receptors modulators (tlr1, tlr2, tlr3, tlr4, tlr5, tlr6, tlr7, tlr8, tlr9, tlr10, tlr11, tlr12 and tlr13), rintatolimod and IR-103;

(15) HIV vaccines selected from the group consisting of peptide vaccines, recombinant subunit protein vaccines, live vector vaccines, DNA vaccines, virus-like particle vaccines (pseudovirion vaccine), CD4-derived peptide vaccines, vaccine combinations, rgp120 (AIDSVAX), ALVAC HIV (vCP1521)/AIDSVAX B/E (gp120) (RV144), monomeric gp120 HIV-1 subtype C vaccine (Novartis), Remune, ITV-1, Contre Vir, Ad5-ENVA-48, DCVax-001 (CDX-2401), PEP-6409,Vacc-4x, Vacc-C5, VAC-3S, multiclade DNA recombinant adenovirus-5 (rAd5), Pennvax-G, VRC-HIV MAB060-00-AB, AVX-101, Tat Oyi vaccine, AVX-201, HIV-LAMP-vax, Ad35, Ad35-GRIN, NAcGM3/VSSP ISA-51, poly-ICLC adjuvanted vaccines, Tatimmune, GTU-multiHIV (FIT-06), AGS-004, gp140[delta]V2.TV1+ MF-59, rVSVIN HIV-1 gag vaccine, SeV-Gag vaccine, AT-20, DNK-4, Ad35-GRIN/ENV, TBC-M4, HIVAX , HIVAX-2, NYVAC-HIV-PT1, NYVAC-HIV-PT4, DNA-HIV-PT123, rAAV1-PG9DP, GOVX-B11, GOVX-B21, ThV-01, TUTI-16, VGX-3300, TVI-HIV-1, Ad-4 (Ad4-env Clade C + Ad4-mGag), EN41-UGR7C, EN41-FPA2, ProVaxTat, TL-01, SAV-001, AE-H, MYM-V101, CombiHIVvac, ADVAX, MYM-V201, MVA-CMDR, ETV-01, CDX-1401, rcAd26.MOS1.HIV-Env and DNA-Ad5 gag/pol/nef/nev (HVTN505);

(16) HIV antibodies, bispecific antibodies and "antibody-like" therapeutic proteins (such as DARTs®, Duobodies®, Bites®, XmAbs®, TandAbs ®, Fab derivatives) including BMS-936559, TMB-360 and those targeting HIV gp120 or gp41 selected from the group consisting of bavituximab, UB-421, C2F5, C2G12, C4E10, C2F5+C2G12+C4E10, 3-BNC-117 , PGT145, PGT121, MDX010 (ipilimumab),

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VRC01, A32, 7B2, 10E8, VRC-07-523 and VRC07;

(17) latency reversing agents selected from the group consisting of Histone deacetylase inhibitors such as Romidepsin, vorinostat, panobinostat; Proteasome inhibitors such as Velcade; protein kinase C (PKC) activators such as Indolactam, Prostratin, Ingenol B and DAG-lactones, Ionomycin, GSK-343, PMA, SAHA, BRD4 inhibitors, IL-15, JQ1, disulfram, and amphotericin B;

(18) HIV nucleocapsid p7 (NCp7) inhibitors selected from the group consisting of azodicarbonamide;

(19) HIV maturation inhibitors selected from the group consisting of BMS-955176 and GSK-2838232;

(20) PI3K inhibitors selected from the group consisting of idelalisib, AZD-8186, buparlisib, CLR-457, pictilisib, neratinib, rigosertib, rigosertib sodium, EN-3342, TGR-1202, alpelisib, duvelisib, UCB-5857, taselisib, XL-765, gedatolisib, VS-5584, copanlisib, CAI orotate, perifosine, RG-7666, GSK-2636771, DS-7423, panulisib, GSK-2269557, GSK-2126458, CUDC-907, PQR-309, INCB-040093, pilaralisib, BAY-1082439, puquitinib mesylate, SAR-245409, AMG-319, RP-6530, ZSTK-474, MLN-1117, SF-1126, RV-1729, sonolisib, LY-3023414, SAR-260301 and CLR-1401;

(21) the compounds disclosed in WO 2004/096286 (Gilead Sciences), WO 2006/110157 (Gilead Sciences), WO 2006/015261 (Gilead Sciences), WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), US20140221380 (Japan Tobacco), US20140221378 (Japan Tobacco), WO 2013/006792 (Pharma Resources), WO 2009/062285 (Boehringer Ingelheim), WO 2010/130034 (Boehringer Ingelheim), WO 2013/091096A1 (Boehringer Ingelheim), WO 2013/159064 (Gilead Sciences), WO 2012/145728 (Gilead Sciences), WO2012/003497 (Gilead Sciences), WO2014/100323 (Gilead Sciences), WO2012/145728 (Gilead Sciences), WO2013/159064 (Gilead Sciences) and WO 2012/003498 (Gilead Sciences); and

(22) other drugs for treating HIV selected from the group consisting of BanLec, MK-8507, AG-1105, TR-452, MK-8591, REP 9, CYT-107, alisporivir, NOV-205, IND-

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02, metenkefalin, PGN-007, Acemannan, Gamimune, Prolastin, 1,5-dicaffeoylquinic acid, BIT-225, RPI-MN, VSSP, Hiviral, IMO-3100, SB-728-T, RPI-MN, VIR-576, HGTV-43, MK-1376, rHIV7-shl-TAR-CCR5RZ, MazF gene therapy, BlockAide, ABX-464, SCY-635, naltrexone, AAV-eCD4-Ig gene therapy and PA-1050040 (PA-040);

and combinations thereof.

[0084] In certain embodiments, a compound disclosed herein is combined with two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The two, three four or more additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0085] In certain embodiments, a compound disclosed herein, is combined with one, two, three, four or more additional therapeutic agents. In certain embodiments, a compound disclosed herein is combined with one additional therapeutic agent. In certain embodiments, a compound disclosed herein is combined with two additional therapeutic agents. In other embodiments, a compound disclosed herein is combined with three additional therapeutic agents. In further embodiments, a compound disclosed herein is combined with four additional therapeutic agents. The one, two, three, four or more additional therapeutic agents

can be different therapeutic agents selected from the same class of therapeutic agents, and/or they can be selected from different classes of therapeutic agents. In a specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase and an HIV non-nucleoside inhibitor of reverse transcriptase. In another specific embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In a further embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and an HIV protease inhibiting compound. In an additional embodiment, a compound disclosed herein is combined with an HIV nucleoside or nucleotide inhibitor of reverse transcriptase, an HIV non-nucleoside inhibitor of reverse transcriptase, and a pharmacokinetic enhancer. In certain embodiments, a compound disclosed herein is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer. In another embodiment, a compound disclosed herein is combined with two HIV nucleoside or nucleotide inhibitors of reverse transcriptase.

[0086] In certain embodiments, a compound disclosed herein is combined with at least one HIV nucleoside inhibitor of reverse transcriptase, an integrase inhibitor, and a pharmacokinetic enhancer.

[0087] In a particular embodiment, a compound disclosed herein is combined with abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0088] In a particular embodiment, a compound disclosed herein is combined with tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

[0089] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent selected from the group consisting of emtricitibine and lamivudine.

[0090] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: tenofovir, tenofovir

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disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitibine.

[0091] In a particular embodiment, a compound disclosed herein is combined with one, two, three, four or more additional therapeutic agents selected from Triumeq® (dolutegravir+abacavir +lamivudine), dolutegravir + abacavir sulfate + lamivudine, raltegravir, raltegravir + lamivudine, Truvada® (tenofovir disoproxil fumarate +emtricitabine, TDF+FTC), maraviroc, enfuvirtide , Epzicom® (Livexa®, abacavir sulfate +lamivudine, ABC+3TC), Trizivir® (abacavir sulfate+zidovudine+lamivudine, ABC+AZT+3TC), adefovir, adefovir dipivoxil, Stribild ® (elvitegravir+cobicistat+tenofovir disoproxil fumarate +emtricitabine), rilpivirine, rilpivirine hydrochloride, Complera® (Eviplera®, rilpivirine+tenofovir disoproxil fumarate +emtricitabine), Cobicistat, atazanavir sulfate + cobicistat, atazanavir + cobicistat, darunavir + cobicistat, Atripla® (efavirenz+tenofovir disoproxil fumarate +emtricitabine), atazanavir, atazanavir sulfate, dolutegravir, elvitegravir, Aluvia® (Kaletra®, lopinavir+ritonavir), ritonavir , emtricitabine , atazanavir sulfate + ritonavir, darunavir, lamivudine, Prolastin, fosamprenavir, fosamprenavir calcium, efavirenz, Combivir® (zidovudine+lamivudine, AZT+3TC), etravirine, nelfinavir, nelfinavir mesylate, interferon, didanosine, stavudine, indinavir, indinavir sulfate, tenofovir + lamivudine, zidovudine, nevirapine, saquinavir, saquinavir mesylate, aldesleukin, zalcitabine, tipranavir, amprenavir, delavirdine, delavirdine mesylate, Radha-108 (Receptol), Hiviral, lamivudine + tenofovir disoproxil fumarate, efavirenz + lamivudine + tenofovir disoproxil fumarate , phosphazid, lamivudine + nevirapine + zidovudine, abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, darunavir + cobicistat, atazanavir sulfate + cobicistat, atazanavir + cobicistat, tenofovir alafenamide and tenofovir alafenamide hemifumarate.

[0092] In a particular embodiment, a compound disclosed herein is combined with abacavir, abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, tenofovir alafenamide or tenofovir alafenamide hemifumarate.

[0093] In a particular embodiment, a compound disclosed herein is combined with tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, or tenofovir alafenamide hemifumarate.

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[0094] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: abacavir sulfate, tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent selected from the group consisting of emtricitabine and lamivudine.

[0095] In a particular embodiment, a compound disclosed herein is combined with a first additional therapeutic agent selected from the group consisting of: tenofovir, tenofovir disoproxil, tenofovir disoproxil fumarate, tenofovir alafenamide, and tenofovir alafenamide hemifumarate and a second additional therapeutic agent, wherein the second additional therapeutic agent is emtricitabine.

[0096] In certain embodiments, a compound disclosed herein is combined with 5-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 5-10; 5-15; 5-20; 5-25; 25-30; 20-30; 15-30; or 10-30 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 10 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0097] In certain embodiments, a compound disclosed herein is combined with 200-400 mg tenofovir disproxil, tenofovir disoproxil fumarate, or tenofovir disoproxil hemifumarate and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 200-250; 200-300; 200-350; 250-350; 250-400; 350-400; 300-400; or 250-400 mg tenofovir disoproxil, tenofovir disoproxil fumarate, or tenofovir disoproxil hemifumarate and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 300 mg tenofovir disoproxil fumarate, tenofovir disoproxil hemifumarate, or tenofovir disoproxil and 200 mg emtricitabine. A compound as disclosed

herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

[0098] In certain embodiments, when a compound disclosed herein is combined with one or more additional therapeutic agents as described above, the components of the composition are administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0099] In certain embodiments, a compound disclosed herein is combined with one or more additional therapeutic agents in a unitary dosage form for simultaneous administration to a patient, for example as a solid dosage form for oral administration.

[0100] In certain embodiments, a compound disclosed herein is administered with one or more additional therapeutic agents. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of the compound disclosed herein and one or more additional therapeutic agents are both present in the body of the patient.

[0101] Co-administration includes administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound disclosed herein is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound disclosed herein within seconds or minutes. In some embodiments, a unit dose of a compound disclosed herein is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound disclosed herein.

XRPD Data

[0102] In certain embodiments, the crystalline forms are characterized by the interlattice plane intervals determined by an X-ray powder diffraction pattern (XRPD). The diffractogram of XRPD is typically represented by a diagram plotting the intensity of the peaks versus the location of the peaks, i.e., diffraction angle 2θ (two-theta) in degrees. The intensities are often given in parenthesis with the following abbreviations: very strong = vst; strong = st; medium = m; weak = w; and very weak = vw. The characteristic peaks of a given XRPD can be selected according to the peak locations and their relative intensity to conveniently distinguish this crystalline structure from others.

[0103] Those skilled in the art recognize that the measurements of the XRPD peak locations and/or intensity for a given crystalline form of the same compound will vary within a margin of error. The values of degree 2θ allow appropriate error margins. Typically, the error margins are represented by "±". For example, the degree 2θ of about "8.7±0.3" denotes a range from about 8.7+0.3, i.e., about 9.0, to about 8.7-0.3, i.e., about 8.4. Depending on the sample preparation techniques, the calibration techniques applied to the instruments, human operational variation, and etc, those skilled in the art recognize that the appropriate error of margins for a XRPD can be ±0.5; ±0.4; ±0.3; ±0.2; ±0.1; ±0.05; or less. In certain embodiments of the invention, the XRPD margin of error is ±0.2.

[0104] Additional details of the methods and equipment used for the XRPD analysis are described in the Examples section.

[0105] The XRPD peaks for the crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) of the present invention can be found below in Table 1

[0106] Table 1: XRPD peaks for crystalline forms of Formula II Form I

Formula II Form I	
Peak Position [°2θ]	Relative Intensity [%]
5.5	100.0
16.1	87.3
17.9	22.4
19.5	38.0
22.1	61.8
22.5	42.2
23.3	60.4
26.6	27.3
28.5	42.9

Preparation of the Polymorphs

[0107] One method of synthesizing (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (*e.g.* a compound of Formula (I)) has been previously described in PCT Publication No. WO2014/100323. This reference is hereby incorporated herein by reference in its entirety, and specifically with respect to the synthesis of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. One method of synthesizing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (*e.g.* a compound of Formula (II)) is described herein.

[0108] For example, in one aspect, provided is a method of producing a composition comprising one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining a compound of Formula (II) with a suitable solvent or a mixture of suitable solvents to produce a composition comprising one or more polymorphs of the compound of Formula (II). In another aspect, provided is another method of producing a composition comprising one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-

trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate with a suitable solvent or a mixture of suitable solvents.

[0109] The choice of a particular solvent or combination of solvents affects the formation favoring one polymorphic form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate over another. Solvents suitable for polymorph formation may include, for example, methanol, ethanol, water, isopropyl acetate, acetonitrile, tetrahydrofuran, methyl isobutyl ketone, and any mixtures thereof.

[0110] In another aspect, provided is also one or more polymorphs of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced according to any of the methods described herein.

[0111] It should be understood that the methods for preparing the polymorphs described herein (including any polymorphic Form I) may yield quantity and quality differences compared to the methods for preparing sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate produced on laboratory scale.

Formula II, Form I

[0112] In one embodiment, provided is a method of producing a composition comprising polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the method comprises combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a sodium base (*e.g.* sodium hydroxide) in a solvent to produce a composition comprising polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, wherein the solvent is selected

from the group consisting of ethanol, dimethylformamide, and any mixture thereof. In an embodiment, the solvent is a mixture of ethanol and dimethylformamide.

[0113] Provided is also polymorphic Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate prepared by combining (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide with a sodium base (*e.g.* sodium hydroxide) in a solvent, wherein the solvent is selected from the group consisting of ethanol, dimethylformamide, and any mixture thereof. In an embodiment, the solvent is a mixture of ethanol and dimethylformamide.

Uses in Manufacturing of Drug Product

Formula II

[0114] Provided are also a use of the polymorphs described herein in the manufacture of a drug product. The one or more of the polymorphic forms described herein (*e.g.*, polymorphic Form I) may be used as an intermediate in the manufacturing process to produce the drug product.

[0115] In certain embodiments, Form I of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate are used in the manufacture of an active pharmaceutical ingredient.

Articles of Manufacture and Kits

[0116] Compositions comprising one or more of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate and formulated in one or more pharmaceutically acceptable carriers, excipients or other ingredients can be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Accordingly, there also is contemplated an article of manufacture, such as a container comprising a dosage form of one or more of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-

methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, and a label containing instructions for use of the compound(s).

[0117] In some embodiments, the article of manufacture is a container comprising a dosage form of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, and one or more pharmaceutically acceptable carriers, excipients or other ingredients. In one embodiment of the articles of manufacture described herein, the dosage form is a tablet.

[0118] Kits also are contemplated. For example, a kit can comprise a dosage form of a pharmaceutical composition and a package insert containing instructions for use of the composition in treatment of a medical condition. The instructions for use in the kit may be for treating HIV. In certain embodiments, the instructions for use in the kit may be for treating HIV.

[0119] In certain embodiments, the polymorphic and solvate forms described herein may potentially exhibit improved properties. For example, in certain embodiments, the polymorphic and solvate forms described herein may potentially exhibit improved stability. Such improved stability could have a potentially beneficial impact on the manufacture of the Compound of Formula I, such as for example offering the ability to store process intermediate for extended periods of time. Improved stability could also potentially benefit a composition or pharmaceutical composition of the Compound of Formula II. In certain embodiments, the polymorphic and solvate forms described herein may also potentially result in improved yield of the Compound of Formula II, or potentially result in an improvement of the quality of the Compound of Formula II. In certain embodiments, the polymorphic and solvate forms described herein may also exhibit improved pharmacokinetic properties and/or potentially improved bioavailability.

Methods

Synthesis

Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II)

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[0120] (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (20 g) and ethanol (80 mL) were added to a reaction vessel and warmed to about 75 °C. Aqueous sodium hydroxide (22 mL 2 M solution) was added over approximately 30 minutes, after which the slurry was cooled to approximately 20 °C over approximately one hour. Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was collected by filtration, washed with EtOH (50 mL) and dried under vacuum.

[0121] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.63 (t, J = 5.8 Hz, 1H), 7.88 (s, 1H), 7.29 – 7.07 (m, 2H), 5.20 (dd, J = 8.6, 3.6 Hz, 1H), 5.09 (t, J = 4.1 Hz, 1H), 4.52 (m, 3H), 4.35 (dd, J = 12.8, 3.6 Hz, 1H), 3.87 (dd, J = 12.7, 8.7 Hz, 1H), 2.03 – 1.80 (m, 3H), 1.76-1.64 (m, 2H), 1.50 – 1.40 (m, 1H).

Characterization

[0122] Sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was characterized by various analytical techniques, including X-ray powder diffraction pattern (XPPD), differential scanning calorimetry (DSC), thermographic analysis (TGA), and dynamic vapor sorption (DVS) using the procedures described below.

[0123] *X-Ray Powder Diffraction:* XRPD analysis was conducted on a diffractometer (PANanalytical XPERT-PRO, PANanalytical B.V., Almelo, Netherlands) using copper radiation (Cu Kα, λ = 1.5418 Å). Samples were prepared for analysis by depositing the powdered sample in the center of an aluminum holder equipped with a zero background plate. The generator was operated at a voltage of 45 kV and amperage of 40 mA. Slits used were Soller 0.02 rad., antiscatter 1.0°, and divergence. The sample rotation speed was 2 sec. Scans were performed from 2 to 40° 2θ during 5-15 min with a step size of 0.0167° 2θ. Data analysis was performed by X'Pert Highscore version 2.2c (PANalytical B.V., Almelo, Netherlands) and X'Pert data viewer version 1.2d (PANalytical B.V., Almelo, Netherlands).

[0124] The XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure

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1. The calculated XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I represented in Figure 1 was calculated by using Mercury 3.1 Development (Build RC5). Single crystal data for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was input into Mercury 3.1 Development (Build RC5) to calculate the XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. Bulk material, such as stoichiometry arity between the temperature was obtained on a Rigaku Miniflex II XRD using power settings of 40kV, 15mA, scan speed of 2.0000 degrees per minute, a Miniflex 300/600 goniometer and an ASC-6 attachment, a scan range of 3.000 to 40.000 degrees, an incident slit of 1.250 degress, a length limiting slit of 10.0 mm, and SC-70 detector, a receiving slit #1 of 1.250 degrees, continuous scan mode, and a receiving slit #2 of 0.3mm. The sample was prepared by smoothing about 20 mg of solids on a silicon disk mounted in a metal holder. Acquisition temperature was ~21 °C.

[0125] The XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is further represented in Figure 8. The calculated XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I represented in Figure 8 was calculated by using Mercury 3.1 Development (Build RC5). Single crystal data for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was input into Mercury 3.1 Development (Build RC5) to calculate the XRPD pattern for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. Bulk material, such as stoichiometry arity between the temperature was obtained on a Rigaku Miniflex II XRD using power settings of 40kV, 15mA, scan speed of 2.0000 degrees per minute, a Miniflex 300/600 goniometer and an ASC-6 attachment, a scan range of 3.000 to 40.000 degrees, an incident slit of 1.250 degress, a length limiting slit of 10.0 mm, and SC-70 detector, a receiving slit #1 of 1.250 degrees, continuous scan mode, and a receiving slit #2 of

0.3mm. The sample was prepared by smoothing about 20 mg of solids on a silicon disk mounted in a metal holder. Acquisition temperature was ~21 °C.

[0126] Figure 8 compares the calculated XRPD pattern of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I to the experimental XRPD pattern of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I. The comparison shows the degree to which the calculated XRPD and experimental XRPD agree. Strong agreement indicates the solved crystal structure is also the crystal structure of the material analyzed directly by XRPD. This determination can support orthogonal data about the composition of the bulk material, such as stoichiometry.

[0127] XRPD peaks are found in Table 1 above.

[0128] *Differential scanning calorimetry*: Thermal properties of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I were evaluated using a Differential Scanning Calorimetry (DSC) instrument (TA Q1000, TA Instruments, New Castle, DE, USA). Approximately 1 to 10 mg of solid sample was placed in a standard aluminum pan vented with a pinhole for each experiment and heated at a rate of 10 °C/min under a 50 mL/min nitrogen purge. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA). Heat of fusion analysis was conducted by sigmoidal integration of the endothermic melting peak.

[0129] The DSC for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 2.

[0130] *Thermogravimetric analysis*: Thermogravimetric analysis (TGA) of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was performed on a TGA instrument (TA Q500, TA Instruments, New Castle, DE, USA). Approximately 1 to 10 mg of solid sample was placed in an open aluminum pan for each experiment and heated at a rate of 10 °C/min under a 60 mL/min nitrogen purge using. Data analysis was conducted

using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA).

[0131] The TGA for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 3.

[0132] *Dynamic vapor sorption*: The hygroscopicity of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was evaluated at about 25 °C using a dynamic vapor sorption (DVS) instrument (TGA Q5000 TA Instruments, New Castle, DE). Water adsorption and desorption were studied as a function of relative humidity (RH) over the range of 0 to 90% at room temperature. The humidity in the chamber was increased from the initial level 50% RH to 60% RH and held until the solid and atmosphere reached equilibration. The equilibrium test was continued until passed or expired after 10 hours. At this point, RH was raised 10% higher and the process was repeated until 90% RH was reached and equilibrated. During this period, the water sorption was monitored. For desorption, the relative humidity was decreased in a similar manner to measure a full sorption/desorption cycle. The cycle was optionally repeated. All experiments were operated in dm/dt mode (mass variation over time) to determine the equilibration endpoint. Approximately 3 mg of solid sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate was used. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA).

[0133] The DVS for sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I is represented in Figure 4.

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[0134] The indexing data for Formula II Form I is summarized in Table 2 below.

Table 2: Indexing Data for Formula II Form I

Form and Identification	Solvent	Unit Cell Dimensions					
		Distance (Å)			Angle (°)		
		a	b	c	α	β	γ
Formula II Form I	methanol	9.105	13.986	31.384	90	90	90

[0135] The single crystal X-ray diffraction studies were carried out on a Bruker APEX II Ultra diffractometer equipped with Mo K_α radiation ($\lambda = 0.71073$ Å). Crystals of the subject compound were cut into a 0.22 x 0.18 x 0.04 mm section and mounted on a Cryoloop with Paratone-N oil. Data were collected in a nitrogen gas stream at 100 (2) K. A total of 15725 reflections were collected covering the indices, $-9 \leq h \leq 10$, $-13 \leq k \leq 16$, $-37 \leq l \leq 36$. 7163 reflections were found to be symmetry independent, with a R_{int} of 0.0682. Indexing and unit-cell refinement indicated an orthorhombic lattice. The space group, which was uniquely defined by the systematic absences in the data, was found to be $P2_12_12_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model compatible with the proposed structure.

[0136] All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 2A. The absolute stereochemistry was set to conform to previously studied samples of the same compound.

[0137] The single crystal X-ray crystallography data for Formula II Form I is summarized in Table 2A below.

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Table 2A: Single Crystal Data for Formula II, Form I

C42 H34 F6 N6 Na2 O10	Acquisition Temp.	Space Group	Z	Unit Cell Dimensions					
	103(2) K	P212121	4	Distance (Å)			Angle (°)		
Form and Identification	Solvent	Solvent in lattice	Density (Mg/m^3)	a	b	c	α	β	γ
Formula II Form I	Ethanol/DMF	none	1.614	8.9561 (10)	13.9202 (14)	31.115 (3)	90	90	90

Dissolution Profile

[0138] The intrinsic dissolution profile of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) Form I of the present invention and the intrinsic dissolution profiles of Form I and Form III of Formula I, the free acid, (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (disclosed in the co-pending United States Provisional Application 62/015,238 filed on June 20, 2014 titled CRYSTALLINE FORMS OF (2R,5S,13AR)-8-HYDROXY-7,9-DIOXO-N-(2,4,6-TRIFLUOROBENZYL)-2,3,4,5,7,9,13,13A-OCTAHYDRO-2,5-METHANOPYRIDO[1',2':4,5]PYRAZINO[2,1-B][1,3]OXAZEPINE-10-CARBOXAMIDE), were measured by characterizing API dissolution from a constant surface area. Approximately 150 mg of the drug substance was compressed at 1500 psi for approximately 3 seconds using a hydraulic press (Carver Press, Fred Carver, NJ, USA). The compressed drug substance formed a flat disk (surface area ~0.49 cm^2), which was mounted onto a dissolution apparatus (VanKel Industries Inc., Edison, NJ, VK7000, W1120A-0288). The rotating disk (100 rpm) was then lowered into the dissolution medium (500 mL of 0.01N HCl) which was equilibrated to 37±1°C. Samples were pulled at pre-determined time points and drug concentrations were measured using an appropriate UPLC-UV method. The intrinsic dissolution rate constant (K) was calculated using the following equation:

$$C = \frac{KA}{V}t$$

[0139] Where C is the concentration of the active at time t, A is the surface area of the

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tablet (~0.49 cm^2) and V is the volume of the media (500 mL). Note that the term active as used herein refers to the parent molecule, whose structure is shared by both Formula I and Formula II.

[0140] The dissolution profiles can be found in Figure 5.

Solubility

[0141] The solubility of the sodium form of the present invention and the free acid, (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III in biorelevant media was determined at room temperature as a function of time. Solubility was determined in the following biorelevant media: 0.1 mM Fasted-State Simulated Gastric Fluid (FaSSGF) pH 1.6 (0.08 mM taurocholate, 0.02 mM lecithin, 34.2 mM NaCl); 18.75 mM Fed-State Simulated Intestinal Fluid (FeSSIF) pH 5 (15 mM taurocholate, 3.75 mM lecithin, 0.12 M NaCl); and 3.75mM Fasted-State Simulated Intestinal Fluid (FaSSIF) pH 5 (3 mM taurocholate, 0.75 mM lecithin, 0.10 M NaCl). Approximately 20 mg of the drug substance was mixed on a magnetic stir-plate in 50 mL of biorelevant media. Samples (~1 mL) were pulled every 5-10 min for 2 hours. The samples were immediately filtered/centrifuged for 10 min in a Spin-X tube equipped with a 0.45 µm nylon filter. The resulting filtrate was analyzed using an appropriate UPLC-UV method.

[0142] The solubility profiles in FaSSGF can be found in Figure 6. The solubility profiles in FeSSIF and FaSSIF can be found in Figure 7.

Bioavailability

[0143] The bioavailability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate (Formula II) Form I was compared to the bioavailability of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I) Form III.

[0144] Each dosing group consisted of 6 male, non-naïve purebred beagle dogs. At dosing, the animals weighed between 10 to 13 kg. The animals were fasted overnight prior to

dose administration and up to 4 hr after dosing. Each subject was pre-treated with pentagastrin (6 µg/kg) and dosed 30 minutes later with a single 25 mg strength tablet of Formula II Form I or Formula I Form III. Each subject was given 10 mL of water to aid in swallowing.

[0145] Serial venous blood samples (approximately 1 mL each) were taken from each animal at 0, 0.250, 0.483, 0.583, 0.750, 1.00, 1.50, 2.00, 4.00, 8.00, 12.0, and 24.0 hours after dosing. The blood samples were collected into Vacutainer™ tubes containing EDTA-K2 as the anti-coagulant and were immediately placed on wet ice pending centrifugation for plasma. An LC/MS/MS method was used to measure the concentration of the test compound in plasma. An aliquot of 100 µL of each plasma sample was added to a clean 96 well plate, and 400 µL of cold acetonitrile/internal standard solution (ACN)/(ISTD) was added. After protein precipitation, an aliquot of 110 µL of the supernatant was transferred to a clean 96-well plate and diluted with 300 µL of water. An aliquot of 25 µL of the above solution was injected into a TSQ Quantum Ultra LC/MS/MS system utilizing a Hypersil Gold C_{18} HPLC column (50 X 3.0 mm, 5 µm; Thermo-Hypersil Part # 25105-053030). An Agilent 1200 series binary pump (P/N G1312A Bin Pump) was used for elution and separation, and an HTS Pal autosampler (LEAP Technologies, Carrboro, NC) was used for sample injection. A TSQ Quantum Ultra triple quadrupole mass spectrometer was utilized in selective reaction monitoring mode (Thermo Finnigan, San Jose, CA). Liquid chromatography was performed using two mobile phases: mobile phase A contained 1% acetonitrile in 2.5 mM ammonium formate aqueous solution with pH of 3.0, and mobile phase B contained 90% acetonitrile in 10 mM ammonium formate with pH of 4.6. Non-compartmental pharmacokinetic analysis was performed on the plasma concentration-time data. The resulting data are shown in Table 3: F (%) refers to oral bioavailability; AUC refers to area under the curve and is a measure of total plasma exposure of the indicated compound; C_{max} refers to the peak plasma concentration of the compound after administration.

Table 3: Bioavailability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I and (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide Form III.

Form	Formulation	%F	AUC_{inf} (uM x hr)	C_{max} (uM)
Formula I Form III	Dry Granulation[1]	10 ± 6	27 ± 13	6 ± 2
Formula II Form I	Dry Granulation[2]	28 ± 7	71 ± 16	13 ± 1

[1] *Tablet:* 30% active, 56% microcrystalline cellulose, 13% croscarmellose sodium, 1% magnesium stearate
[2] *Tablet:* 30% active, 56% microcrystalline cellulose, 13% croscarmellose sodium, 1% magnesium stearate

Stability

[0146] The stability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I was tested. As seen in Table 4, below, the compound is stable after four weeks of storage under accelerated conditions. In Table 5, AN refers to area normalization and is the relative peak area of the active with respect to other impurities and components contained in the sample. LS refers to labile strength and is the amount of active present relative to the theoretical amount.

Table 4: Stability of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I

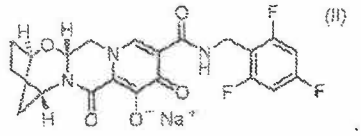
Storage Conditions	Storage Time (weeks)	% AN	% LS
Starting material	0	94.4 ± 0.1	99.8 ± 0.1
40°C (closed)	1	95.2 ± 0.3	108.0 ± 0.2
	2	94.4 ± 0.1	102.4 ± 0.1
	4	94.4 ± 0.0	97.0 ± 0.0
40°C/75% RH (open)	1	94.9 ± 0.1	103.3 ± 6.9
	2	94.4 ± 0.0	108.5 ± 0.4
	4	94.4 ± 0.0	102.9 ± 0.1
25°C/60% RH (open)	1	95.0 ± 0.2	104.8 ± 0.1
	2	94.4 ± 0.1	101.6 ± 0.1
	4	94.4 ± 0.0	103.0 ± 0.8

[0147] Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application. Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

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What is Claimed:

1. A compound of Formula II:



(II)

2. The compound of claim 1, characterized by being crystalline.

3. The compound of claim 2, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 5.5°, 16.1°, and 23.3° 2-θ ± 0.2° 2-θ.

4. The compound of claim 3, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 22.1°, and 28.5° 2-θ ± 0.2° 2-θ.

5. The compound of claim 4, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 22.5 and 19.5° 2-θ ± 0.2° 2-θ.

6. The compound of claim 5, wherein the x-ray powder diffraction (XRPD) pattern has further peaks at about 26.6° and 17.9° 2-θ ± 0.2° 2-θ.

7. The compound of claim 2, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 1.

8. The compound of claim 2, characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 2.

9. The compound of claim 2, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in Figure 4.

10. The compound of any one of claims 1 to 9, characterized in being partially or fully hydrated.

11. The compound of any one of claims 1 to 9, characterized in being anhydrous or essentially anhydrous.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 11, and a pharmaceutically acceptable carrier or excipient.

13. The pharmaceutical composition of claim 12, further comprising one to three additional therapeutic agents.

14. The pharmaceutical composition of claim 13, wherein the additional therapeutic agents are each anti-HIV drugs.

15. The pharmaceutical composition of claim 13 or claim 14, wherein the additional therapeutic agents are each independently selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors

of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and other drugs for treating HIV.

16. The pharmaceutical composition of any one of claims 12 to 14, wherein at least two of the additional therapeutic agents are each HIV nucleoside inhibitors of reverse transcriptase.

17. The pharmaceutical composition of claim 12, further comprising tenofovir disoproxil fumarate and emtricitabine.

18. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide and emtricitabine.

19. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide hemifumarate and emtricitabine.

20. The pharmaceutical composition of any one of claims 12 to 18, wherein the pharmaceutical composition is in a unit dosage form.

21. The pharmaceutical composition of claim 20, wherein the unit dosage form is a tablet.

22 Use of a compound of any one of claims 1 to 11 for treating or prophylactically preventing an HIV infection.

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23. Use of a compound of any one of claims 1 to 11 for the manufacture of a medicament for treating or prophylactically preventing an HIV infection.

24. A compound of any one of claims 1 to 11 for use in a method for treating or prophylactically preventing an HIV infection.

25. A method for treating or prophylactically preventing an HIV infection in a human in need thereof, comprising administering to the human a therapeutically effective amount of a compound of any one of claims 1 to 11.

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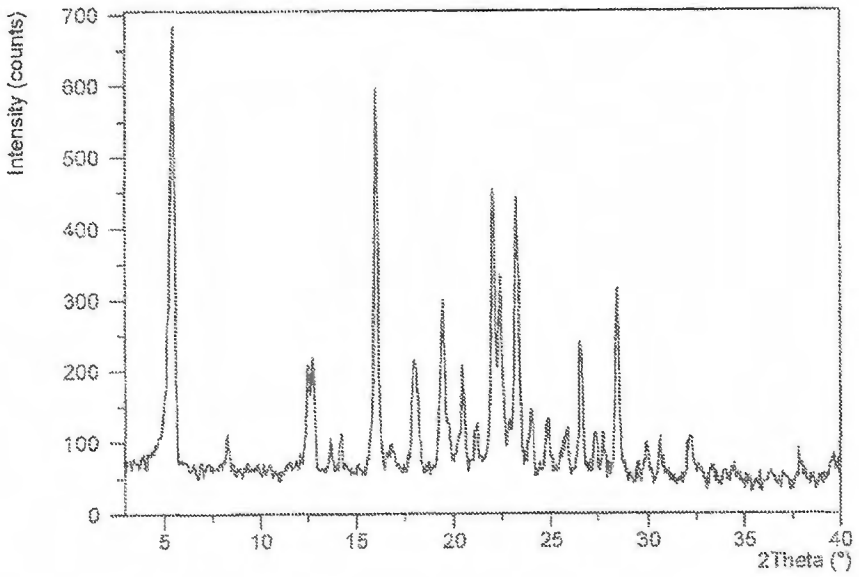

Intensity (counts)
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300
200
100
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5
10
15
20
25
30
35
40
2Theta (°)

Figure 1

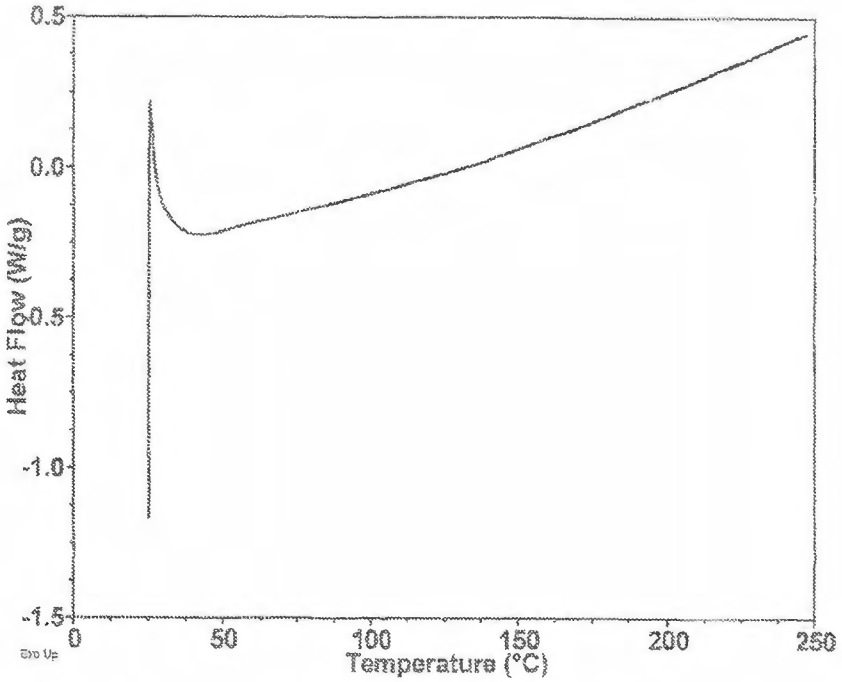

0.5
0.0
-0.5
-1.0
-1.5
Heat Flow (W/g)
Exo Up
0
50
100
150
200
250
Temperature (°C)

Figure 2

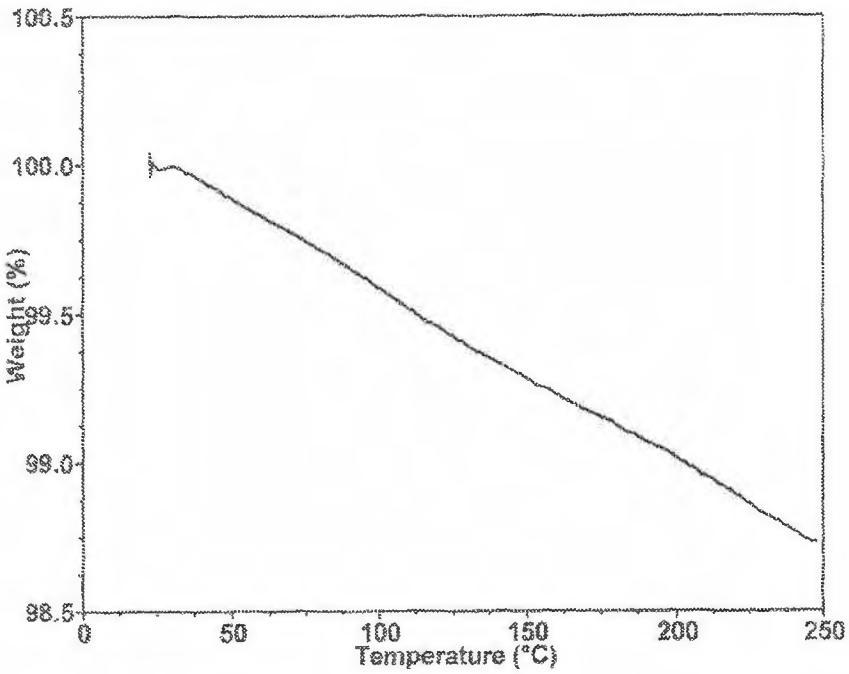

100.5
100.0
99.5
99.0
98.5
Weight (%)
0
50
100
150
200
250
Temperature (°C)

Figure 3

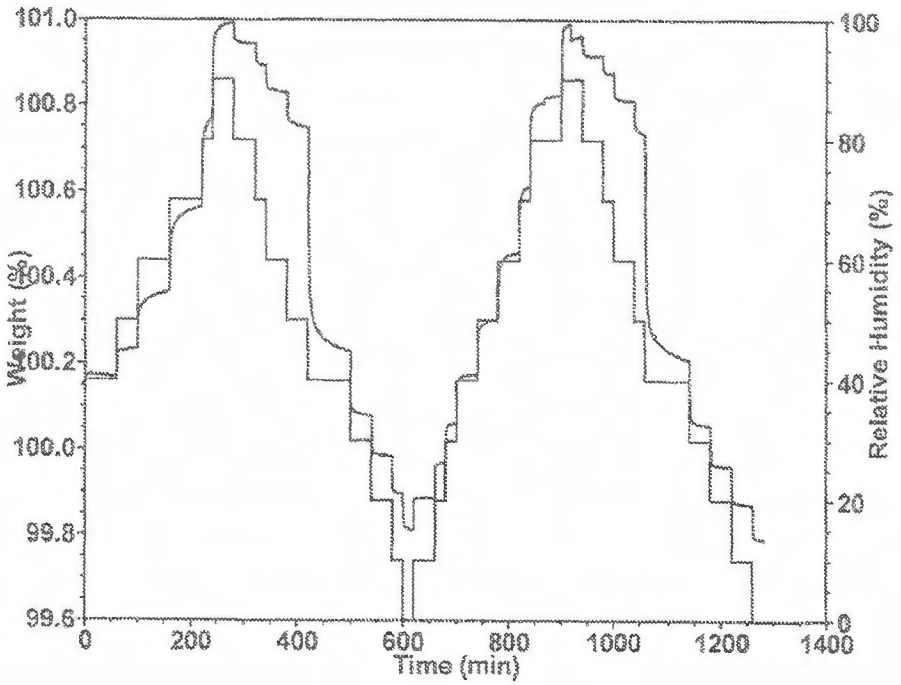

101.0
100.8
100.6
100.4
100.2
100.0
99.8
99.6
Weight (%)
0
200
400
600
800
1000
1200
1400
Time (min)
100
80
60
40
20
0
Relative Humidity (%)

Figure 4

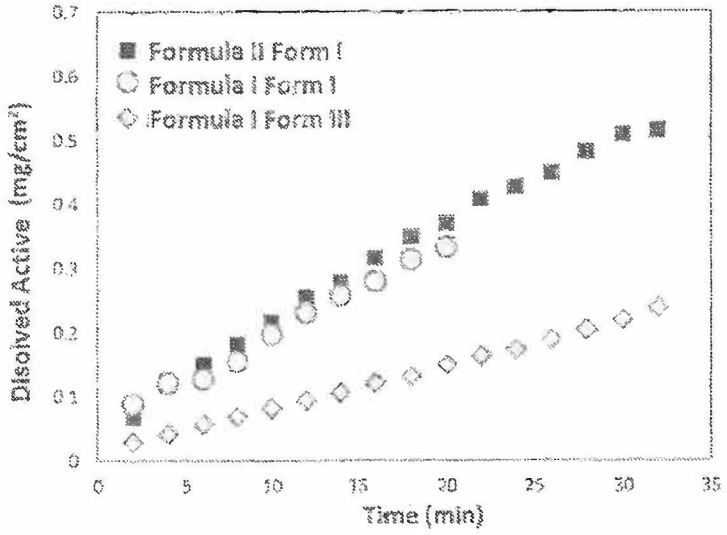


Figure 5

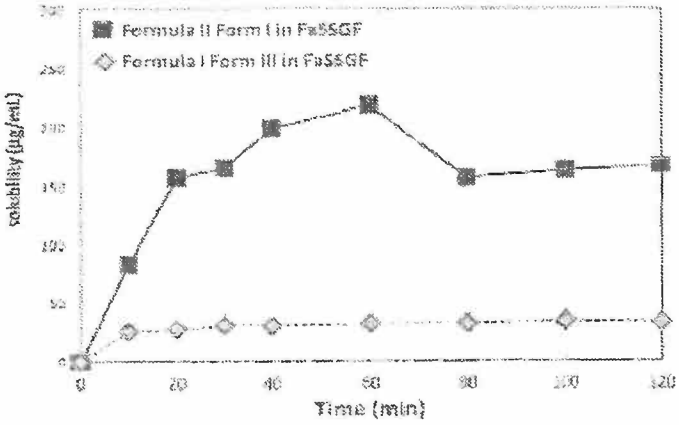


Figure 6

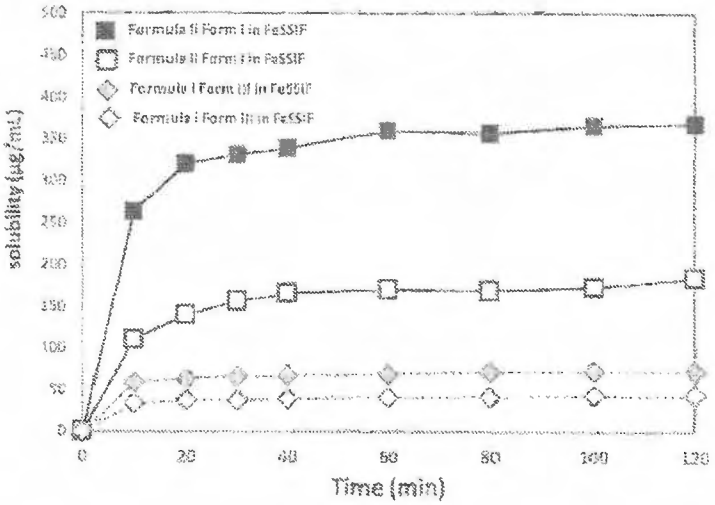

Formula II Form I in FeSSIF
Formula II Form I in FeSSIF
Formula I Form III in FeSSIF
Formula I Form III in FeSSIF
solubility (µg/mL)
0
20
40
60
80
100
120
Time (min)

Figure 7

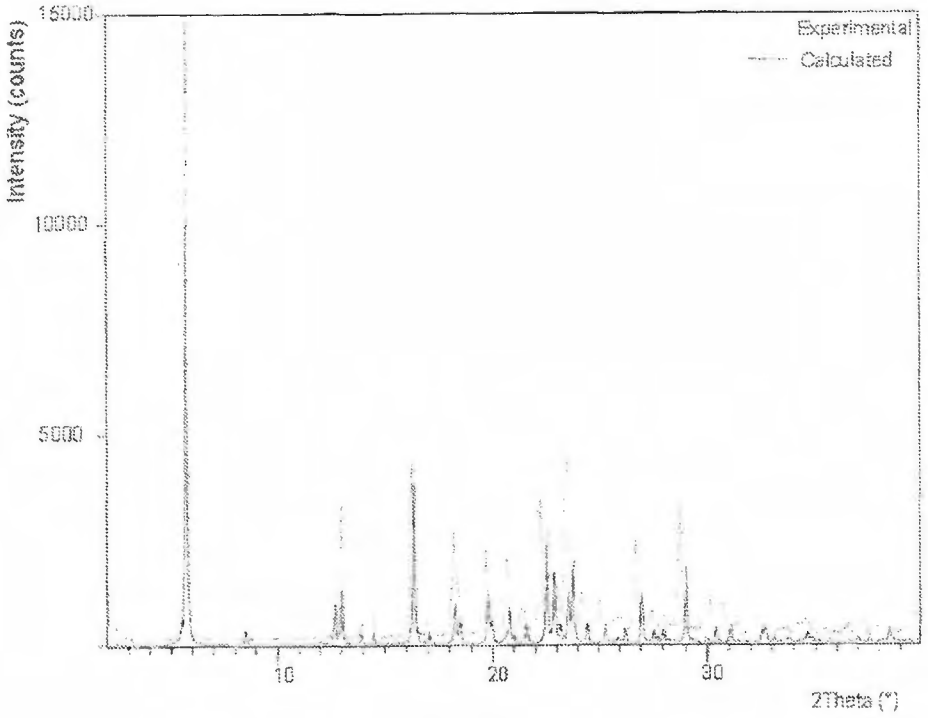

15000
10000
5000
Intensity (counts)
Experimental
Calculated
10
20
30
2Theta (°)

Figure 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/036757

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/14 A61K31/535 A61P31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) cited in the application example 42 claim 32	1-25
A	EP 2 465 580 A1 (GLAXOSMITHKLINE LLC [US]; SHIONOGI & CO [JP]) 20 June 2012 (2012-06-20) claims 1-6	1-25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2015	09/09/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Götz, Gerhard

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/036757

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014100323 A1	26-06-2014	CA 2893843 A1	26-06-2014
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		VN 34404 A1	25-07-2013
		WO 2006116764 A1	02-11-2006

Form PCT/ISA/210 (patent family annex) (April 2005)

Bibliographic Data

Application No: 17/738,803

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /JESSICA WORSHAM/ (Examiner's Signature) ____ (Initials)

Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/06/2022	424	1615	1147-US-P2C2DC
RULE			

APPLICANTS

Gilead Sciences, Inc., Foster City, CA.

INVENTORS

Benjamin Micah Collman, San Mateo, CA, UNITED STATES

Lei Hong, Cupertino, CA, UNITED STATES

Joanna M. Koziara, Foster City, CA, UNITED STATES

CONTINUING DATA

This application is a CON of 16987081 08/06/2020ABN

16987081 is a CON of 16713380 12/13/2019ABN

16713380 is a CON of 15346335 11/08/2016 PAT 10548846

15346335 has PRO of 62399999 09/26/2016

15346335 has PRO of 62253042 11/09/2015

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

05/10/2022

STATE OR COUNTRY

UNITED STATES

ADDRESS

GILEAD SCIENCES, INC

333 LAKESIDE DR

FOSTER CITY, CA 94404

UNITED STATES

FILING FEE RECEIVED

$2,620

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	735	((("GILEAD") near3 ("SCIENCES") near3 ("INC"))).AS,AANM.	(USPAT)	OR	ON	ON	2022/12/01 01:36 PM
L2	127	((("COLLMAN") near3 ("Benjamin")) OR (("HONG") near3 ("Lei")) OR (("KOZIARA") near3 ("Joanna"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:37 PM
L3	2	"10548846".pn.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:37 PM
L4	4491	tenofovir ADJ alafenamide	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:43 PM
L5	2629	L4 SAME emtricitabine	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:43 PM
L6	2067	L5 AND tablet	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO,	OR	ON	ON	2022/12/01 01:43 PM

			MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)				
L7	104	L5 AND pyrazino	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2022/12/01 01:43 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1002
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CAS SciFinder®

Task History

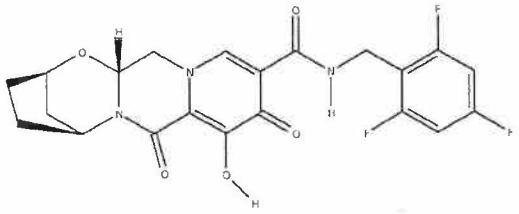
Initiating Search

December 1, 2022, 1:50PM

Substances:

Filtered By:

Stereochemistry: Absolute Stereo Match, Absolute Stereo Mirror Image



Structure Match: As Drawn

Search Tasks

Task	Search Type	View
Returned Substance Results + Filters (148)	Substances	View Results
Exported: Retrieved Related Reference Results + Filters (2)	References	View Results

Filtered By:

Publication Year: 2012 to 2016

Search Within Results: emtricitabine, tenofovir

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References (2)

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1

Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile

By: Tsiang, Michael, Jones, Gregg S., Goldsmith, Joshua, Mulato, Andrew, Hansen, Derek, Kan, Elaine, Tsai, Lueming, Bam, Rajesh A., Stepan, George, Stray, Kirsten M., et al

Antimicrobial Agents and Chemotherapy (2016), 60(12), 7086-7097 | Language: English, Database: CAplus and MEDLINE

Bictegravir (BIC; GS-9883), a novel, potent, once-daily, unboosted inhibitor of HIV-1 integrase (IN), specifically targets IN strand transfer activity (50% inhibitory concentration [IC50] of 7.5 ± 0.3 nM) and HIV-1 integration in cells. BIC exhibits potent and selective in vitro antiretroviral activity in both T-cell lines and primary human T lymphocytes, with 50% effective concentrations ranging from 1.5 to 2.4 nM and selectivity indexes up to 8,700 relative to cytotoxicity. BIC exhibits synergistic in vitro antiviral effects in pairwise combinations with tenofovir alafenamide, emtricitabine, or darunavir and maintains potent antiviral activity against HIV-1 variants resistant to other classes of antiretrovirals. BIC displayed an in vitro resistance profile that was markedly improved compared to the integrase strand transfer inhibitors (INSTIs) raltegravir (RAL) and elvitegravir (EVG), and comparable to that of dolutegravir (DTG), against nine INSTI-resistant site-directed HIV-1 mutants. BIC displayed statistically improved antiviral activity relative to EVG, RAL, and DTG against a panel of 47 patient-derived HIV-1 isolates with high-level INSTI resistance; 13 of 47 tested isolates exhibited >2-fold lower resistance to BIC than DTG. In dose-escalation experiments conducted in vitro, BIC and DTG exhibited higher barriers to resistance than EVG, selecting for HIV-1 variants with reduced phenotypic susceptibility at days 71, 87, and 20, resp. A recombinant virus with the BIC-selected M50I/R263K dual mutations in IN exhibited only 2.8-fold reduced susceptibility to BIC compared to wild-type virus. All BIC-selected variants exhibited low to intermediate levels of cross-resistance to RAL, DTG, and EVG (<8-fold) but remained susceptible to other classes of antiretrovirals. A high barrier to in vitro resistance emergence for both BIC and DTG was also observed in viral breakthrough studies in the presence of constant clin. relevant drug concentrations. The overall virol. profile of BIC supports its ongoing clin. investigation in combination with other antiretroviral agents for both treatment-naive and -experienced HIV-infected patients.

Keywords: bictegravir HIV1 integrase strand transfer inhibitor antiviral drug resistance

Substances (9) Biosequences (0) Cited By (166)

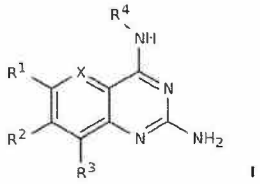
Preparation of toll-like receptor modulating 4,6-diamino-pyrido[3,2-d]pyrimidines and use in mono- and combination therapy

By: Akinyanju, Evangelos; Chen, Gregory; Mackman, Richard L.; Metobo, Samuel E.; Mish, Michael R.; Pyun, Hyung-jung; Zablocki, Jeff

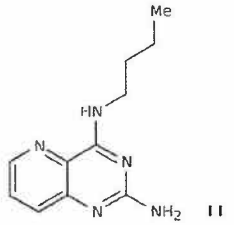
World Intellectual Property Organization, WO2016141092 A1 20160909 | Language: English, Database: CAplus

The invention relates to preparation of aminopyridopyrimidines of formula I wherein all the variables are as defined in the disclo sure, as toll like receptor modulators, and pharmaceutical compositions containing the same. The example compound II was prepared according the disclosed procedure and was tested for modulatory activity of toll-like receptors (data shown). Compounds I can modulate toll-like receptors (e.g. TLR-8), and can be used in treatment and prevention of various diseases in mono and combin ation therapy.

Keywords: aminopyridopyrimidine preparation toll like receptor modulator disease treatment prevention



I



II

PatentPak available

Substances (637) Reactions (1,805) Cited By (11)

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Dated: April 5, 2023
Electronic Signature for Frances Tsai: /Frances Tsai/

Docket No.: 1147-US-P2C2DC
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Benjamin Micah Collman et al.

Application No.: 17/738,803

Confirmation No.: 2232

Filed: May 6, 2022

Art Unit: 1615

For: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Examiner: J. N. Worsham

RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated December 6, 2022, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

A request for a one-month extension of time is submitted herewith. Accordingly, this response is timely filed.

#5005970v1

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of the claims in the application:

1-51. (Canceled)

52. (Previously Presented) A tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

53. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof.

54. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof.

55. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

56. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I.

57. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 25 mg tenofovir alafenamide as tenofovir alafenamide fumarate.

58. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 28 mg tenofovir alafenamide hemifumarate.

59. (Previously Presented) The tablet of claim 52, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

60. (Previously Presented) The tablet of claim 52, wherein the tablet has a total weight of less than 1000 mg.

61. (Previously Presented) The tablet of claim 60, wherein the tablet has a total weight of less than 800 mg.

62. (Previously Presented) The tablet of claim 61, wherein the tablet has a total weight of less than 730 mg.

63. (Previously Presented) The tablet of claim 52, wherein the tablet contains less than 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

64. (Previously Presented) The tablet of claim 52, wherein the tablet contains less than 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

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REMARKS

Claims 52-64 are currently pending.

Claim Rejections Under 35 U.S.C. § 102

Claims 52-59 are rejected under 35 U.S.C. § 102(a)(2) as allegedly being anticipated by Carra et al. (WO2015/196116, hereinafter "Carra 1") and by Carra et al. (US2016/0016973, hereinafter "Carra 2").

Applicant respectfully submits that Carra 1, Carra 2, and the instant application are commonly owned by Gilead Sciences, Inc. The ownership of Carra 1 and Carra 2 and the instant application is further evidenced by the assignments recorded with the United States Patent and Trademark Office:

	Publication No.	Application No.	Assignment Reel/Frame	Recorded
Carra 1	WO2015/196116	PCT/US2015/036757	035878/0643	June 22, 2015
Carra 2	US2016/0016973	14/744,915		
Instant application	a child of	15/346,335	041889/0981	April 6, 2017

Carra 1 was published on December 23, 2015, and Carra 2 was published on January 21, 2016. As such, both references were published after the effective filing date of the instant application, November 9, 2015. Accordingly, Carra 1 and Carra 2 are not available as prior art against the instantly claimed invention. Withdrawal of the rejection is therefore respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

Claims 52-64 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Carra 1 in view of Dahl et al. (US2007/0099902) and over Carra 2 in view of Dahl et al. (US2007/0099902).

As noted above, Carra 1 and Carra 2 are not available as prior art against the instantly claimed invention.

Regarding the secondary reference, the Examiner cites Dahl et al. for its teaching of a bilayer tablet of efavirenz, emtricitabine, and tenofovir. However, Dahl et al. does not teach or suggest a tablet comprising tenofovir alafenamide, much less a tablet comprising the compound of Formula I. Accordingly, Dahl et al. alone does not render the instant claims obvious.

In view of the foregoing, applicant respectfully requests withdrawal of the rejection.

Obviousness-Type Double Patenting

The Office has rejected claims 52-64 on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-10 of U.S. Patent No. 10,548,846.

Without conceding the validity of the Examiner's remarks, Applicant submits herewith a Terminal Disclaimer under 31 C.F.R. 1.321 over U.S. Patent No. 10,548,846. The cited reference patent and the instant application are commonly owned by Gilead Sciences, Inc. Withdrawal of the nonstatutory obviousness-type double patenting rejection is respectfully requested.

CONCLUSION

Applicant requests reconsideration of this application in view of the above amendments and remarks. If the Office finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147-US-P2C2DC from which the undersigned is authorized to draw.

Dated: April 5, 2023

Respectfully submitted,

Electronic signature: /Donna Johnson Gressler/
Donna Johnson Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 574-3000
Agent For Applicant

D39

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/688326/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Genvoya

International non-proprietary name: elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/004042/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5520
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List of abbreviations

3TC	lamivudine
ABC	abacavir
ADME	absorption, distribution, metabolism, and elimination
aGFR	actual glomerular filtration rate
AN(C)OVA	analysis of (co) variance
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
BCS	Biopharmaceutics Classification System
BMD	bone mineral density
BMI	body mass index
COBI, C	cobicistat (Tybost)
C telopeptide	type I collagen C telopeptide
CQA	Critical Quality Attribute
ddI	didanosine
dNTP	2' deoxynucleoside triphosphate
DoE	Design of experiments
DRV, D	darunavir
DSC	Differential Scanning Calorimetry
DTG	dolutegravir
DXA	dual-energy x ray absorptiometry
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated)
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eGFRCG	estimated glomerular filtration rate calculated using the Cockcroft Gault equation
ESRD	end-stage renal disease
EU	European Union
EVG, E	elvitegravir (Vitekta)
FAS	Full Analysis Set
FTC, F	emtricitabine (Emtriva)
FTC-DP	emtricitabine diphosphate

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GC	Gas Chromatography
HDL	high density lipoprotein
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
INSTI	integrase strand transfer inhibitor
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
KF	Karl Fischer titration
LDL	low-density lipoprotein
LOCF	last observation carried forward
LSM	least-squares mean
M = F	missing = failure
MA	Marketing Authorisation
mg	milligram
MS	Mass Spectrometry
mtDNA	mitochondrial DNA
N or n	number of subjects in a population (N) or subset (n)
N/A	Not applicable
NAS	New Active Substance
NCEP	National Cholesterol Education Program
NMR	Nuclear Magnetic Resonance
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OATP	organic anion transporting polypeptide
P1NP	procollagen type 1 N-terminal propeptide
PAR	Proven Acceptable Range
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia

PI	protease inhibitor
PRT	proximal renal tubulopathy
PIP	Paediatric Investigational Plan
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QbD	Quality by design
RBP	retinol binding protein
RH	Relative humidity
rNTP	ribonucleoside triphosphate
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SI	selectivity index (ratio of CC50 to IC50)
SmPC	Summary of Product Characteristics
STB	elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild)
TAF	tenofovir alafenamide
TAF fumarate	tenofovir alafenamide fumarate
TAM	thymidine analogue mutation
TDF	tenofovir disoproxil fumarate (Viread)
TFV	tenofovir
TFV DP	tenofovir diphosphate
TSE	Transmissible Spongiform Encephalopathy
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada)
UACR	urine albumin to creatinine ratio
UGT	uridine diphosphate glucuronosyltransferase
UPCR	urine protein to creatinine ratio
UPLC	Ultra-high performance liquid chromatography
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 28 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Genvoya, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 June 2014.

The applicant applied for the following indication: treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and adolescents 12 years of age and older, without any known mutations associated with resistance to the individual components of Genvoya (see sections 4.2 and 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tenofovir alafenamide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 off Regulation (EC) No 1901/2006, the application included an EMA Decision P/0026/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0026/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New Active Substance Status

The applicant requested the active substance tenofovir alafenamide contained in the above medicinal product to be considered as a new active substance in comparison to the known derivative tenofovir disoproxil previously authorised in the Union as active substance in Atripla, Eviplera, Stribild, Truvada, and Viread, and claimed that tenofovir alafenamide differs significantly in properties with regard to safety and efficacy from the already authorised substance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18-10-2012 and 25-04-2013. The Scientific Advice pertained to non-clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Pierre Demolis

- The application was received by the EMA on 28 November 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 March 2015 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2015 .
- During the PRAC meeting on 10 April 2015, the PRAC adopted an RMP Advice and assessment overview .
- During the meeting on 23 April 2015 the CHMP agreed on the consolidated List of Questions to be sent to the applicant .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2015
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 June 2015 .
- During the PRAC meeting on 9 July 2015, the PRAC adopted an RMP Advice and assessment overview .
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 September 2015 .
- During the PRAC meeting on 10 September 2015, the PRAC adopted an RMP Advice and assessment overview .
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Genvoya.

2. Scientific discussion

2.1. Introduction

HIV-1 infection is a life threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide.

Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naive HIV infected patients, current treatment guidelines suggest that initial therapy consist of two nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI) or an integrase strand-transfer inhibitor (INSTI). Virologically suppressed, HIV infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once daily fixed dose combination (FDC) regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes.

The success of ART means that morbidity and mortality in the HIV infected population is increasingly driven by non AIDS-associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long term safety, and adherence to potent ART regimens. There remains a significant medical need for new, effective therapies that take into consideration the non-HIV comorbidities, demographics of the aging HIV infected population, antiretroviral (ARV) resistance and regimen simplification.

Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and death. Moreover, HIV associated nephropathy present in up to 30% of patients and this is a common cause of end-stage renal disease (ESRD) requiring dialysis.

ART with proven efficacy and safety in the both elderly and young patients is important; limited data and treatment options are available in both populations. The elderly have increased risks for comorbidities, including those related to renal and bone. There are specific and complex challenges for the treatment of adolescents, who also represent the population that will require ART for the longest time.

Tenofovir (TFV) is a nucleotide analogue with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, has improved bioavailability, and delivers high systemic exposures of TFV with favourable efficacy and safety data. TDF is a preferred NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

While TDF is used broadly in the treatment of HIV-1 infection, an important identified risk with its use is nephrotoxicity, which is associated with increased creatinine in some patients, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi syndrome). These risks necessitate increased renal monitoring with use of TDF-containing products, placing burden on the patient and healthcare provider. Reductions in bone mineral density (BMD) have also been seen after the initiation of ART, with larger decreases in BMD observed with TDF than with other NRTIs.

Tenofovir alafenamide (TAF) is an investigational oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF. The distinct metabolism of TAF offers the potential for an improved safety profile compared with TDF.

2.2. Quality aspects

2.2.1. Introduction

Genvoya is a medicinal product containing tenofovir alafenamide (as fumarate), a new active substance previously not authorised within the Union and three known active substances: elvitegravir, cobicistat, and emtricitabine.

The finished product is presented as film-coated tablets containing the following active substances: 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as 11.2 mg of the fumarate).

Other ingredients of the tablet core are: lactose (as monohydrate), microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, silicon dioxide, sodium lauryl sulphate, and magnesium stearate. Ingredients of the film-coating are: polyvinyl alcohol (E1203), titanium dioxide (E171), polyethylene glycol (E1521), talc (E553b), indigo carmine aluminium lake (E132), and iron oxide yellow (E172).

The product is packaged in high density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner containing 30 film-coated tablets. Each bottle contains silica gel desiccant and polyester coil.

2.2.2. Active Substance

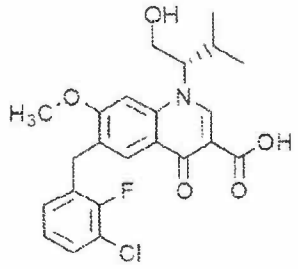
Elvitegravir

The information on chemistry, manufacturing and control of elvitegravir active substance has been previously assessed through centralised procedure and approved in the EU as part of the marketing authorisation applications for Vitekta (EU/1/13/883/001-2) and Stribild (EU/1/13/830/001-2).

The Module 3.2.S sections of the dossier for elvitegravir provided by the Applicant are identical to the 3.2.S sections submitted and approved with the aforementioned marketing authorisations.

General information

The chemical name of elvitegravir is 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and has the following structure:



Elvitegravir appears as a white to pale yellow crystalline non-hygroscopic powder, sparingly soluble in methanol and ethanol and practically insoluble in water and aqueous solutions at pH 2.0 to 8.3. Its pKa is 5.6 and the distribution coefficient Log D is 4.5 (at pH 6.8).

Elvitegravir exhibits polymorphism and appears in three polymorphs. The most thermodynamically stable polymorphic form has been determined and the crystallisation process is designed to consistently deliver this form. It contains a single asymmetric centre at C-11. The absolute configuration was established by single crystal X-ray crystallography and has been determined to be of "S" configuration. Enantiomeric purity is controlled routinely by chiral HPLC.

Manufacture, characterisation and process controls

Elvitegravir is manufactured in six well-defined synthetic steps using commercially available starting materials. The active substance is obtained from three manufacturers. The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Information about the formation, presence, origin and fate of impurities during manufacture has been satisfactorily discussed.

Representative batch analysis data provided for all three proposed manufacturing sites produced with the proposed synthetic route show that the active substance can be manufactured reproducibly.

Specification

The elvitegravir active substance specification includes tests and limits for appearance (visual inspection), identification (IR, HPLC, UV), water content (Ph. Eur.), assay (HPLC), enantiomeric purity (chiral HPLC), impurities (HPLC), residual solvents (GC), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), polymorphic form (DSC-Ph. Eur.), and particle size (laser light scattering).

Impurities, including genotoxic impurities, have been evaluated and qualified where necessary. The proposed limits are found to be acceptable from a safety point of view and therefore they are considered justified.

A microbial limit test for the active substance is not required in accordance with ICH Q6A because the latter steps of the active substance manufacturing process conducted in aqueous organic solvent mixtures and are expected to limit microbial content. In addition, confirmatory testing demonstrated that elvitegravir is moderately to completely inhibitory to microbial growth. Furthermore, data presented in the dossier indicate that no significant bioburden is present.

The analytical methods have been well described and validated according to ICH Q2 (R1) and are suitable to control the quality of the active substance.

Batch analysis data on commercial scale batches of the active substance manufactured by all three proposed manufacturers have been provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process regardless of the manufacturing site.

Stability

Stability studies have been conducted for four commercial scale batches from the first manufacturer and one batch from the second under ICH long term (25 °C±2 °C/60±5% RH) and accelerated conditions (40 °C±2 °C / 75%±5% RH) in the proposed packaging. Results were submitted for up 36 months at long term conditions and for up to 9 months at accelerated.

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Long term and accelerated stability samples were tested for appearance, assay, impurity content, and water content. The enantiomeric purity and polymorphic form were tested annually during the long term studies. Enantiomeric purity was determined for 1 batch, at the beginning and end of the accelerated study and polymorphic form was tested at the end of the accelerated study. The analytical methods used are stability indicating.

All parameters remained within the specification limits under both conditions over the duration of study for all four batches. The data show no discernible trends for assay, total impurity content, individual specified impurities, degradation products or any other tested parameter.

In addition, a photostability study of elvitegravir has been assessed as per the ICH Q1B Guideline on one batch from the second manufacturer. No significant difference was observed between the control sample and exposed sample in appearance, assay, impurity content, polymorphic form and enantiomeric purity. The data indicate that elvitegravir is not sensitive to light.

Based on the presented stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is acceptable.

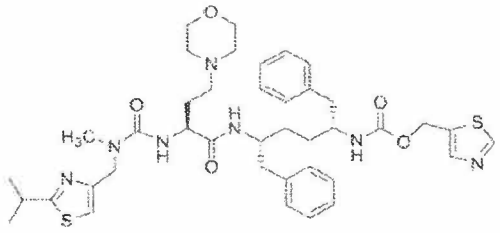
Cobicistat

The information on chemistry, manufacturing and control of cobicistat active substance has been previously assessed through centralised procedure and approved in the EU as part of the marketing authorisation applications for Tybost (EU/1/13/872/001-2) and Stribild (EU/1/13/830/001 2).

The Module 3.2.S sections of the dossier for cobicistat provided by the Applicant are identical to the 3.2.S sections submitted and approved with the aforementioned marketing authorisations.

General information

The chemical name of cobicistat is 1,3-thiazol-5-ylmethyl [(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl] methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate and has the following structure:



Cobicistat is an amorphous solid with a low glass transition temperature of 35 °C. Because of the low glass transition temperature, cobicistat under ambient conditions undergoes moisture and temperature induced phase transition from a foam into a rubber-like material. To increase physical stability of cobicistat it is adsorbed on silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow amorphous powder and as cobicistat is also hygroscopic as determined by dynamic vapour sorption at

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room temperature. The relatively higher water uptake of cobicistat on silicon dioxide compared to cobicistat is due to the hygroscopic nature of the silicon dioxide carrier. Importantly however and contrary to cobicistat itself, moisture uptake of cobicistat on silicon dioxide is reversible and therefore cobicistat is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture.

It shows three pKa; 1.8 (thiazole group), 2.5 (alkylthiazole group) and 6.4 (morpholino group). The partition coefficient Log P is 4.3 (at pH 8.5 buffer). No crystal forms have been found. It has three chiral centres and is produced as a single isomer. The stereochemical configuration is defined through the synthetic process and the use of starting material with suitable chirality. Appropriate specifications for these starting materials ensure consistent quality during manufacture of cobicistat.

Manufacture, characterisation and process controls

Three sites are proposed for the manufacture of the active substance. Cobicistat on silicon dioxide is manufactured in four well-defined synthetic steps. Details about possible reprocessing have been provided. The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Because the actual loading value of cobicistat on silicon dioxide is subject to manufacturing variability, a target loading with an appropriate range was adopted to ensure a robust down-stream manufacturing process.

All three sites have manufactured commercial scale batches of cobicistat on silicon dioxide and many smaller scale batches during the development of the product. Batch analysis data show that the active substance produced by both manufacturers is of similar quality and can be manufactured reproducibly.

Specification

Cobicistat on silicon dioxide specification includes tests and limits for appearance (visual), identification (cobicistat: IR, HPLC, UV; silicon dioxide: USP/NF), water content (Ph. Eur.), assay (HPLC), enantiomeric purity (chiral HPLC), impurities (HPLC), residual solvents (GC) and heavy metals (Ph. Eur.).

No crystal forms have been identified and since the active substance is produced as an amorphous solid adsorbed onto silicon dioxide, a test for polymorphism is not required as per ICH Q6A.

Cobicistat genotoxic potential has been evaluated in accordance with the recommendations in ICH Q3A. All the identified impurities are of low concern for genotoxicity, and therefore no further qualification studies were considered necessary. The proposed test and limits are acceptable.

A microbial limit test for the active substance is not required in accordance with ICH Q6A because the latter steps of the active substance manufacturing process are non-aqueous and been shown to limit microbial content. In addition data presented on several batches during development indicate no significant bioburden is present.

All in-house analytical methods have been validated according to ICH Q2A principles.

Batch analysis data on commercial scale batches of the active substance manufactured by all three proposed manufacturers have been provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process regardless of the manufacturing site.

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Stability

Two pilot scale and one production scale batch from the first manufacturer and on one full scale batch from the second manufacturer packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions at 5 °C for up to 36 months and accelerated at 25 °C/60% RH for up to 36 months. Appearance, water content, assay, impurities and chiral purity have been monitored. The analytical methods used are stability indicating. All physicochemical attributes of cobicistat on silicon dioxide remained within the specification acceptance limits following 36 months of long-term storage at 5 °C and no apparent trend has been observed. A statistical analysis performed for assay, total impurities and the major chiral impurity also demonstrate that there is little change over time. The physicochemical attributes of cobicistat on silicon dioxide remained also within the specification acceptance limits following 36 months of storage at 25 °C/60% RH.

Furthermore, two of the above batches were also tested under 30 °C/75% RH for up to 12 months to evaluate the stability of cobicistat on silicon dioxide at elevated temperatures that may be encountered during shipping and handling. The duration of temperature and humidity excursions is limited to 3 months.

In addition, a photostability study was conducted on cobicistat on silicon dioxide according to ICH Q1B Guideline. The results showed no significant change in appearance, assay, and impurity content following exposure to light. The data indicate that cobicistat on silicon dioxide is not sensitive to light.

Based on the presented stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is acceptable.

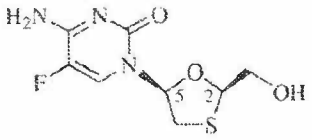
Emtricitabine

The information on chemistry, manufacturing and control of emtricitabine active substance has been previously assessed through centralised procedure and approved in the EU as part of the marketing authorisation applications for Emtriva (EU/1/03/261/001-3), Truvada (EU/1/04/305/001-2), Atripla (EU/1/07/430/001-2), Eviplera (EU/1/11/737/001-2) and Stribild (EU/1/13/830/001-2).

The Module 3.2.S sections of the dossier for emtricitabine provided by the Applicant are identical to the 3.2.S sections submitted and approved with the aforementioned marketing authorisations.

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one and has the following structure:



Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in methanol and water. Its pKa is 2.65 and the partition coefficient Log P is -0.43. It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. Two enantiomeric pairs of diastereomers can exist; cis-(-)-FTC and cis-(+)-FTC, trans-(-)-FTC and trans-(+)-FTC. The synthetic route has been chosen to be stereoselective for the formation of the desired cis-(-) enantiomer, emtricitabine. Three polymorphs of

emtricitabine have been observed. However, the most stable thermodynamically form at room temperature, is consistently produced.

Manufacture, characterisation and process controls

Emtricitabine is manufactured by two possible synthetic routes sharing a common first step and followed by two options comprising either one or two extra steps. The synthesis was described in sufficient detail. The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. Five manufacturing sites are involved. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown to consistently produce emtricitabine that meets the required quality standards.

Specification

Emtricitabine specification includes tests and limits for appearance (visual), identification (IR, HPLC), clarity of solution (visual), water content (Ph. Eur.), enantiomeric purity (chiral HPLC), assay (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), residual solvents (GC), and particle size (Laser Light Scattering). Analytical methods have been validated in accordance with ICH guidelines. The testing and the proposed limits applied, conform to current ICH guidelines and are acceptable from a toxicological and clinical perspective.

Extended testing during development has demonstrated that only a single polymorphic form results from the synthetic process of emtricitabine. Therefore as per ICH Q6A, testing for polymorphic form at release is not necessary. Development data demonstrate the absence of indicator organisms and therefore as per ICH Q6 indicate that microbial testing of the active substance is not required.

Batch analysis data on 22 commercial scale batches of the active substance from all proposed manufacturers were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Thirteen commercial scale and additional pilot scale batches of emtricitabine manufactured using both synthetic routes and packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions at 25 °C/60% RH for up to 36 months. Of the above batches, eight commercial scale and five pilot batches were put under accelerated at 40 °C/75% RH for up to 6 months. In addition another three batches were put under intermediate 30 °C/65% RH conditions for up to 12 months. Samples are tested for appearance, impurities and degradation products, assay, water content and for enantiomeric purity by validated stability indicating methods. Stability data for emtricitabine manufactured by both synthetic routes were comparable. All tested parameters remained within the specification limits throughout the tested period for all three stability conditions. In one isolated batch one degradation product exceeded the specification limit at the last time point (36 months). The same degradation product, is observed in emtricitabine stored at accelerated storage. Four batches exceeded the specification limit at 6 months. These data indicate that emtricitabine should not be exposed to elevated temperatures for extended periods of time but poses no quality issue for the active substance.

A photostability study was conducted on one batch of emtricitabine. The results showed no significant changes in appearance, purity, and impurity content and indicate that emtricitabine is not sensitive to light.

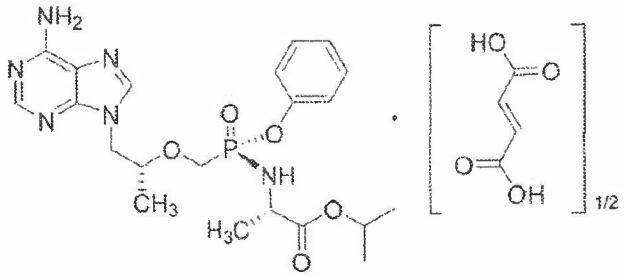
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Based on the long-term stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is considered acceptable.

Tenofovir alafenamide

General information

The chemical name of tenofovir alafenamide fumarate is propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2E)-but-2-enedioate (2:1) and has the following structure.



The chemical structure of tenofovir alafenamide fumarate has been adequately demonstrated by infrared spectroscopy, nuclear magnetic resonance spectroscopy (1H, 13C, and 31P), mass spectrometry, elemental analysis, ultraviolet absorption spectroscopy, and X-ray crystallography.

The active substance is a white to off-white or tan, slightly hygroscopic powder. Tenofovir alafenamide fumarate is a BCS Class 3 compound, with high aqueous solubility throughout the physiological pH range. The solubility of the active substance in aqueous media slightly decreases with increasing pH values. It is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. Tenofovir alafenamide fumarate is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone.

Tenofovir alafenamide exhibits stereoisomerism due to the presence of three chiral centres. The chiral centre at the propyloxy side chain is in the R-configuration. The absolute stereoconfiguration of the carbonylethylamino substituent is derived from the amino acid L-alanine, which has the S-configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the Sp configuration. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for tenofovir alafenamide fumarate. A single polymorphic form is consistently generated through the manufacturing process and this form has been adequately characterized.

The applicant has provided justification for TAF to be considered as a NAS on the basis of its unique chemical structure. However, both TAF and TDF which is a known active substance are prodrugs being metabolised to the same major active metabolite (TFV) in vivo. Therefore, both active substances share the same therapeutic moiety and as such, TAF is not considered a NAS on quality grounds.

Manufacture, characterisation and process controls

Tenofovir alafenamide fumarate is obtained from two manufacturers using the same synthetic route.

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The active substance is synthesized in multiple steps. During the evaluation procedure, the active substance starting materials were redefined to be in line with ICH Q11. Commercially available well-defined starting materials with acceptable specifications are used.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Critical process parameters were identified using a risk assessment approach.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance packaging is in compliance with the EC directive 2002/72/EC and EC 10/2011 as amended.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Specification

The active substance specification includes tests for: appearance (visual examination), identity (IR, HPLC), identity of fumaric acid (HPLC), clarity of solution (visual examination), water content (Ph. Eur.), assay (HPLC), impurities (HPLC, HPLC-MS, GC), residual solvents (GC), elemental impurities (ICP MS), and melting point (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data (n=16 using the proposed commercial process; 13 of which were commercial scale and 3 pilot scale) of the active substance, manufactured at both proposed manufacturing sites are provided. Additional batch analysis data for development batches used in pre-clinical pharmacokinetics and toxicological studies are provided. The results are within the specifications and consistent from batch to batch.

The active substance specifications are based on the active substance critical quality attributes (CQA).

Stability

Stability data on 6 commercial scale batches of active substance from the both proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions at 5 °C and for up to 24 months under accelerated conditions at 25 °C / 60% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions for up to 6 months at 40 °C / 75% RH on 5 batches were provided. Additionally, results for 4 days at 60 °C / ambient RH; for 4 days at 50 °C / ambient RH; and for 4 days at -20 °C were also provided on one batch.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

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Degradation products increased under accelerated conditions but remained within the specification.

Photostability testing following the ICH guideline Q1B was performed on one batch, indication that the active substance is not photosensitive.

The stability results indicate that the active substance manufactured by the both proposed suppliers is sufficiently stable. The stability results justify the proposed retest period at the recommended long term storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The proposed commercial finished product formulation is a green, capsule shaped, film-coated tablet with the dimensions of 19 mm x 8.5 mm, debossed with "GSI" on one side of the tablet and "510" on the other side of the tablet, containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as fumarate) as active substances.

The overall goal of Genvoya film coated tablet development was to create a tablet containing the same amounts of elvitegravir, cobicistat and emtricitabine active substances as currently combined in Stribild fixed dose combination film-coated tablet and to replace tenofovir disoproxil contained in Stribild with tenofovir alafenamide, a second-generation prodrug of tenofovir. The commercial formulation accommodates the required formulation and manufacturing process changes to incorporate tenofovir alafenamide fumarate (TAF fumarate) at a much lower dose than tenofovir disoproxil fumarate (TDF) while maintaining the established doses and biopharmaceutical performance of the other active substances, as well as ensuring satisfactory TAF fumarate chemical stability and content uniformity.

The aim of pharmaceutical development was to develop a stable immediate release solid dosage form for oral use, providing high bioavailability of the four active substances. The critical quality attributes (CQA) of the finished product are: size and colour, strength, content uniformity, % dissolved, degradation product content, water content, and microbiological quality.

Elvitegravir (EVG) and cobicistat (COBI) are BCS Class 2 compounds with low aqueous solubility and high permeability, and emtricitabine (FTC) is a BCS Class 1 compound with high aqueous solubility and high permeability. TAF fumarate is a BCS Class 3 compound with high aqueous solubility and low permeability. Co-formulation of EVG, COBI on silicon dioxide, FTC and TAF fumarate was enabled by the choice of the solid oral tablet as a dosage form and avoiding physical and chemical interactions between the four active substances. This was achieved through selection of appropriate intra- and extragranular excipients in amounts that achieve: chemical and physical stability, rapid and complete dissolution, consistent pharmacokinetic performance, satisfactory powder properties to ensure acceptable tablet content uniformity, and adequate tablet tensile strength to ensure physical tablet integrity.

Formulation composition, manufacturing process design and selection of excipients were intended to ensure content uniformity of all active substances within specifications.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except the coating material which is commercially available and tested according to an in house standard. All the components of the coating material comply with the standards in EU Regulation 231/2012 or compendial monographs. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The physical and chemical compatibility between EVG, COBI, FTC, and excipients have been established previously for Stribild film-coated tablets. The compatibility between TAF fumarate and the other ingredients was established with stability studies.

The formulations used during clinical studies following the definition of the desired tablet composition and TAF fumarate strength were differing only in the type of non-functional coating material used and therefore no bioequivalence study comparing early development formulations to the one proposed for marketing was required.

The discriminatory power of the dissolution method for routine release and stability testing of the finished medicinal product has been demonstrated.

Pharmaceutical development of the finished product contains QbD elements.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development and process design. The critical process parameters have been adequately identified.

The primary packaging is high density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains silica gel desiccant and polyester coil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of multiple main steps: blending of the active substance with intragranular/extragranular excipients, fluid-bed granulation/dry granulation and milling, compression, tablet film-coating and packaging. Critical process parameters have been identified. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. The complete process will be validated at commercial scale prior to commercialisation; which was considered acceptable based on the enhanced development results presented and on experience gained in several commercial scale batches already manufactured. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Proven acceptable ranges have been defined for several steps. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual examination), identification (HPLC, UPLC, UV), water content (Ph. Eur.), assay (UPLC), degradation products (UPLC), uniformity of dosage units (HPLC), dissolution (UPLC), and microbiological examination (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

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Batch analysis results are provided for 16 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional batch results of 3 commercial scale batches used in clinical studies were provided as supporting data.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 7 commercial scale batches of finished product stored under long term conditions for up to 24 months at both 25 °C / 60% RH and 30 °C / 75% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided. Results on stress conditions for up to 4 days at 60 °C / ambient RH; at 50 °C / ambient RH; and at -20 °C were also provided on one batch. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

It was demonstrated that stability data of the finished product manufactured using active ingredients from different suppliers is representative and there are no differences in stability.

Samples were tested for the same parameters as for release. The analytical methods used were the same as for release and were stability indicating. The specification acceptance limits were met for all quality attributes at long-term storage conditions. It was shown that the finished product is not photosensitive; however it should be stored in the original packaging in order to protect it from moisture.

Based on available stability data, the shelf-life of 24 months and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2018
EMA/293559/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Biktarvy

International non-proprietary name: bictegravir / emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/004449/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Administrative information

Name of the medicinal product:	Biktarvy
Applicant:	Gilead Sciences International Limited Flowers Building Granta Park Abington Cambridge CB21 6GT UNITED KINGDOM
Active substance:	Bictegravir / Emtricitabine / Tenofovir Alafenamide
International Non-proprietary Name/Common Name:	Bictegravir / Emtricitabine / Tenofovir Alafenamide
Pharmaco-therapeutic group (ATC Code):	Direct acting antivirals, antivirals for treatment of HIV infections, combinations (J05AR)
Therapeutic indication(s):	Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus 1 (HIV 1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	50 mg / 200 mg / 25 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	30 tablets and 90 (3 x 30) tablets

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List of abbreviations

%CV percentage coefficient of variation

3TC lamivudine

ABC abacavir

AE adverse event

AIDS acquired immunodeficiency syndrome

ALT alanine aminotransferase

ANOVA analysis of variance

anti-HBe antibody against hepatitis B e antigen

anti-HBs antibody against hepatitis B surface antigen

ART antiretroviral therapy

ARV antiretroviral

ATV atazanavir

AUC area under the concentration versus time curve

AUClast area under the concentration versus time curve from time zero to the last quantifiable concentration

AUCtau area under the concentration versus time curve over the dosing interval

B/F/TAF bictegravir/emtricitabine/tenofovir alafenamide (coformulated)

BCS Biopharmaceutics Classification System

BIC bictegravir

BIC Bictegravir sodium

BLQ below the limit of quantitation

BMD bone mineral density

BMI body mass index

CHB chronic hepatitis B

CI confidence interval

Clast last observed quantifiable concentration of the drug

Cmax maximum observed concentration of drug

CMH Cochran-Mantel-Haenszel

COBI cobicistat (Tybost)

CPK creatine phosphokinase

CQA Critical Quality Attribute

CRF case report form

CSR clinical study report

Ctau observed drug concentration at the end of the dosing interval

CV coefficient of variation

DAVG11 time-weighted average change from baseline to study Day 11

DNA deoxyribonucleic acid

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DRV darunavir

DSC Differential Scanning Calorimetry

DTG dolutegravir

EC European Commission

EC50 estimated concentration of drug for a half maximal response

ECG electrocardiogram

eCRF electronic case report form

eGFRCG estimated glomerular filtration rate calculated using the Cockcroft-Gault equation

EU European Union

EVG elvitegravir (Vitekta)

F/TAF emtricitabine/tenofovir alafenamide (coformulated; Descovy®)

FAS Full Analysis Set

FDA Food and Drug Administration

FDC fixed-dose combination

FSH follicle-stimulating hormone

FTC emtricitabine (Emtriva)

FTC Emtricitabine

FTC/TDF emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)

GC Gas Chromatography

GCP Good Clinical Practice

GEN elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®)

GI gastrointestinal

GLSM geometric least-squares mean

GS-9883 bictegravir

HBeAb hepatitis B e antibody

HBeAg hepatitis B e antigen

HBsAb hepatitis B surface antibody

HBsAg hepatitis B surface antigen

HBV hepatitis B virus

HCV hepatitis C virus

HDPE High Density Polyethylene

HIV human immunodeficiency virus

HIV-1 human immunodeficiency virus type 1

HLA human leukocyte antigen

HPLC High performance liquid chromatography

HPLC-CAD High performance liquid chromatography – charged aerosol detection

HPLC-MS High performance liquid chromatography – mass spectrometry

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-MS Inductively coupled plasma mass spectrometry

IDMC independent data monitoring committee

IN integrase
INSTI integrase strand-transfer inhibitor
INSTI-R integrase strand-transfer inhibitor resistant
IPC In-process control
IQ inhibitory quotient
IQ95 inhibitory quotient of 95%
IR Infrared
ISE Integrated Summary of Efficacy
ISS Integrated Summary of Safety
IV intravenous
KF Karl Fischer titration
LC-MS/MS liquid chromatography/tandem mass spectrometry
LDH lactate dehydrogenase
LDL low-density lipoprotein
LLOQ lower limit of quantitation
LOCF last observation carried forward
LSM least-squares mean
M = E missing = excluded
M = F missing = failure
MedDRA Medical Dictionary for Regulatory Activities
MH Mantel-Haenszel
N number of subjects in a population (N)
NLT Not less than
NMR Nuclear Magnetic Resonance
NMT Not more than
NNRTI nonnucleoside reverse transcriptase inhibitor
NRTI nucleoside reverse transcriptase inhibitor
OL open label
paEC95 protein-adjusted 95% effective concentration
paIC95 protein-adjusted concentration that results in 95% inhibition
paIQ95 protein-adjusted inhibitory quotient of 95%
PAR Proven Acceptable Range
PD pharmacodynamic(s)
PDE Permitted Daily Exposure
PE Polyethylene
Ph. Eur. European Pharmacopoeia
PI protease inhibitor
PK pharmacokinetic(s)
PP per protocol
PR protease

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PrEP pre-exposure prophylaxis
Q1 first quartile
Q3 third quartile
QD once daily
RAL raltegravir
RAM resistance-associated mutation
RAP resistance analysis population
RBC red blood cell
RE relative error
RH Relative Humidity
RNA ribonucleic acid
ROW rest of world
RT reverse transcriptase
RTV ritonavir
SAE serious adverse event
SAP statistical analysis plan
SBR stay on baseline regimen
SD standard deviation
SDS Sodium dodecyl sulfate
SmPC Summary of Product Characteristics
t1/2 estimate of the terminal elimination half-life of the drug
TAF tenofovir alafenamide (Vemlidy)
TAF Tenofovir alafenamide
TDF tenofovir disoproxil fumarate (Viread)
TFV tenofovir
Tmax time (observed time point) of Cmax
TSH thyroid-stimulating hormone
UGT1A1 uridine diphosphate glucuronosyltransferase 1A1
ULN upper limit of normal
UPLC Ultra performance liquid chromatography
USP United States Pharmacopoeia
USP United States Pharmacopoeia
UV Ultraviolet
XRPD X-Ray Powder Diffraction

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Limited submitted on 21 June 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Biktarvy through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2016.

The applicant applied for the following indication: *The treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the individual components (see section 5.1).*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0339/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0339/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active substance status

The applicant requested the active substance bictegravir contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

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Scientific advice

The applicant received scientific advices from the CHMP:

Scientific advice	date	Area
EMA/CHMP/SAWP/629722/2012	18 October 2012	Non-clinical
EMA/CHMP/SAWP/214541/2013	25 April 2013	Quality, non-clinical and clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Bruno Sepodes

The application was received by the EMA on	21 June 2017
The procedure started on	13 July 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	29 September 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	27 September 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	12 October 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 December 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	31 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2018
The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 February 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 April 2018
The Rapporteurs circulated Updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 April 2018

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The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Biktarvy	26 April 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

HIV-1 infection is a blood-born infection. HIV is a retrovirus that infects and replicates primarily in human CD4+ T cells and macrophages. HIV can be transmitted via blood, blood products, sexual fluids, other fluids containing blood, and breast milk. Most individuals are infected with HIV through sexual contact, before birth or during delivery, during breast-feeding, or when sharing contaminated needles and syringes (intravenous drug users). Sexual intercourse is the most common, albeit inefficient, mode of HIV transmission. The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative STDs, high HIV viral load in the subject, and lack of antiretroviral therapy.

2.1.2. Epidemiology

There are approximately 37 million people worldwide living with HIV-1. HIV-1 infection remains a life-threatening disease in infected persons who do not receive adequate treatment sufficiently early in the course of the infection and/or are infected with virus that is resistant to anti-retroviral agents of several classes such that an adequate treatment regimen cannot be constructed from approved agents.

2.1.3. Clinical presentation, diagnosis and prognosis

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms (including fever, rash, or diarrhoea), or goes without clinical symptoms. If symptoms are present, these generally emerge approximately 2 weeks following HIV infection. Among those presenting with symptoms, the number of symptoms correlates with higher pre-seroconversion peak plasma viral load.

Diagnosis most often occurs during chronic infection. Recent estimates suggest that even in high income settings; about 25-35% of people living with HIV starting ART have a CD4 cell count of less than 200 cells/mm3. In some settings, up to half of people present to care with advanced HIV disease – defined by WHO as having a CD4 cell count <200 cells/mm3 or a WHO clinical stage 3 or 4 disease.

Most HIV-infected individuals will eventually develop progressive immunodeficiency marked by CD4 T lymphocyte (CD4) cell depletion and leading to AIDS-defining illnesses and premature death, if remain untreated. Leading causes of mortality among adults with advanced HIV disease globally include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia.

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Diagnostic tests for HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and HIV-1 and HIV-2 antibodies.

2.1.4. Management

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV-infected patients, current treatment guidelines suggest that initial therapy consists of 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) and either an integrase strand transfer inhibitor (INSTI), the non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, or the boosted protease inhibitor (PI), darunavir (DRV). Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes.

Integrase strand-transfer inhibitors (INSTI), such as raltegravir (RAL) and elvitegravir (EVG), exhibit strong antiviral activity, good clinical tolerability and have become attractive options as third agents in combination therapy for HIV-1 infected patients. Both RAL and EVG have relatively short human half-lives and must be administered twice daily (BID) (for RAL) or in combination with a boosting agent (for EVG) for once daily (QD) administration. The most recently approved INSTI, dolutegravir (DTG), has a PK profile that allows administration once a day (QD) without a boosting agent; however, BID dosing is recommended when DTG is co-administered with CYP and/or UGT inducers (e.g., EFV, fos-APV/r, TPV/r, or rifampin) and in patients with INSTI associated resistance substitutions or clinically suspected INSTI resistance. Dolutegravir is available as a fixed dose combination with abacavir and lamivudine and is currently used as first line therapy. The new fixed dose combination with Bictegravir as INSTI contains tenofovir alafenamide (TAF) and emtricitabine as a backbone.

About the product

Bictegravir is a potent INSTI that is being evaluated for the treatment of HIV-1 infection and that has demonstrated a terminal half-life suitable for once-daily administration without a boosting agent.

Emtricitabine and TAF form a guideline-recommended N(t)RTI backbone for ART-naive HIV-infected patients. Tenofovir alafenamide is also approved as a single agent for the treatment of chronic hepatitis B infection, and F/TAF is a guideline-recommended backbone for patients co-infected with HIV and hepatitis B virus (HBV).

B/F/TAF is a potent, convenient, tolerable, and practical regimen for the long-term treatment of patients with HIV infection. The small tablet size of the FDC is expected to provide an additional benefit, especially in patients for whom pill swallowing can be a barrier to treatment compliance, (eg, the elderly). Based on the clinical studies performed within this application, the Applicant claims that:

- High rates of virologic suppression with B/F/TAF in studies of ART-naive subjects and those switching therapy

- No subject in the Phase 2 or Phase 3 studies developed treatment-emergent resistance to any component of B/F/TAF

- B/F/TAF is generally safe and well tolerated in HIV-infected subjects

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- The bone and renal safety profiles of B/F/TAF are comparable with those of abacavir (ABC)/DTG/lamivudine (3TC)

The Applicant's proposed indication was:

TRADENAME is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the individual components

The Applicant's proposed posology was:

One tablet to be taken once daily in adults.

2.2. Quality aspects

2.2.1. Introduction

Biktarvy is a fixed dose combination product presented as film-coated tablets containing bictegravir sodium equivalent to 50 mg bictegravir free acid, 200 mg of emtricitabine and tenofovir alafenamide fumarate equivalent to 25 mg tenofovir alafenamide as active substances.

Other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

Film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide red (E172) and iron oxide black (E172).

The product is available in white, high density polyethylene (HDPE) bottles with polypropylene continuous-thread child-resistant caps, lined with induction activated aluminium foil liners. Each bottle contains silica gel desiccant and a polyester coil.

2.2.2. Active Substance

Emtricitabine (FTC)

The information on chemistry, manufacturing and control of emtricitabine active substance has been assessed previously *via* the centralised procedure and approved in the EU as part of the marketing authorisations for Emtriva, Truvada, Atripla, Eviplera, Stribild, Descovy, Genvoya and Odefsey.

The Module 3.2.S sections of the dossier for emtricitabine provided by the applicant are identical to the 3.2.S sections submitted and approved with the aforementioned marketing authorisations.

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.24 g/mol and the following structure (figure 1).

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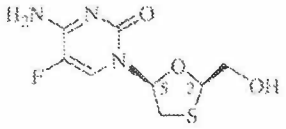


Figure 1: emtricitabine structure

The structure of emtricitabine was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and single crystal x-ray determination.

Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in methanol and water. Its pKa is 2.65 and the partition coefficient Log P is -0.43. It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. Two enantiomeric pairs of diastereomers can exist: *cis*-(-)-FTC and *cis*-(+)-FTC, *trans*-(-)-FTC and *trans*-(+)-FTC. The synthetic route has been chosen to be stereoselective for the formation of the desired *cis*-(-) enantiomer, emtricitabine. Three polymorphs of emtricitabine have been observed. However, the most stable thermodynamically form at room temperature, is consistently produced.

Manufacture, characterisation and process controls

Emtricitabine is manufactured by two possible synthetic routes sharing a common first step and followed by two options comprising either one or two extra steps. The synthesis was described in sufficient detail.

The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. Five manufacturing sites are involved. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown to consistently produce emtricitabine that meets the required quality standards.

The active substance is packaged in double polyethylene (PE) bags inside HDPE drums which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Emtricitabine specification includes tests and limits for appearance (visual), identification (IR, HPLC), clarity of solution (visual), water content (Ph. Eur.), enantiomeric purity (chiral HPLC), assay (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.), residual solvents (GC), and particle size (Laser Light Scattering). Analytical methods have been validated in accordance with ICH guidelines. The testing and the proposed limits applied, conform to current ICH guidelines and are acceptable from a toxicological and clinical perspective.

Extended testing during development has demonstrated that only a single polymorphic form results from the synthetic process of emtricitabine. Therefore as per ICH Q6A, testing for polymorphic form at release is not necessary. Development data demonstrate the absence of indicator organisms and therefore, as per ICH Q6, microbial testing of the active substance is not required. Satisfactory information regarding the reference standards used for assay testing has been presented.

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Batch analysis data on 22 commercial scale batches of emtricitabine from all proposed manufacturers were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Stability data from 3 production scale batches of finished product covering both manufacturers and processes stored for up to 24 months under long term conditions (30 °C / 65% RH) according to the ICH guidelines were provided. The batches were packaged in the primary packaging proposed for marketing. Samples were tested for appearance, assay, impurity content and water content. No changes were observed to any of the measured parameters over time, and no trends were visible. Emtricitabine is known not to be photosensitive.

Based on the long-term stability data, the proposed re-test period and storage conditions when emtricitabine is packed in the proposed packaging materials is considered acceptable.

Tenofovir Alafenamide Fumarate (TAF Fumarate)

The information on chemistry, manufacturing and control of tenofovir alafenamide fumarate has been assessed previously *via* the centralised procedure and approved in the EU as part of the marketing authorisations Descovy, Genvoya, Odefsey, Vemlidy and Symtuza.

The Module 3.2.S sections of the dossier for tenofovir alafenamide fumarate provided by the applicant are identical to the 3.2.S sections submitted and approved within the aforementioned marketing authorisations.

General information

The chemical name of tenofovir alafenamide fumarate is propan-2-yl *N*-[(*S*)-({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-*L*-alaninate, (2*E*)-but-2-enedioate (2:1) corresponding to the molecular formula $C_{23}H_{31}N_6O_7P$. It has a relative molecular mass of 534.5 g/mol and the following structure (Figure 2):

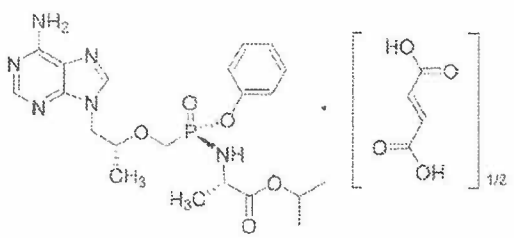


Figure 2: tenofovir alafenamide fumarate structure

The chemical structure of tenofovir alafenamide fumarate has been adequately demonstrated by infrared spectroscopy, NMR spectroscopy (^1H, ^{13}C, and ^{31}P), mass spectrometry, elemental analysis, ultraviolet absorption spectroscopy, and X-ray crystallography.

The active substance is a white to off-white or tan, slightly hygroscopic powder. Tenofovir alafenamide fumarate is a BCS Class III compound, with pH-dependent aqueous solubility decreasing with

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increasing basicity. It is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. Tenofovir alafenamide fumarate is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone.

Tenofovir alafenamide exhibits stereoisomerism due to the presence of three chiral centres. The chiral centre at the propyloxy- side chain is in the *R*-configuration. The absolute stereoconfiguration of the carbonylethylamino- substituent is derived from the amino acid *L*-alanine, which has the *S*-configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the *S*- configuration. Enantiomeric purity is controlled routinely by chiral HPLC at the point of the introduction of the chiral starting material and in a manufacturing process intermediate.

Polymorphism has been observed for tenofovir alafenamide fumarate. A single polymorphic form is consistently generated through the manufacturing process and this form has been adequately characterised.

Manufacture, characterisation and process controls

Tenofovir alafenamide fumarate is obtained from two manufacturers using the same synthetic route.

The active substance is synthesized in multiple steps using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Potential and actual impurities were well discussed with regards to their origin and characterised.

Critical process parameters and material attributes were identified using a risk assessment approach.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double-lined polyethylene bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bags are held in high-density polyethylene drums (or other suitable secondary container) with lids of appropriate size and fitted with a security seal.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Specification

The specification for tenofovir alafenamide fumarate includes tests for appearance (visual examination), identity (IR, HPLC), identity of fumaric acid (HPLC), clarity of solution (visual examination), water content (Ph. Eur.), assay (HPLC), impurities (HPLC, HPLC-MS, GC), residual solvents (GC), elemental impurities (ICP MS), and melting point (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay testing has been presented.

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Batch analysis data from 16 batches of tenofovir alafenamide fumarate, (13 of which were commercial scale and 3 pilot scale), manufactured at both proposed manufacturing sites were provided. Additional batch analysis data for development batches used in pre-clinical pharmacokinetics and toxicological studies were also provided. The results were within the specifications and consistent from batch to batch.

The tenofovir alafenamide fumarate specifications are based on the active substance critical quality attributes (CQA).

Stability

Stability data on 6 commercial scale batches of tenofovir alafenamide fumarate from the both proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions at 5 °C and for up to 24 months under accelerated conditions at 25 °C / 60% RH according to the ICH guidelines were provided. Results under stressed conditions for up to 6 months at 40 °C / 75% RH on 5 batches were provided. Additionally, results for 4 days at 60 °C / ambient RH, for 4 days at 50 °C / ambient RH and for 4 days at -20 °C were also provided on one batch.

Samples were tested for appearance, impurities, assay, water content, and solid state characteristics (XRD and melting point). The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on one batch, indicating that the active substance is not photosensitive.

The stability results indicate that tenofovir alafenamide fumarate manufactured by the both proposed suppliers is sufficiently stable. The stability results justify the proposed re-test period at the recommended long-term storage condition in the proposed container.

Bictegravir sodium (BIC)

Bictegravir sodium is a new active substance. Information is provided by the applicant in a full module 3.2.S.

General information

The chemical name of bictegravir sodium is sodium (2*R*,5*S*,13a*R*)-7,9-dioxo-10-[(2,4,6-trifluorobenzyl)carbamoyl]-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate corresponding to the molecular formula $C_{21}H_{17}F_3N_3NaO_5$. It has a relative molecular mass of 471.4 g/mol and the following structure (figure 3):

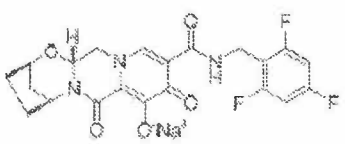


Figure 3: bictegravir sodium structure

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The chemical structure of bictegravir sodium was elucidated by a combination of ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass spectrometry, UV and IR spectroscopy, elemental analysis and x-ray crystallography.

Bictegravir sodium contains 3 chiral centres. Overall stereochemistry is tested in the active substance by chiral HPLC before release.

The solid state properties of bictegravir sodium were established by x-ray powder diffraction, differential scanning calorimetry and dynamic vapour sorption. The active substance is an off-white to yellow slightly hygroscopic crystalline solid. Only 1 polymorphic form was identified during development. It is practically insoluble in aqueous media across the physiological pH range, including simulated fed and fasted state intestinal fluids, and very slightly soluble at pH 8.8. Particle size is limited in the active substance specification.

Manufacture, characterisation and process controls

Bictegravir sodium is synthesized in multiple steps using well-defined starting materials with acceptable specifications. The starting materials were justified in line with the expectations in ICH Q11 and its Q&A and are deemed acceptable.

Adequate in-process controls are applied during the synthesis. The process was optimised through a series of univariate and multivariate experiments, informed by risk assessment as to which steps were likely to be most critical. Operational ranges and set-points are defined for each step of the manufacturing process and are justified by the data provided. No design spaces are claimed.

Detailed information on the origin, fate and purge of impurities was provided in order to justify limits for impurities in the starting materials, intermediates, and the active substance. A risk assessment for mutagenic impurities was carried out in line with ICH M7. One impurity with a structural alert was shown to be negative in an Ames test. Another known mutagenic impurity was consistently found in an intermediate at levels well below 30% of the TTC and is thus controlled according to ICH M7 option 4. The specifications and control methods for intermediates, starting materials and reagents have been presented and are deemed acceptable.

The active substance is packaged in double PE bags, inside an HDPE drum, which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), clarity of solution (visual inspection), water content (KF), sodium content (HPLC-CAD), assay (HPLC), impurities (HPLC), residual solvents and organic volatile impurities (GC), enantiomeric purity (chiral HPLC) and particle size (laser light scattering).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. A risk assessment and batch analysis carried out for the finished product in line with ICH Q3D demonstrated that no test for elemental impurities, other than the sodium content, is needed. The active substance has low water activity and no significant bioburden was noted during release testing and stability studies so no test for microbiological quality is included. Only 1 polymorphic form has been identified, which is stable and routinely produced by the manufacturing process as determined by XRPD, so no test is needed.

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The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 22 lab, pilot and production scale batches of bictegravir sodium covering both manufacturers and an additional manufacturer used in early development, were provided. These included the 3 productions scale validation batches from each manufacturer. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from 8 pilot scale batches of active substance covering both proposed manufacturers, and an additional manufacturer used in early development, stored in the intended commercial package for up to 24 months under long term conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. Samples were tested for appearance, assay, related substances, water content, enantiomeric purity, polymorphic form and microbial purity. No significant changes were noted over time and all parameters remained within specification throughout the study period. In addition, studies have begun using the 3 process validation batches from each proposed commercial manufacturer which will be tested according to the accepted protocol.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Bictegravir sodium is not photosensitive.

Samples were also stored at either -20 or 60 °C for up to 2 weeks. No changes to any of the measured parameters were observed.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period when stored at the recommended long term storage condition in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Biktarvy is a fixed dose combination, immediate release, film-coated tablet containing bictegravir sodium, emtricitabine and tenofovir alafenamide fumarate as active substances. The tablets are purplish-brown capsule-shaped, and debossed with GSI on one face and "9883" on the other.

Bictegravir sodium is a crystalline, stable, BCS class II compound exhibiting low solubility but high permeability. Emtricitabine is a crystalline BCS class I compound with high solubility and permeability which degrades by hydrolysis in aqueous solution and to a much smaller degree, in the solid phase. TAF fumarate is a BCS class III molecule, highly soluble but poorly permeable, which undergoes pH-dependent hydrolysis in aqueous solution.

The formulation evolved throughout development. The commercial formulation is the same as that used in phase III clinical trials, which was shown to be equivalent to earlier clinical formulations by suitable bridging studies.

The choice of manufacturing process and excipients was based on the properties of the active substances. Process parameters for the film-coating process are considered suitable.

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The development of the dissolution method took into account the differing solubilities and stabilities of the 3 active substances. Emtricitabine and TAF fumarate are soluble in aqueous media, whereas bictegravir is poorly soluble in aqueous media across the physiological pH range. However, TAF fumarate is unstable below pH 5 and above pH 6, so a medium with pH 5.5 was selected.

Various manufacturing parameters with potential to impact the dissolution rate were examined during development and have been set at levels guaranteed to produce Biktarvy tablets of the required quality. The dissolution method was developed in order to identify tablets manufactured outside of the defined process and its discriminatory power is considered adequate.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development and process design. The critical process parameters have been adequately identified. No design space is claimed.

All excipients other than the Opadry film coat are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Opadry is commercially available and the constituent ingredients are of compendial grade. The colourants comply with directive 2009/35/EC. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The primary packaging is a white HDPE bottle with polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains silica gel desiccant and a polyester coil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process is carried out at 2 different sites and consists of production of final blends by granulation, milling and lubrication followed by tabletting. The process is considered to be a standard manufacturing process.

It has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. A process validation protocol has been provided, explaining how validation will be carried out at both manufacturing sites on full production scale prior to commercialization. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form, and suitable limits have been set for the individual tests.

Product specification

The finished product release specifications comprise appropriate tests for this kind of dosage form including appearance, identity (UV, UPLC), water content (KF), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (UPLC) and microbiological quality (Ph. Eur.).

The limits for impurities have been justified 7 batches of finished product were analysed for all class 1, class 2A and selected class 3 elemental impurities as defined in ICH Q3D. The amount of each tested element was well below 30% of the PDE and this justifies their omission from the finished product specification.

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The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 14 pilot to production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 pilot scale batches of finished product from each manufacturer stored for up to 12 months under long term conditions (25 °C / 60% RH), up to 12 months under intermediate conditions (30 °C / 75% RH), and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, water content, assay, degradation products, dissolution and microbiological quality. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that the product is photostable.

Stressed studies were carried out on another batch, stored at either -20 °C or 50 °C for 1 week at ambient humidity. No significant changes were observed.

An in-use stability study was carried out on 1 batch of product. Bottles were stored at 30 °C / 75% RH with the induction seals removed. One tablet was removed each day for 30 days to simulate the recommended dosing regimen. No significant changes to any of the measured parameters were observed.

Based on available stability data the proposed shelf-life of 24 months stored in the original container with the lid tightly closed in order to protect from moisture as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetal origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The control strategy, combining a mixture of process parameters and release tests, is considered sufficient to ensure the quality of the product. No design spaces are claimed.

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2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The definitive safety pharmacology, toxicology, and toxicokinetic studies provided for BIC, FTC, and TAF were conducted in accordance with guidelines issued by the International Council for Harmonisation (ICH) and with Good Laboratory Practice (GLP) or other applicable regulations promulgated by international health authorities. Pilot, exploratory, and mechanistic studies were either conducted in full compliance with GLP procedures or were conducted using appropriate protocols and documentation to assure data integrity.

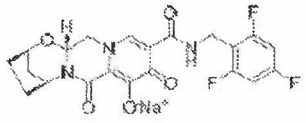
2.3.2. Pharmacology

Brief summary

BIC

Bictegravir is a potent investigational integrase strand-transfer inhibitor (INSTI) with in vitro activity against wild-type HIV-1 and HIV-1 with INSTI-resistance associated mutations. Bictegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle, demonstrating high potency and selectivity in antiviral assays. Bictegravir displays a high resistance barrier and has an improved phenotypic resistance profile compared to dolutegravir (DTG), raltegravir (RAL) and elvitegravir (EVG; E). Bictegravir has a longer dissociation half-life from both wild-type and mutant HIV-1 integrase/DNA complexes compared with DTG, RAL, and EVG.

Figure 4. BIC chemical structure

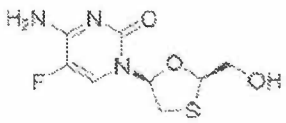


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FTC

Emtricitabine (FTC) is a NRTI and a (-) enantiomer of a thio analogue of cytidine, which differs from other cytidine analogues in that it has a fluorine in the 5-position. Intracellularly, FTC is phosphorylated by enzymes to form emtricitabine triphosphate (FTC-TP), the active metabolite. Emtricitabine is an NRTI that has activity against HIV and hepatitis B virus (HBV). Following absorption, FTC is phosphorylated by cellular enzymes to emtricitabine triphosphate (FTC-TP), the active metabolite, an analog of 2'-deoxycytidine triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase through high-affinity binding, competing with the natural substrate 2'-deoxycytidine 5'-triphosphate. Emtricitabine 5'-triphosphate is efficiently incorporated into the nascent viral DNA chain by HIV-1 reverse transcriptase resulting in termination of DNA synthesis due to the lack of a hydroxyl group at the 3'- position of the sugar moiety of FTC, which in turn inhibits viral replication. In a clinical study, the intracelular half-life of FTC-TP in peripheral blood mononuclear cells (PBMCs) was 39 hours. Intracellular triphosphate levels increased with dose but reached a plateau at doses of 200 mg or greater. Emtricitabine has activity against retroviruses and hepadnaviruses.

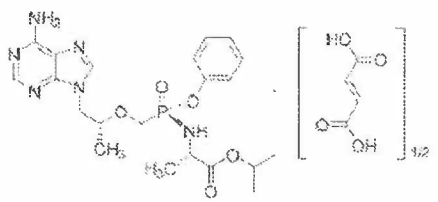
Figure 5. Chemical structure of FTC



TAF

Tenofovir alafenamide is a prodrug of tenofovir (TFV), a nucleotide reverse transcriptase inhibitor (NtRTI). After absorption, TAF is converted to TFV intracellularly, which is phosphorylated to the active metabolite, tenofovir diphosphate (TFV-DP) (Robbins 1998). Tenofovir diphosphate is a very weak inhibitor of mammalian DNA polymerases α, β, δ, and ε and mitochondrial DNA (mtDNA) polymerase γ. Cells are permeable to TAF and, due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading tenofovir into PBMCs (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite, tenofovir diphosphate. Tenofovir diphosphate inhibits HIV and HBV replication through incorporation into viral DNA by the HIV-1 or HBV reverse transcriptase, which results in DNA chain-termination.

Figure 6. Chemical structure of TAF hemi-fumarate



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B/F/TAF

The proposed FDC is based on the complimentary pharmacology of BIC, FTC and TAF and the body of clinical experience with INSTI or N[t]RTIs in HIV-infected patients. Combinations of these agents in cell-based *in vitro* assays show favourable anti-HIV activity and no evidence for antagonism. The anti-HIV-1 activity of 3-drug combination of BIC, FTC, and TAF was found to be highly synergistic with no evidence of antagonism in vitro, supporting the use of these agents in combination in HIV-1 infected patients. The resistance profiles of the individual agents BIC, FTC, and TAF are distinct and non-overlapping.

Primary pharmacodynamic studies

BIC

Bictegravir is a novel strand transfer inhibitor of HIV-1 integrase with high potency and selectivity in antiviral assays and does not require metabolic modification to exert ARV activity. Using lymphoblastoid T-cell lines and primary human T-lymphocytes in HIV-1 antiviral assays, the estimated concentration of drug for a half-maximal response (EC50) of BIC ranged from 1.5 to 2.4 nM and the selectivity indices ranged from 1500 to 8800. When tested in primary human PBMCs against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G, BIC displayed similar antiviral activity across all clinical isolates with mean and median EC50 values of 0.60 and 0.55 nM, respectively, based on a range of EC50 values between < 0.05 and 1.71 nM. HIV-2 was similarly susceptible to BIC with an EC50 value of 1.1 nM. Bictegravir is a specific inhibitor of HIV with no measurable antiviral activity against non-HIV viruses, including HBV, hepatitis C virus (HCV), influenzas A and B, human rhinovirus, and respiratory syncytial virus (RSV).

Bictegravir maintained potent antiviral activity against HIV-1 variants resistant to currently approved ARVs from the NRTI, NNRTI, and protease inhibitor (PI) classes. Bictegravir displays a resistance profile similar to that of dolutegravir (DTG) and markedly improved compared with that of raltegravir (RAL) and elvitegravir (EVG; E). Bictegravir maintained full activity against clonal isolates from virologic failures treated with Stribild. Bictegravir had an improved resistance profile compared to EVG, RAL, and DTG in patient isolates, particularly for isolates with high-level INSTI resistance containing combinations of mutations such as E92Q + N155H or G140C/S + Q148R/H/K ± additional INSTI mutations, and may have unmet clinical utility in these patients. Bictegravir had a longer dissociation half-life from HIV-1 integrase-DNA complexes compared with DTG, RAL, and EVG.

HIV-1 isolates with reduced susceptibility to BIC have been selected in cell culture. These selections showed that BIC displayed a comparable barrier to resistance emergence as DTG, and a higher barrier than EVG. Bictegravir selected the M50I + R263K combination and S153F with a transient T66I substitution in HIV-1 integrase. The R263K single mutant and M50I + R263K double mutant viruses had low-level reduced susceptibility to BIC, but the single M50I mutant was fully sensitive to BIC. The M50I + R263K selected variants exhibited low-level cross-resistance to RAL and DTG and intermediate cross-resistance to EVG but remained susceptible to other classes of ARVs. The effect of the T66I and S153F/Y single mutants and the T66I + S153F double mutant in integrase on BIC susceptibility was minimal.

Similar to a number of other ARV agents, the in vitro activity of BIC was reduced in the presence of human serum due to significant protein binding. Bictegravir exhibited approximately 70-fold increase in the EC50 value in the presence of 100% serum relative to its activity in cell culture medium. The 95% effective concentration (EC95) calculated from the high density antiviral dose response was used in

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conjunction with the human serum shift determined by equilibrium dialysis to calculate the protein-adjusted EC95 (PAEC95) of 361 nM.

FTC

Emtricitabine, an NRTI, is a synthetic analogue of the naturally occurring pyrimidine nucleoside, 2' -deoxycytidine. Intracellularly, FTC is converted through 3 phosphorylation reactions to its active tri-phosphorylated anabolite emtricitabine 5' -triphosphate (FTC-TP) [Furman 1992, Paff 1994]. Emtricitabine 5'-triphosphate inhibits the activity of viral polymerases, including HIV-1 RT by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine triphosphate) and by being incorporated into nascent viral DNA, which results in chain termination (Wilson 1993). FTC has activity that is specific to HIV (HIV-1 and HIV-2) and HBV. The EC50 of FTC against laboratory adapted strains of HIV-1 ranged from 0.001 to 0.62 μM depending on cell type and virus strain used in the assay [Jeong 1993, Painter 1995, Schinazi 1992]. With clinical isolates of HIV-1, EC50 values ranged from 0.002 to 0.028 μM [Schinazi 1992]. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and ε and mtDNA polymerase γ [Painter 1995]. There was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. The EC50 values for FTC were in the range of 0.001 to 0.62 μM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC50 values ranged from 0.007 to 0.140 μM) and showed activity against HIV-2 (EC50 values ranged from 0.007 to 1.5 μM).

HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 RT.

TAF

TAF is a phosphonamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). Cells are permeable to TAF, and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading TFV into PBMCs, including T cells and macrophages [Birkus 2008, Birkus 2007]. Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate (TFV-DP) [Robbins 1998]. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination [Cherrington 1995, Yokota 1994]. Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and HBV [Delaney 2006, Kalayjian 2003, Lee 2005]. In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mtDNA polymerase γ [Cherrington 1994, Kramata 1998], and there is no evidence of mitochondrial toxicity in vitro based on several assays including mtDNA analyses [Birkus 2002, Stray 2017].

The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4-T lymphocytes. The EC50 values for TAF were in the range of 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC50 values ranged from 0.10 to 12.0 nM) and activity against HIV-2 (EC50 values ranged from 0.91 to 2.63 nM) (m2.6.3, Section 1.3, PC-120-2004). The antiviral activity of two TAF metabolites, M18 (GS-645552; isopropylalaninyl TFV) and M28 (GS-652829; alaninyl TFV), were evaluated in two T-lymphoblastoid cell lines (MT-2 and MT-4) following 5 days of compound exposure. GS-645552 is also a drug product

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degradant. Both metabolites showed weak inhibition of HIV-1 replication with 1723 to 2630-fold lower inhibitory potency relative to TAF (EC50 values of 7.41 to 21.0 µM) for metabolite M28 and 121 to 130-fold lower inhibitor potency relative to TAF (EC50 values of 0.56 to 0.97 µM) for metabolite M18.

HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed [Margot 2006]. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, FTC, TFV, and lamivudine (LAM) [Kagan 2007, Margot 2006]. In vitro drug resistance selection studies with TAF have shown no development of high-level resistance after extended time in culture.

Tenofovir has activity that is specific to HBV in addition to HIV-1 and HIV-2. The antiviral activity of TAF against a panel of HBV clinical isolates representing genotypes A-H was assessed in HepG2 cells. The EC50 values for TAF ranged from 34.7 to 134.4 nM, with an overall mean EC50 of 86.6 nM. The concentration that resulted in 50% cytotoxicity (CC50) in HepG2 cells was >44,400 nM. The combination of TFV and FTC was studied for cytotoxicity in MT-2 cells. No cytotoxicity was observed at the highest concentrations tested, up to 50 µM TFV and 5 µM FTC. Cytotoxicity studies were also conducted on the combination of TFV and FTC in HepG2 cells and no cytotoxicity was observed.

The antiviral activity of TAF was evaluated against a panel of HBV isolates containing nucleos(t)ide RT inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with resistance to LAM remained susceptible to TAF (< 2-fold change in EC50). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to TAF. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to TAF; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to TAF (3.7-fold change in EC50). The clinical relevance of these substitutions is not known.

B/F/TAF

Bictegravir, FTC, and TAF are potent and selective inhibitors of HIV-1. All 3 drugs show potent ARV activity against diverse subtypes of HIV-1 in vitro. Emtricitabine and TFV are phosphorylated intracellularly through non-overlapping pathways, and in combination show no antagonism for the formation of their active metabolites. Bictegravir does not require metabolic modification for activity. The anti-HIV-1 activity of the 3-drug combination of BIC, FTC, and TAF was found to be highly synergistic with no evidence of antagonism in vitro, supporting the use of these agents in combination in HIV-1 infected patients. In addition, in vitro combination studies have shown that in 2-drug combination studies BIC, FTC, and TFV have additive to synergistic anti-HIV-1 activity with other approved NRTIs, NNRTIs, and PIs [Hill 1997, Miller 1999, Rimsky 2001]. The resistance profiles of the individual agents BIC, TFV, and FTC are distinct and non-overlapping.

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Secondary pharmacodynamic studies

Cytotoxicity

BIC

For BIC, the concentration that resulted in 50% cytotoxicity (CC50) in primary CD4+ T-lymphocytes, MT-4, MT-2, resting and activated PBMCs, and monocyte-derived macrophages cells ranged from of 3700 to 29800 nM.

FTC

The cytotoxicity of FTC has been evaluated extensively in vitro. In all the cell lines examined, cell growth was not affected at concentrations of FTC≥ 100 µM (Schinazi 1994, Van Draanen 1994, Furman 1992).

TAF

Both TAF and its metabolites M18 and M28 had no cytotoxicity up to the highest tested concentration (57 µM).

Safety pharmacology programme

BIC

Bictegravir was evaluated in safety pharmacology studies of the central nervous system (CNS), respiratory, and cardiovascular systems. At the highest doses tested, BIC had no effects on the central nervous and respiratory systems of rats (300 mg/kg), no effects on the cardiovascular system of monkeys (1000 mg/kg), and no notable inhibition of the human ether-a-go-go-related gene (hERG) potassium channel current at a concentration > 7.1 µM. Plasma exposures (free [unbound] Cmax) in the in vivo studies were at least 0.92-fold (rats) and 22-fold (monkeys) of the free BIC Cmax concentration following clinical administration of the B/F/TAF fixed-dose combination (FDC). In the hERG study, exposures were at least 200-fold above free BIC Cmax concentration following clinical administration of the B/F/TAF FDC.

FTC

A comprehensive range of safety pharmacology studies revealed no treatment-related adverse effects on any organ system at systemic exposure levels much higher than those anticipated in patients at the recommended clinical dose (10- to more than 50-fold).

No effects on the CV system were reported in anesthetized dogs administered a cumulative dose of 38.5 mg/kg of FTC intravenously over a 1-hour period. In addition, there were no abnormalities reported on the electrocardiogram (ECG) data obtained from the repeated-dose toxicity studies in monkeys, where plasma AUC exposures were up to 26-fold higher than in humans administered the 200-mg dose.

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TAF

Tenofovir alafenamide was evaluated in safety pharmacology studies of the rat central nervous, renal, gastrointestinal (GI), and CV systems. In vivo safety pharmacology experiments were conducted using TAF as the monofumarate form in 50 mM citric acid. The 50% inhibitory concentration (IC50) for the inhibitory effect of TAF on hERG potassium current was estimated to be > 10 µM, far above human plasma exposure. There were no adverse effects detected in the CNS in rats dosed at 1000 mg/kg or in the renal system in rats administered 1000 mg/kg. In the chronic repeat dose dog study, a dose-related prolongation of PR interval was noted at Week 39; however, in the single dose CV safety pharmacology study in dogs dosed t 100 mg/kg (80 mg free base equivalents/kg), there were no findings. There was reduced gastric emptying in rats dosed at 1000 mg/kg but not at 100 mg/kg.

B/F/TAF

A comprehensive safety pharmacology program has been conducted for the 3 individual components of the B/F/TAF regimen. While the designs for these safety studies varied between the agents, the major organ systems were evaluated. Bictegravir had no effect on vital organ systems in safety pharmacology studies. Neither FTC nor TAF had clinically relevant effects on vital organ systems in safety pharmacology studies. Although TAF showed some potential to prolong the PR interval in the 39-week dog study (TOX-120-002), no PR prolongation or any change in ECG results occurred in the CV safety pharmacology study r in the thorough QT study (GS-US-120-0107). Neither BIC nor FTC had an effect on PR interval in safety pharmacology studies; therefore, there is no potential for overlapping toxicity. Overall, the pharmacological assessment of BIC, FTC, and TAF supports the effective use of these 3 agents together in combination therapy for HIV-1 infection.

Pharmacodynamic drug interactions

The anti-HIV-1 activity of 2-drug and 3-drug combinations of BIC, FTC, and TAF were found to be additive to highly synergistic with no evidence of antagonism in multiple in vitro assay systems, supporting the use of these agents in combination in HIV-infected patients.

In vitro two-drug combination studies have shown that BIC has additive to synergistic anti- HIV-1 activity with other approved NRTIs, NNRTIs, and PIs, including synergistic activity with TAF, FTC, and darunavir (DRV). No antagonistic antiviral interaction was found between BIC and the tested clinically relevant classes of antiretrovirals.

In two-drug combination studies of FTC with NRTIs, NNRTIs, PIs, and INSTIs, additive to synergistic effects were observed. No antagonism was observed for these combinations (Hill 1997, Rimsky 2001).

Pharmacokinetics

A comprehensive nonclinical program defining the absorption, distribution, metabolism, excretion and drug interaction potential of BIC, FTC and TAF/TFV has been completed. The nonclinical pharmacokinetic and disposition studies discussed in this section provide an adequate basis for comparing and interpreting results from toxicology and clinical studies.

Methods of analysis

The plasma BIC concentrations in nonclinical PK studies in mouse, rat, rabbit, dog, and monkey were quantified by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) or by liquid chromatography (LC) coupled to ultraviolet (UV) detection (LC-UV) methods.

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FTC: Analytical methods used to quantify FTC in mouse, rat, and monkey plasma from the early preclinical absorption, distribution, metabolism, and excretion studies employed reverse-phase high performance liquid chromatography (HPLC), and HPLC-MS (plasma and urine). LC-radio-profiling has been utilised to detect [3H]FTC in mice and monkeys, and to detect [14C]FTC in rats and monkeys.

TAF: Levels of TAF and TFV in rats and dog plasma and PBMCs were determined using fluorescence derivitization/HPLC. Additional methods to detect levels of TAF and TFV in mouse, rat, rabbit and dog plasma/PMBCs included validated LC/MS/MS methods, and HPLC detection methods. The absorption, distribution, metabolism, and excretion of TAF were assessed in various species following a single oral administration of [14C]TAF, and levels of TAF and its metabolites were measured using LSC, HPLC or LC/MS/MS coupled with flow-through detector (RFD). *In vitro* determination of TAF levels were in the main determined by LC/MS/MS, with some LC-radio-profiling. Induction potential of TAF on CYP activity measured mRNA levels using qRT PCR methods.
The bioanalytical methods are considered adequate.

Absorption

Bictegravir was absorbed quickly following oral solution administration, reaching maximal plasma concentrations (C_{max}) within 4 hours post-dose. The oral bioavailability of BIC solution formulation was moderate to high (42% to 74%).

Bictegravir was highly permeable and showed efflux transport in Caco-2 cell monolayers. Bictegravir was a substrate of P-glycoprotein (P-gp). The PK of BIC was determined in male rats, dogs, and monkeys following administration of oral solutions. Bictegravir systemic plasma clearance was low in nonclinical species (0.1% to 1.3% of hepatic blood flow). Bictegravir volume of distribution (Vss; 0.09 to 0.22 L/kg) in animals was lower than total body water. Bictegravir showed moderate to high oral bioavailability (42% to 74%) in nonclinical species. Bictegravir plasma exposure increased following repeat oral administration of BIC; the increases in C_{max} and AUC were less than dose proportional. In rats, females had higher BIC Cmax and AUC0-24 values than males, with gender-based differences of 2-to 3-fold on study days 90 and 181 for animals administered the high dose (300 mg/kg/day). In female rats administered the low dose (5 mg/kg/day), an accumulation (~ 3-fold) was observed. In monkeys, gender-based differences in BIC Cmax and AUC values were less than 2-fold and no accumulation (< 2-fold) of BIC was observed after repeat dosing.

FTC: No *in vitro* permeability studies have been carried out with FTC, as FTC shows high, dose-independent bioavailability *in vivo* in mice and monkeys. Single-dose pharmacokinetics of FTC have been studied in mice, rats and cynomolgus monkeys. FTC was rapidly and well absorbed with oral bioavailability ranging from 58% to 97% over the dose range of 10 to 600 mg/kg.

The multiple-dose pharmacokinetic parameters for FTC were derived as part of the repeat-dose toxicity studies in mice (80 to 3000 mg/kg/day; Study Nos. TOX109; IUW00701; TOX599; TOX628), in rats (60 to 3000 mg/kg/day; Study Nos. TOX108; TOX097), and monkeys (40 to 2000 mg/kg/day; Study Nos. TOX600; TOX627; TOX032) dosed for periods of 3 days to 104 weeks. There were no significant differences in pharmacokinetics following single and multiple dosing. Exposure to FTC (Cmax and AUC) increased approximately proportionally with dose and was similar between males and females.

TAF: Permeability of TAF was examined using Caco-2 cells (Study No. AD-120-2037). TAF was applied to monolayers of these cells at 10, 100, and 1000 µM, and TAF showed a dose dependent increase in forward permeability and a decrease in efflux ratio indicating saturable efflux transport. Addition of the efflux transport inhibitor, cyclosporine A (CsA) diminished the efflux ratio and increased the permeability.

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In rats, no consistent differences in plasma pharmacokinetic parameters were found between male and female rats. Mean tenofovir Cmax and AUC values increased dose proportionally over the dose range of 5 to 100 mg/kg/day. Mean TFV AUC obtained on Day 1 was slightly lower than that measured during Weeks 13 and 26, which suggested that there was a slight accumulation of tenofovir with repeat dosing. In dogs, there was some accumulation of tenofovir following repeat dosing (~3-fold).

Distribution

BIC was highly protein bound in plasma from all species tested (> 98% bound) and was 99.75% bound in humans. BIC is widely distributed with a rapid distribution but a very slow elimination (radioactivity was not eliminated from most tissues by 168h). BIC poorly crosses the blood:brain, blood:eye and blood:testis barriers and there is no preferential association with melanin. Pups were exposed to BIC according prenatal and postnatal development study in rats.

FTC: The protein binding of FTC was very low (< 5%) in mouse, rabbit, monkey, and human plasma (Study No. TBZZ/93/0025). The tissue distribution of [14C]FTC was characterized in rats and cynomolgus monkeys after a single oral dose of 200 mg/kg (Study Nos. TOX092 and TOX063, respectively). Distribution was extensive and rapid; levels were detected within 1 h post oral administration. There was no sign of FTC accumulation and elimination was rapid, no radioactivity was observed after 72 hours post-dose.

Pharmacokinetic parameters for FTC in pregnant animals appeared to be generally similar to those reported for non-pregnant animals. Emtricitabine was readily transferred across the placenta. Excretion into milk has not been evaluated for FTC.

TAF: The protein binding of TFV has been determined in human plasma and serum using centrifugal ultrafiltration (Study No. P0504-00039.1). Percent of unbound TFV was 99.3 ± 3.3% in human plasma, and 92.8 ± 3.6% in human serum. Tenofovir therefore showed very low protein binding in either human plasma or serum. There was rapid distribution to most tissues, both to mice, pigmented and non-pigmented rats. The tissues showing the highest maximum concentrations of radioactivity included kidney cortex, kidney(s), kidney medulla, and liver in mice and rats. In animal studies it has been shown that tenofovir was transferred across the placenta and was excreted in milk.

Metabolism

Unchanged BIC was the principal radiolabel component in all species (≥ 67 % in plasma). Bictegravir is metabolized by CYP3A oxidation and UGT conjugation and, hence, BIC plasma exposure may be altered by inducers or inhibitors of these enzymes. Despite the fact that the sulfate conjugate of hydroxylated BIC (M20) was present at higher concentrations in human than other species (20.1% in human versus 11.3% in rat and 0.77% in monkey), exposure of M20 in rats is estimated to be approximately 9-fold higher than observed human exposure at the clinical dose of 50 mg, and therefore further nonclinical characterization according to ICH M3 (R2) is not warranted.

There are no metabolism data in rabbit and therefore it cannot be concluded if findings in the EFD study in rabbit are caused by rabbit specific metabolites. However, rabbit have been exposed to BIC and rats have been well exposed to the major human metabolite M20.

FTC: FTC is not subject to significant metabolism by CYP enzymes. Generation of a minor (~1%) sulfoxide metabolite (M1 and/or M2) was catalysed by CYP3A4, and inhibitor studies suggested that at least one other enzyme, possibly flavin-containing monooxygenase, may play a role (Study No. 15396 v1). A minor direct glucuronide metabolite, M3, was also detected.

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FTC was not extensively metabolised and is eliminated primarily as unchanged drug by renal excretion in mice, rats, and cynomolgus monkeys. Over 90% of the radioactivity in mouse and rat urine and 64% of the radioactivity in monkey urine was unchanged drug. Only trace levels of metabolites were found in faeces (Study Nos. TEIN/93/0015, TEIN/93/0016, TOX063). In all 3 species, metabolism accounted for only a minor percentage of FTC elimination. FTC is subject to Phase I metabolism (oxidation to a diastereomeric sulfoxide) and to some direct conjugation (glucuronidation of hydroxymethyl group) as minor metabolic routes.

TAF: Tenofovir alafenamide is subject to intracellular metabolism to TFV, which is further phosphorylated to the anabolites, TFV-MP and TFV-DP with TFV-DP being the pharmacologically active form.

The Applicant has proposed a possible metabolism pathway based upon the findings from mice, rats, dogs and humans. TAF is also subject to intracellular metabolism to TFV, which is further phosphorylated to the anabolites, tenofovir-monophosphate and TFV-DP with TFV-DP being the pharmacologically active form.

Excretion

BIC was mainly eliminated through metabolism by the liver (34-40%) followed by excretion into feces (20-40%) and urine (7-15%).

FTC: The primary route of elimination of [3H]FTC and [14C]FTC was via renal excretion of parent drug after oral and IV administration in mice, rats, and cynomolgus monkeys. The majority of the FTC recovered in the faeces after oral administration most likely represents unabsorbed drug, rather than biliary excretion. Although FTC is metabolized to only a minor extent, its metabolites are also excreted via the kidneys. Excretion into milk has not been evaluated for FTC.

TAF: Recovery of radioactivity was 41.3 and 27.7% in faeces and urine, respectively, by 168 hours post-dose in mice. [14C]TAF was rapidly excreted within 24 hours after oral dosing in bile duct-intact and BDC male SD rats. The mean values of 71.9 and 22.2% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose. In dogs the excretion of [14C]TAF was determined after administration of a single 15-mg/kg oral dose of 14C-TAF to bile duct-intact and BDC male dogs. [14C]TAF was readily excreted mostly within 48 hours after oral dosing. The mean values of 37.4% and 35.9% of the administered radioactivity were excreted in faeces and urine, respectively, by 168 hours post-dose. Mean values of 2.11% and 14.0% of the administered radioactivity were excreted in bile in rat and dog, respectively, through 168 hours post-dose.

Excretion to milk: The extent of TFV excretion in lactating monkeys was evaluated. Milk was obtained from 2 lactating adult female rhesus monkeys following a single 30 mg/kg subcutaneous dose of TFV (Study No. PZ000116). TFV was detected in the milk, the AUC in milk was between 18.6-21.5% of that seen in plasma.

2.3.3. Toxicology

The toxicological profiles of BIC, FTC and TAF have been evaluated in a comprehensive set of non-clinical studies where the compounds have been evaluated separately. The performed studies include repeat-dose toxicity studies up to 6 months in rodents and 9 months in a non-rodent species, in vitro and in vivo genotoxicity, carcinogenicity, male and female fertility and early embryonic development in rodent, embryo-foetal development toxicity, peri- and post-natal development studies in rodents, phototoxicity studies.

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Single dose toxicity

No new single dose toxicity studies have been conducted, namely, no studies using bictegravir or the bictegravir/emtricitabine/tenofovir alafenamide combination. Studies conducted with emtricitabine, tenofovir disoproxil and tenofovir alafenamide, administered separately, revealed no risks of acute toxicity. The lack of dedicated single dose toxicity studies with bictegravir was considered acceptable. Other toxicological studies using this active substance indicate no risk of acute toxicity.

Repeat dose toxicity

Bictegravir

The oral toxicity of BIC has been studied in rats, and monkeys for treatment periods up to 39 weeks. Preliminary carcinogenicity study in transgenic mouse was also conducted for up to 4 weeks.
In rats, no major effect have been observed at up to 300 mg/kg/d for 26-weeks (20 fold the exposure following clinical administration of the B/F/TAF FDC).
However, BIC induced a high liver toxicity (bile duct hyperplasia, hepatocyte hypertrophy, regenerative hyperplasia, neutrophil infiltrate) with increased ALT activities in monkeys that persisted through the recovery phase at high dose of 1000 mg/kg/day (16 fold the exposure following clinical administration of the B/F/TAF FDC) in a 39-week toxicology study at the exception of increased ALT activities. The Applicant's conclusion on that the hepatobiliary effects observed in monkeys are not of relevance for humans is essentially solely based on the results of 4 Phase 3 clinical studies. It is not to be excluded the possibility that, depending on systemic exposure levels, the hepatobiliary effects observed in monkeys may represent a potential risk to humans, for which there is not a high safety margin. This information is considered of potential relevance to the prescriber and is included in section 5.3 of the SmPC.

FTC

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies repeated dose toxicity. Treatment-related effects were confined to high-dose groups only and included changes in red blood cell (RBC) parameters, interpreted as a mild, reversible anaemia (mice 1 month, 6 months; rat 3 months; monkey 1 year); changes in various organ weights without any associated adverse histopathological effects in rodents (mouse 1 month, 6 months; rat 3 months), increased urine output (mice 6 months), and soft faeces (monkeys 1 month, 3 months). No observed effect levels (NOELs) could be established for all treatment-related effects, and in several cases the minor effects observed were reversible after a recovery period.

TAF

Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of Descovy. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of Descovy.

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Bictegravir/FTC/TAF

No repeated dose toxicity studies have been conducted with the bictegravir/emtricitabine/tenofovir alafenamide triple combination. This is accepted, taking into account the lack of overlapping toxicities and the already available clinical experience with the combination. The Applicant considers that the increased phosphorous levels observed in rat repeat dose toxicity studies with bictegravir is not biologically significant and not relevant for consideration of the safety profile of the combination. This is based mostly on the lack of bone or renal microscopic findings in the rat 26 week repeated dose toxicity and carcinogenicity studies conducted with bictegravir and on an, as claimed, acceptable renal and bone clinical safety data for B/F/TAF.

Genotoxicity

Bictegravir

Despite precipitate and toxicity, no increase in the numbers of revertant colonies was observed in Ames test. In chromosome aberration test, an increase in the number of polyploid cells has been observed and the reason of this event is not fully understood. However, no increase in the number of cells with chromosomal aberrations or endoreduplication. No effect have been observed *in vivo* in micronucleus assessment at doses up to 29 fold the exposure following clinical administration of the B/F/TAF FDC, and therefore could be considered as non-genotoxic.

FTC / TAF

FTC and tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays.

Carcinogenicity

Bictegravir

The transgenic Tg-rasH2 model is acceptable for regulatory authorities as an alternative to the standard mouse long-term study (CHMP SWP Conclusions and recommendations on the use of genetically modified animal models for carcinogenicity assessment, CPMP/SWP/2592/02 Rev, June 2004). BIC did not induce a significant carcinogenic response in this animal model at exposures 15-fold above clinical exposure levels. It could be noted that disturbing data have been observed in the rat carcinogenicity study (tumours with statistically significant increase in treated rats) in addition to carcinoma observed in the 26-weeks study in rats, hyperplasia not reversed in the 39-weeks in monkeys, the lack of the major human metabolite M20 in TG mice in carcinogenicity study and the increase of combined spleen/urinary bladder/uterus/vagina b-hemangioma/m-hemangiosarcoma tumors at the mid-dose in the TG mice carcinoma study. However tumours observed in the rat carcinogenicity study were comparable to historical control data.

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Reproductive and developmental toxicity

Bictegravir

In rats, BIC did not affect fertility or early embryonal development in rats at exposure margins of up to 22 times the 50 mg human clinical exposure based on AUC.

Concerning embryo-foetal development in rats, BIC did not affect implantations, percent preimplantation loss, litter sizes, live foetuses, early resorptions or percent post-implantation loss.

BIC was shown to be devoid of embryo-foetotoxic or teratogenic potential in rabbits at exposure margins at the NOAEL of 0.59 times the 50 mg human clinical exposure based on AUC. The high dose level induced some maternal toxicity, as shown notably by significant decreases in body weight with abortion in 2 does.

Concerning prenatal and postnatal development study in rats, the Applicant states that no test article-related effects were noted at any dosage level during the study and the NOEL for F0 maternal systemic toxicity, and F1 neonatal/developmental toxicity, parental systemic toxicity, and reproductive toxicity, and F2 neonatal/early postnatal toxicity was 300 mg/kg/day.

FTC / TAF

No special hazard for humans was revealed in conventional studies of toxicity to reproduction and development with FTC.

Because there is a lower tenofovir exposure in rats and mice after the administration of tenofovir alafenamide compared to tenofovir disoproxil fumarate, a rat peripostnatal study was conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of toxicity to reproduction and development. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peri-postnatal toxicity study at maternally toxic doses.

Juvenile toxicity

Bictegravir / FTC / TAF

No juvenile toxicity studies have been conducted with BIC, F or TAF. This is acceptable, since the presently sought indication of BIC/F/TAF is confined to the adult population.

Local Tolerance

Bictegravir

BIC could be considered to be non-corrosive, non-irritant in the in vitro skin model EpiDerm.

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FTC / TAF

No specific local tolerance studies have been conducted with FTC and no particular alert in repeat dose toxicity studies has been observed.

In a bovine corneal opacity and permeability assay (BCOP) TAF elicited an in vitro irritancy score of 21.0 ± 8.7 with a 4-hour incubation and was predicted to be a noncorrosive/non-severe eye irritant.

In a dermal irritation study in rabbits animals were given a single 4 hour, semi-occlusive, dermal administration of approximately 0.5 g of TAF and were observed for 4 days (Study number: TX-120-2011). No local dermal reaction was observed in any animal throughout the duration of the study. The Primary Irritation Index was calculated to be 0.0; TAF was classified as a 'non-irritant'.

The potential for additive effects among the three agents in the B/F/TAF FDC is minimal.

Immunotoxicity

Bictegravir / FTC / TAF

No specific immunotoxicity studies have been conducted with BIC and TAF and no particular alert in repeat dose toxicity studies has been observed.

An immunotoxicity study was conducted with FTC and there was no effect on the immune system as evaluated by IgM antibody response in the rat to sheep red blood cells with doses up to 1000 mg/kg/day.

Antigenicity

Bictegravir

BIC is not a potential skin sensitizer.

FTC / TAF

No specific antigenicity studies have been conducted with FTC and no particular alert in repeat dose toxicity studies has been observed.

Female mice were given TAF (GS-7340-03) at of 10, 25 or 50% w/v. The animals were administered TAF by daily application of 25 µL of the appropriate concentration or control (vehicle or positive), to the dorsal surface of both ears for 3 consecutive days. The proliferative response of the lymph node cells (LNCs) from the draining auricular lymph nodes was assessed 5 days following the initial application, by measurement of the incorporation of 3H-methyl thymidine (3HTdR) by β-scintillation counting of LNC suspensions.

The response was expressed as radioactive disintegrations per minute per lymph node (dpm/node) and as the ratio of 3HTdR incorporation into LNC of test nodes relative to that recorded for control nodes (test/control ratio), termed as SI. The test substance is regarded as a sensitizer if at least one concentration of the chemical has a SI of 3 or more. The SI obtained for 10%, 25%, and 50% w/v were 0.9, 1.0, and 1.0, respectively, which indicates that TAF did not show the potential to induce skin sensitisation. The EC3 value (the "estimated concentration of 3" is the concentration of test substance

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which would result in a SI of 3 in the LLNA) was determined to be higher than 50% w/v. The SI for the positive control substance hexyl cinnamic aldehyde was 6.3, which demonstrates the validity of this study.

Impurities

Bictegravir / FTC / TAF

The impurities and degradation products in the BIC, FTC or TAF drug substance have been identified and qualified in toxicology studies.

Phototoxicity

Bictegravir

The irradiation sources used in the positive in vitro study and negative in vivo study differ. The emission spectra of the light source used for the in vitro study starts at 300-310 nm while the spectra of the light source used for the in vivo study starts at 310-320 nM. It remains that the absorbance of BIC is substantially equivalent between 290 and 320 nm, and the animals have been well exposed to BIC in the in vivo study.

FTC / TAF

FTC and TAF fumarate does not absorb light within the range of natural sunlight; therefore no phototoxicity studies are not considered necessary for FTC or TAF.

Other toxicity studies

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TAF - Bone metabolism

Three relevant non-GLP rat studies and one GLP dog study were conducted to evaluate the potential for TAF to alter bone metabolism.

Male rats were given 400 mg/kg TAF by oral gavage daily for 6 days. One animal was due to non-drug related injury (study number: RS90177). The results of this study demonstrated that TAF had effects on selected urinary and serum parameters. The Applicant states that due to the lack of strong statistical comparison to controls and lack of correlation between data, interpretation on overall toxicity was not possible.

In the second study, an additional dose was evaluated. This study examined changes in markers of calcium homeostasis in male Sprague-Dawley rats after once daily oral administration of TAF. Animals were given 100 or 400 mg/kg TAF by oral gavage on Days 0, 1, 2, 3, 4, and 5. The results indicated that daily administration of TAF to rats for 6 days altered plasma vitamin D, calcium and phosphate levels as well as urinary excretion of calcium. It is stated that the mechanistic basis of these changes and their biological relationships in terms of cause and effect are unknown.

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Dogs were given oral doses of 37.5 or 75 mg/kg/day of TAF for 5 days (1/dose). The Applicant states that there were no biologically important changes observed in mean values for ionized calcium or N telopeptide. The Applicant states that the lack of the expected age-related reduction in mean serum bone ALP (B-ALP) suggested increased bone remodelling. The mean serum calcitriol (1, 25 dihydroxycholecalciferol) concentration was reduced by approximate 68% at both doses. The mean serum 25-hydroxyvitamin D (25 hydroxycholecalciferol) concentration was reduced approximately 35% and 33% at 37.5 and 75 mg/kg/day. Gastrointestinal lesions characterised by epithelial cell necrosis, regenerative hyperplasia, and cyst formation were most prevalent in animals at 75 mg/kg/day. Lymphoid cell depletion was noted in the lymph nodes, thymus and tonsil at 75 mg/kg/day animals. Bile duct hyperplasia and peri-portal inflammation was observed at both doses.

TAF - Renal Function

An investigative study was conducted in SD rats to evaluate renal parameters. Animals were given a single oral dose of 100 or 1000 mg/kg/day TAF. Urinary output of calcium was increased at 1000 mg/kg/day which correlated with an increase in serum calcium concentration and indicated that the kidneys were functioning in order to reduce the serum calcium load.

2.3.4. Ecotoxicity/environmental risk assessment

Bictegravir

This environmental risk assessment is in accordance with guidelines, and based on the data generated for the Phase II A assessment, the proposed use of BIC poses no unacceptable risk to the environment. The Phase II B assessment is ongoing and the final results from the required studies are pending. The Applicant committed to submit the completed study reports post-authorisation (December 2018) along with an updated risk assessment. The results of the environment risk assessment of BIC are summarised below.

Summary of main study results

Substance (INN/Invented Name): BIC			
CAS-number (if available): 1807988-02-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Dow = 2.2 at pH 7	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.2	
	BCF		not B
Persistence	DT50 or ready biodegradability	96.5 - 911 d (Sediment)	vP
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.3 (*Fpen* 0.012)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	KF^{ads} soil 1089 - 4123 L/kg $KFoc^{ads}$ soil 67640-248373	

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		L/kg KF^{ads} sewage sludge 5605 - 5683 L/kg $KFoc^{ads}$ sewage sludge 12829-14634 L/kg			
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.4-1.1 d $DT_{50, sediment}$ = 45.2-437 d $DT_{50, whole system}$ =2.6-439 d *(At 12°C: $DT_{50, sediment}$ = 911 $DT_{50, whole system}$ = 369 d (calculation with Cake3.3 according assessor's assessment))* % shifting to sediment >10% AR in sediment at or after 14 d			Very persistent BIC distributes to the sediment with more than 10% of the applied dose associated with sediment after Day 14
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *species*	OECD 201	NOEC	0.066	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.17	mg/L	
Fish, Early Life Stage Toxicity Test/ *species*	OECD 210	NOEC	1.2	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	26	mg/L	*Sewage microorganisms*
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Not required
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			***In progress****
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	***In progress****
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	***In progress****
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	***In progress****
Collembola, Reproduction Test	OECD 232	NOEC		mg/kg	***In progress****
Sediment dweiling organism *Chironomus.sp*	OECD 218	NOEC		mg/kg	***In progress****

* ERA report will be updated by December 2018

FTC / TAF

The environmental risk assessment of Descovy has shown that FTC does not bioaccumulate and is of low risk to the aquatic or terrestrial environments. TAF is a next generation pro-drug of tenofovir (TFV) and TFV has been identified as persistent in the environment, but it is considered to be of low risk to aquatic organisms, it is not bioaccumulative and does not pose significant risk to the environment.

Substance (INN/Invented Name): Emtricitabine			
CAS-number (if available): 143491-57-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *Kow*	OECD107	-0.693 – -0.670	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *Kow*	-0.693 – -0.670	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	$DT_{50, water}$ = 81-209 d $DT_{50, whole system}$ = 92.2-286 d No significant metabolites formed	vP
Toxicity	NOEC or CMR		not T

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PBT-statement :	The compound is not considered as PBT nor vPvB					
Phase I						
Calculation	**Value**	**Unit**				**Conclusion**
PEC surfacewater, refined	1.2 (*Fpen* 0.012)	µg/L				> 0.01 threshold (Y)
Other concerns (e.g. chemical class)						(N)
Phase II Physical-chemical properties and fate						
Study type	**Test protocol**	**Results**				**Remarks**
Adsorption-Desorption	OECD 106	*Kd* sludge =12.9 L.kg-1				
Ready Biodegradability Test	OECD 301	Not readily biodegradable				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 38-98 d $DT_{50, sediment}$ = χ^2 always > 15 % $DT_{50, whole system}$ = 43.2-134 d *(At 12°C: $DT_{50, water}$ = 81-209 d $DT_{50, whole system}$ = 92.2-286 d (calculation with KinGUII 2.1 according assessor's assessment))* % shifting to sediment >10% AR in sediment at or after 14 d				Very persistent in water/whole system. Sediment toxicity assessment is triggered.
Phase IIa Effect studies						
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**		**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥ 110	mg.L-1		*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 110	mg.L-1		
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	6.10	mg.L-1		*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	≥ 1000	mg.L-1		Sewage microorgnisms
Phase IIb studies						
Sediment dwelling organism	OECD 218	NOEC	≥ 38 ≥ 200 (normalised)	mg/kgd wt		*Chironomus riparius* normalised for 10% OC 200 mg.kgdwt -1)

Substance (INN/Invented Name): Tenofovir alafenamide (as environmentally relevant TFV)			
CAS-number (if available): 1392275-56-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log Kow	OECD107	-3.8 - -4.3	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log Kow	-3.8 - -4.3	not B
	BCF	Not required	not B
Persistence	DT50 or ready biodegradability	$DT_{50, water}$ = 8.3-22 d $DT_{50, sediment}$ = 142-303 d $DT_{50, whole system}$ = 12.8-60 d Formation of three significant transformation products, two of which are persistent.	vP
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, refined	0.07 µg/L (*Fpen* 0.012)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc ads soil 351 - 1091 L.kg-1 Koc des soil 968 - 2791 L.kg-1 KF ads sludge 6.0 - 21 L.kg-1 KF des sludge 16 - 62 L.kg-1	
Ready Biodegradability Test	OECD 301	Not readily biodegradable	

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Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.9-10.3 d $DT_{50, sediment}$ = 66.5-142 d $DT_{50, whole\ system}$ = 6.0-25 d *(At 12°C: $DT_{50, water}$ = 8.3-22 d $DT_{50, sediment}$ = 142-303 d $DT_{50, whole\ system}$ = 12.8-60 d (calculation with KinGUII 2.1 according assessor's assessment))* % shifting to sediment >10% AR in sediment at or after 14 d Formation of three significant transformation products, two of which are persistent.			Very persistent in sediment. Formation of three significant transformation products, two of which are persistent. Sediment toxicity assessment is triggered.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	32	mg.L-1	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 100	mg.L-1	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	≥10	mg.L-1	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg.L-1	Sewage microorganisms
Phase II b studies					
Sediment dwelling organism	OECD 219	NOEC	≥ 290 ≥ 1261 (normalised)	mg/kg dwt	*Chironomous riparius* normalised for 10% OC 17.06 mg.kgdwt-1

2.3.5. Discussion on non-clinical aspects

Pharmacology

No novel non-clinical pharmacology studies with F and TAF have been submitted with this application. The studies supporting the use of these substances are well known. There are no findings in the secondary pharmacology or safety pharmacology studies with BIC to be considered in the safety evaluation, and therefore no findings in studies on secondary pharmacology or safety pharmacology to be considered specifically in the safety evaluation of the triple combination.

Pharmacokinetics

The single dose PK of BIC has been determined in rats, dogs and monkeys. In rats, females had higher BIC Cmax and AUC0-24 values than males, with gender-based differences of 2-to 3-fold on study days 90 and 181 for animals administered the high dose (300 mg/kg/day). In female rats administered the low dose (5 mg/kg/day), an accumulation (~ 3-fold) was observed.

Bictegravir was absorbed quickly following oral solution administration, reaching maximal plasma concentrations (C_{max}) within 4 hours post-dose, and is widely distributed with a rapid distribution but a very slow elimination. The oral bioavailability of BIC solution formulation was moderate to high (42% to 74%). Despite the fact that the sulfate conjugate of hydroxylated BIC (M20) was present at higher concentrations in human than other species (20.1% in human versus 11.3% in rat and 0.77% in monkey), exposure of M20 in rats is estimated to be approximately 9-fold higher than observed human exposure at the clinical dose of 50 mg, and therefore further nonclinical characterization according to ICH M3 (R2) is not warranted. There are no metabolism data in rabbit.

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No novel nonclinical pharmacokinetics studies with FTC or TAF have been submitted with this application. There were no findings in these studies on pharmacokinetics to be considered specifically in the safety evaluation of the triple combination.

Toxicology

The oral toxicity of BIC has been studied in rats and monkeys for treatment periods up to 39 weeks. Preliminary carcinogenicity study in transgenic mouse was also conducted for up to 4 weeks.
In rats, no major effect has been observed at up to 300 mg/kg/d for 26-weeks. BIC induced a high liver toxicity (bile duct hyperplasia, hepatocyte hypertrophy, regenerative hyperplasia, neutrophil infiltrate) with increased ALT activities in monkeys that persisted through the recovery phase at high dose of 1000 mg/kg/day. The Applicant considered that there is no evidence for that the hepatobiliary effects observed in the chronic toxicity study with administration of bictegravir to cynomolgus monkeys is significant or relevant for humans. Information on the hepatobiliary effects is included in section 5.3 of the SmPC.

Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies repeated dose toxicity. Treatment-related effects were confined to high-dose groups only and included changes in red blood cell (RBC) parameters. Non-clinical studies of tenofovir alafenamide in rats and dogs revealed bone and kidney as the primary target organs of toxicity.

BIC, FTC and tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxicity assays. No special hazard for humans was revealed in conventional studies of carcinogenic potential for F or TDF. BIC did not induce a significant carcinogenic response in this transgenic mouse or in rats at exposures 15-fold and 21-fold above clinical exposure levels respectively.
Studies in animals with bictegravir have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with bictegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints.

There were no other findings in all non-clinical studies to be considered specifically in the safety evaluation of the triple combination.

Environmental risk assessment
Studies for BIC are ongoing and will be submitted post-authorization.

2.3.6. Conclusion on the non-clinical aspects

There are no objections to an approval of BIC/F/TAF from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

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An overview of clinical studies in support of this application is provided in Table 6 and 7.

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Table 6. Clinical Pharmacology studies

Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-141-1218,	Phase 1 placebo-controlled study to evaluate the safety, tolerability, and PK of single- and multiple-ascending doses of BIC and the DDI potential between BIC and F/TAF in healthy subjects	**BIC** 5-mg tablet (EC1401B1), 25-mg tablet (EC1402C1), 50 mg (2 × 25-mg tablets), 100-mg tablet (EC1402D1), 300 mg (3 × 100-mg tablets), 600 mg (6 × 100-mg tablets) **F/TAF** 200/25-mg tablet (CR1305B2)	130	**Placebo-to-match BIC**
GS-US-141-1219,	Phase 1b placebo-controlled study to evaluate the safety, PK, and short-term antiviral activity of BIC compared with placebo-to-match in HIV-infected subjects	**BIC** 5-mg tablet (EC1401B1), 25-mg tablet (EC1402C1), 50 mg (2 × 25-mg tablets), 100-mg tablet (EC1402D1)	20	**Placebo-to-match BIC**
GS-US-141-1475,	Phase 2, randomized, double-blinded study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF	**BIC** 75-mg tablet (EC1504B1, EC1504B2, EC1506B1) + **F/TAF** 200/25-mg tablet (CR1408B1, CR1412B1) **B/F/TAF** 50/200/25-mg tablet (EN1504B1, EN1602B2)	98	**DTG** 50-mg tablet + **F/TAF** 200/25-mg tablet **Placebo-to-match BIC**
GS-US-141-1478,	Phase 1 study to evaluate the PK of single-dose BIC in subjects with normal or impaired hepatic function	**BIC** 75-mg tablet (EC1504B2)	20	Not applicable
GS-US-141-1479,	Phase 1 study to evaluate the PK of single-dose BIC in subjects with normal or impaired renal function	**BIC** 75-mg tablet (EC1504B1)	18	Not applicable
GS-US-141-1480,	Phase 1 placebo- and positive-controlled study to evaluate the effects of BIC (at therapeutic and supratherapeutic doses) on ΔΔQTcF in healthy subjects	**BIC** 75-tablet (EC1504B1) and 300 mg (4 × 75-mg tablets)	48	**Placebo-to-match BIC** **Moxifloxacin** 400-mg tablet
GS-US-141-1481,	Phase 1 mass balance study to evaluate the PK, metabolism, and excretion of a single oral dose of radiolabeled [^{14}C]BIC in healthy male subjects	**BIC** 100 mg (99 mg of nonradiolabeled BIC [as GS-9883-01] plus approximately 100 µCi [1 mg] radiolabeled [^{14}C]GS-9883 administered orally as an approximately 40-mL ethanolic solution) (EC1505Aand GS017-023-0583-B-20150324CLI, GS017-023-0583-C-20150324CLI, GS017-023-0583-D-20150324CLI, and GS017-023-0583-E-20150324CLI)	8	Not applicable

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Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[b])	n[b]	
GS-US-141-1485,	Phase 1 study to evaluate the effects of the probe drugs, ATV +COBI (a mixed inhibitor of UGT1A1/CYP3A4/P-gp), RIF (a CYP3A4/P-gp/UGT1A1 inducer), ATV (a UGT1A1/CYP3A4 inhibitor), VORI (a CYP3A4 inhibitor), RBT (a CYP3A4/P-gp inducer), and DRV/co (a CYP3A4 inhibitor) on the PK and safety of BIC in healthy subjects	**BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **ATV** 300-mg capsule + **COBI** 150-mg tablet **BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **RIF** 600 mg (2 × 300-mg capsules) **BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **ATV** 400 mg (2 × 200-mg capsules) **BIC** 75 mg (3 × 25-mg tablets) (EC1402C1) + **VORI** 300 mg (2 × 50-mg tablets + 1 × 200-mg tablet) **BIC** 75-mg tablet (EC1504B1) or 3 × 25-mg tablets (EC1402C1) + **RBT** 300 mg (2 × 150-mg capsules) **BIC** 75-mg tablet (EC1504B1) or 3 × 25-mg tablets (EC1402C1) + **DRV/co** 800/150-mg tablet	90	**BIC** 75-mg tablet or 3 × 25-mg tablets
GS-US-141-1487,	Phase 1 placebo-controlled study to evaluate the effect of BIC on renal function as assessed by markers of GFR in healthy subjects	**BIC** 75-mg tablet (EC1504B1)	40	**Placebo-to-match BIC**
GS-US-311-1790 (Cohort 2)[c],	Phase 1 study to evaluate the effect of BIC on the PK of a representative hormonal contraceptive medication, NGM/EE (Ortho Tri-Cyclen® Lo), in healthy women of childbearing age	**BIC** 75-mg tablet (EC1504B1) + **Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg	16	**Ortho Tri-Cyclen Lo** NGM 0.180 mg/0.215 mg/ 0.250 mg/EE 0.025 mg
GS-US-141-1233,	Phase 1 study to evaluate the relative bioavailability of 2 B/F/TAF FDC tablets (75/200/25 mg and 50/200/25 mg) compared with BIC 75-mg + F/TAF 200/25 mg administered simultaneously under fasted conditions and of the effect of food on the PK of BIC, FTC, and TAF when administered as the B/F/TAF FDC in healthy subjects	**B/F/TAF** 75/200/25-mg tablet (EN1501B1) **B/F/TAF** 50/200/25-mg tablet (EN1503B1)	56	**F/TAF** 200/25-mg tablet **BIC** 75-mg tablet
GS-US-380-1489,	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	**B/F/TAF** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1604B2, EN1606B2, EN1608B1, EN1609B1) **Placebo-to-match ABC/DTG/3TG** (EJ1502B1, EJ1501B1R, EJ1601B1, EJ1602B1)	308	**ABC/DTG/3TG** 600/50/300-mg tablet **Placebo-to-match B/F/TAF**

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Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-380-1490,	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	**B/F/TAF** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1604B2, EN1606B2, EN1608B1, EN1609B1) **Placebo-to-match DTG** (EK1501B1, EK1502B1, EK1503B1) **Placebo-to-match F/TAF** (CR1311B1, CR1507B1, CR1507B2, CR1602B1)	98	**DTG** 50-mg tablet + **F/TAF** 200/25-mg tablet **Placebo-to-match B/F/TAF**
GS-US-380-1844,	Phase 3, randomized, double-blinded study to evaluate the safety and efficacy of switching to B/F/TAF from DTG+ABC/3TC or ABC/DTG/3TC vs continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC	**B/F/TAF** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1602B2, EN1604B2, EN1608B1) **Placebo-to-match ABC/DTG/3TG** (EJ1502B1, EJ1501B1R, EJ1601B1)	563	**ABC/DTG/3TG** 600/50/300-mg tablet **Placebo-to-match B/F/TAF**
GS-US-380-1878,	Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF vs continuing on boosted ATV or DRV plus either FTC/TDF or ABC/3TC	**B/F/TAF** 50/200/25-mg tablet (EN1503B2, EN1504B1, EN1601B2, EN1602B2, EN1604B2, EN1606B2, EN1608B1, EN1609B1)	577	Current ARV drug regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC administered orally once daily with food. Investigators provided a prescription for the ARV treatment, and subjects were responsible for obtaining the medication
GS-US-380-1991,	Phase 1 study to investigate the steady-state PK of B/F/TAF in healthy Japanese and Caucasian subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2)	50	Not applicable
GS-US-380-1761,	Phase 1 study to evaluate the steady-state PK of BIC, FTC, TAF, its metabolite TFV, and to evaluate the steady-state PK of SOF, its metabolites GS-566500 and GS-331007, and LDV after administration of LDV/SOF+B/F/TAF in healthy subjects	**LDV/SOF** 90/400-mg tablet + **BIC/F/TAF** 75/200/25-mg tablet (EN1501B1)	30	**LDV/SOF** 90/400-mg tablet **B/F/TAF** 75/200/25-mg tablet

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Study Number, Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Lot Number[a])	n[b]	
GS-US-380-1999,	Phase 1 study to evaluate the DDI potential between B/F/TAF and SOF/VEL/VOX in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B1) + **SOF/VEL/VOX** 400/100/100-mg tablet + **VOX** 100-mg tablet	30	**B/F/TAF** 50/200/25-mg tablet **SOF/VEL/VOX** 400/100/100-mg tablet + **VOX** 100-mg tablet
GS-US-380-3908,	Phase 1 placebo-controlled study to assess the effect of B/F/TAF on metformin PK and PD in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2) **Metformin** 500-mg tablet and 850-mg tablet	32	**B/F/TAF placebo-to-match** **Metformin** 500-mg tablet and 850-mg tablet
GS-US-380-3909,	Phase 1 study to evaluate the effect on BIC PK of simultaneous administration of antacid, calcium, or iron supplements with B/F/TAF compared with administration of B/F/TAF alone under fasted and fed conditions and evaluate the effect on BIC PK of staggered administration of B/F/TAF and antacid, calcium, or iron supplements compared with administration of B/F/TAF alone in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2) + **Maximum strength antacid** 20 mL oral suspension **B/F/TAF** 50/200/25-mg tablet (EN1503B2) + **Calcium carbonate** 2 × 600-mg tablets **B/F/TAF** 50/200/25-mg tablet (EN1503B2) + **Ferrous fumarate** 324-mg tablet	42	**B/F/TAF** 50/200/25-mg tablet
GS-US-380-4270,	Phase 1 study to evaluate the effect of BIC when administered as the B/F/TAF on the PK of the CYP3A probe MDZ in healthy subjects	**B/F/TAF** 50/200/25-mg tablet (EN1503B2) **MDZ** 2-mg oral syrup	14	**MDZ** 2-mg oral syrup

a Lot number provided only for BIC, FTC, or TAF-containing products.

b Number of subjects who were administered any test treatment.

c The study information for Study GS-US-311-1798 (Cohort 2) is provided in this table.

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Clinical Efficacy studies:

Table 7. Primary Studies Supporting Efficacy of B/F/TAF

Study	Study Design	Number of Subjects[a] by Treatment Regimen	Data Presented
HIV-Infected, ART-Naive Adult Subjects			
GS-US-380-1489	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs ABC/DTG/3TC	B/F/TAF (N = 314) ABC/DTG/3TC (N = 315)	Week 48 efficacy, PK, and safety
GS-US-380-1490	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of B/F/TAF vs DTG+F/TAF	B/F/TAF (N = 320) DTG+F/TAF (N = 325)	Week 48 efficacy, PK, and safety
GS-US-141-1475	Phase 2, randomized, double-blind study to evaluate the safety and efficacy of BIC+F/TAF vs DTG+F/TAF Open-label extension phase allowed crossover from DTG+F/TAF to B/F/TAF or continuation of BIC+F/TAF as the B/F/TAF FDC	Double-blind phase: BIC 75 mg + F/TAF (N = 65) DTG+F/TAF (N = 33) Open-label extension phase: Continue BIC and F/TAF as the B/F/TAF FDC (N = 62) Switch to the B/F/TAF FDC from DTG+F/TAF (N = 30)	Double-blind phase: Week 48 efficacy, PK, and safety Open-label extension phase: Week 72 efficacy and safety
HIV-Infected, Virologically Suppressed Adult Subjects			
GS-US-380-1844	Phase 3, randomized, double-blind study to evaluate the safety and efficacy of switching to B/F/TAF from DTG+ABC/3TC or ABC/DTG/3TC vs continuing DTG and ABC/3TC as the ABC/DTG/3TC FDC	Switch to B/F/TAF (N = 282) Stay on DTG and ABC/3TC as the ABC/DTG/3TC FDC (N = 281)	Week 48 efficacy, PK, and safety
GS-US-380-1878	Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF vs continuing on boosted ATV or DRV plus either FTC/TDF or ABC/3TC	Randomized phase: Switch to B/F/TAF (N = 290) Stay on baseline regimen (N = 287) Open-label extension phase: Continue B/F/TAF (N = 241) Switch to B/F/TAF from SBR (N = 213)	Randomized phase: Week 48 efficacy, PK, and safety Open-label extension phase: deaths, SAEs, and discontinuations due to AEs

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

2.4.2. Pharmacokinetics

Absorption

Bioavailability

The absolute bioavailability of BIC has not been evaluated in humans. The absorption of BIC in humans is expected to be > 61% based on the results of the human ADME study in healthy subjects Study GS-US-141-1481.

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Bioequivalence

An FDC formulation containing BIC 75 mg, FTC 200 mg, and TAF 25 mg was initially developed and evaluated for relative bioavailability compared with BIC 75 mg + F/TAF (200/25 mg), each administered under fasted conditions (Study GS-US-141-1233).

Study GS-US-141-1233 – Study Title: *A Phase 1, Open-label, Two-Cohort, Multiple-Period, Fixed-Sequence, Crossover Study to Evaluate 1) the Relative Bioavailability of Two GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets Versus a GS-9883 (75 mg) Tablet and a Emtricitabine/Tenofovir Alafenamide (200/25 mg) Fixed-Dose Combination Tablet Administered Simultaneously and 2) the Effect of Food on the Pharmacokinetics of GS-9883, Emtricitabine and Tenofovir Alafenamide When Administered as GS-9883/Emtricitabine/Tenofovir Alafenamide (75/200/25 mg and 50/200/25 mg) Fixed-Dose Combination Tablets*

Bictegravir AUC_{inf} and C_{max} for single-dose administration of the B/F/TAF (75/200/25 mg) FDC were approximately 27% and 31% higher, respectively, relative to BIC 75 mg + F/TAF (200/25 mg). Therefore, another FDC formulation was developed that contained BIC 50 mg, FTC 200 mg, and TAF 25 mg. Upon single-dose administration of the B/F/TAF (50/200/25 mg) FDC or BIC 75 mg + F/TAF (200/25 mg) under fasted conditions (also in Study GS-US-141-1233), the geometric least-squares mean ratios and their 90% CIs for the BIC primary PK parameters of AUC_{last}, AUC_{inf}, and Cmax were 78.46% (73.38, 83.89), 78.56% (73.44, 84.04), and 78.07% (73.41, 83.01), respectively, and were considered by the Applicant as within the protocol-defined boundary of PK equivalence (70% to 143%). Based on these data, the B/F/TAF 50/200/25 mg FDC was chosen for further evaluation in Phase 3 studies.

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Table 8. BIC, FTC, and TAF PK parameters and statistical comparisons for relative bioavailability between the 75-mg or 50-mg B/F/TAF FDC and BIC 75 mg + F/TAF

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF (75/200/25 mg), fasted (Test) (N = 28) vs BIC 75 mg + F/TAF (200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	151,844.6 (26.9)	119,619.4 (26.6)	126.76 (117.82, 136.37)
AUC_{inf} (hr•ng/mL)	156,637.5 (27.5)	123,174.0 (26.6)	126.82 (117.87, 136.45)
C_{max} (ng/mL)	7123.9 (21.6)	5593.9 (31.0)	130.72 (119.95, 142.45)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	11,412.3 (13.5)	11,199.3 (13.7)	101.89 (99.50, 104.33)
AUC_{inf} (hr•ng/mL)	11,642.8 (13.2)	11,436.4 (13.2)	101.78 (99.45, 104.16)
C_{max} (ng/mL)	2264.3 (22.7)	2153.6 (21.5)	104.86 (97.73, 112.50)
TAF PK Parameter			
AUC_{last} (hr•ng/mL)	205.5 (45.5)	223.6 (45.2)	91.62 (82.13, 102.21)
AUC_{inf} (hr•ng/mL)	206.8 (45.2)	225.1 (45.0)	91.56 (82.27, 101.91)
C_{max} (ng/mL)	253.3 (44.2)	276.7 (51.7)	95.47 (79.88, 114.10)
B/F/TAF (50/200/25 mg), fasted (Test) (N = 27) vs BIC 75 mg + F/TAF (200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	109,061.4 (21.0)	142,396.6 (30.5)	78.46 (73.38, 83.89)
AUC_{inf} (hr•ng/mL)	112,619.6 (21.9)	146,931.6 (31.1)	78.56 (73.44, 84.04)
C_{max} (ng/mL)	5228.1 (16.9)	6791.1 (26.4)	78.07 (73.41, 83.01)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,652.9 (13.6)	11,035.5 (14.4)	96.52 (93.95, 99.15)
AUC_{inf} (hr•ng/mL)	10,873.9 (13.6)	11,234.6 (14.2)	96.76 (94.22, 99.37)
C_{max} (ng/mL)	2220.4 (30.1)	2166.4 (27.0)	102.36 (93.85, 111.64)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	207.1 (46.5)	236.7 (45.3)	85.37 (75.24, 96.85)
AUC_{inf} (hr•ng/mL)	208.8 (46.3)	238.3 (45.9)	85.48 (75.33, 97.00)
C_{max} (ng/mL)	249.2 (51.6)	291.9 (55.4)	84.17 (67.59, 104.81)

a N = 28 for both the Test and Reference groups

Food effect

GS-US-141-1233 showed that after a high-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.13 fold, and after a moderate-fat meal, BIC AUC and C_{max} were increased by 1.24 and 1.20 fold. This food effect was larger with the 75 mg FDC (1.45 fold increase in AUC and 1.27 fold increase in Cmax).

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Table 9. BIC, FTC, and TAF PK parameters and statistical comparisons for food effect for the 75-mg or 50-mg B/F/TAF FDC

	Mean (%CV)		%GLSM Ratio (90% CI) (Test/Reference)
	Test	Reference	
B/F/TAF (75/200/25 mg), high fat (Test) (N = 28) vs B/F/TAF (75/200/25 mg), fasted (Reference) (N = 28)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	216,733.1 (23.4)	151,846.0 (26.9)	144.45 (134.26, 155.40)
AUC_{inf} (hr•ng/mL)	226,142.1 (24.9)	156,637.5 (27.5)	145.88 (135.58, 156.95)
C_{max} (ng/mL)	8941.1 (16.9)	7123.9 (21.6)	126.74 (116.30, 138.12)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	11,483.0 (15.7)	11,412.3 (13.5)	100.34 (97.98, 102.75)
AUC_{inf} (hr•ng/mL)	11,706.5 (15.6)	11,642.8 (13.2)	100.24 (97.95, 102.59)
C_{max} (ng/mL)	1872.5 (20.1)	2264.3 (22.7)	83.18 (77.53, 89.25)
TAF PK Parameter			
AUC_{last} (hr•ng/mL)	313.3 (44.0)	205.5 (45.5)	156.81 (140.57, 174.94)
AUC_{inf} (hr•ng/mL)	319.7 (43.1)	206.8 (45.2)	158.20 (142.14, 176.08)
C_{max} (ng/mL)	212.2 (49.4)	253.3 (44.2)	83.22 (69.63, 99.46)
B/F/TAF (50/200/25 mg), high fat (Test) (N = 27) vs B/F/TAF (50/200/25 mg), fasted (Reference) (N = 27)			
BIC PK Parameter			
AUC_{last} (hr•ng/mL)	135,117.3 (21.1)	109,061.4 (21.0)	123.96 (115.91, 132.57)
AUC_{inf} (hr•ng/mL)	140,032.4 (21.8)	112,619.6 (21.9)	124.41 (116.27, 133.11)
C_{max} (ng/mL)	5936.3 (18.3)	5228.1 (16.9)	113.23 (106.45, 120.43)
FTC PK Parameter			
AUC_{last} (hr•ng/mL)	10,213.0 (12.0)	10,652.9 (12.6)	96.02 (93.47, 98.65)
AUC_{inf} (hr•ng/mL)	10,467.0 (11.9)	10,873.9 (13.6)	96.41 (93.88, 99.02)
C_{max} (ng/mL)	1881.1 (24.2)	2220.4 (30.1)	85.52 (78.37, 93.31)
TAF PK Parameter[a]			
AUC_{last} (hr•ng/mL)	310.3 (34.9)	207.1 (46.5)	162.62 (143.10, 184.80)
AUC_{inf} (hr•ng/mL)	318.4 (32.8)	208.8 (46.3)	166.35 (146.54, 189.29)
C_{max} (ng/mL)	226.6 (65.1)	249.2 (51.6)	91.71 (73.46, 114.49)

a N = 26 for both the Test and Reference groups

Study GS-US-141-1218 – Study Title: *A Phase 1, Double Blind, Randomized, Placebo-Controlled, First-in-Human, Single- and Multiple-Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Oral GS-9883 in Healthy Subjects and a Randomized, Open-Label, 2-Cohort, 3-Period, Crossover, Pharmacokinetic Study Evaluating the Drug Interaction Potential between Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet and GS-9883 in Healthy Subjects*

Study GS-US-141-1218 also provided results on food effect of BIC alone, with the largest food effect: Cmax increased 2 fold and AUCs 1.8 fold after a high-fat meal.

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Table 10. GS-US-141-1218: GS-9883 Plasma Pharmacokinetic Parameters Following Single-Dose Administration of GS-9883 in the Fasted and Fed States (Analysis Set: GS-9883 PK Part C: Food Effect)

GS-9883 PK Parameter[a] Mean (%CV)	GS-9883 100 mg Fasted (n=8)	GS-9883 100 mg Fed (n=8)
AUC_{inf} (hr*ng/mL)	117,777.1 (23.3)	214,146.5 (15.9)
C_{max} (ng/mL)	5885.0 (34.9)	11,268.8 (15.1)
$t_{½}$ (hr)	16.04 (15.32, 17.12)	16.87 (16.30, 17.93)
T_{max} (hr)	1.75 (1.25, 3.50)	3.00 (1.75, 3.00)
V_z/F (mL)	21,685.2 (40.3)	11,699.4 (13.3)
CL/F (mL/hr)	891.6 (24.1)	479.4 (18.6)

a Data are presented as mean (%CV), except for Tmax, and t½, which are presented as median (Q1, Q3)

Summary of main PK parameters

Table 11. PK parameters of BIC, FTC and TAF after multiple doses of the FDC with and without food, in HIV infected adults

Parameter Mean (%CV)	BIC (N = 1193)[a]	FTC (N = 77)[b]	TAF (N = 486)[c]
$C_{max,ss}$ (ng/mL)	6145.8 (22.9)	2127.0 (34.7)	121.3 (15.4)
AUC_{tau} (ng•h/mL)	102,001.0 (26.9)	12,293.6 (29.2)	142.0 (17.3)
C_{tau} (ng/mL)	2609.9 (35.2)	96.0 (37.4)[d]	NA

NA = not applicable

a From Population PK analysis in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878

b From Intensive PK analysis in Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878

c From Population PK analysis in Studies GS-US-380-1489 and GS-US-380-1490

d n = 74

Distribution

Vz/F was observed between 9.919 and 34.770 L (CV 10.7% to 58.85%). Population PK modelling: 12,500 mL (11.1% variability), with extreme weights (5th and 95th percentiles) ranged from 9,800 to 16,200 mL.

Bictegravir is > 99% bound to human plasma proteins.

In subjects with severe renal impairment, the percent bound remained > 99%, but the percent unbound was higher (0.75%) compared with healthy matched control subjects (0.49%) (Study GS-US-141-1479). Similarly, percent unbound was also higher in subjects with severe hepatic impairment (0.81%) compared with healthy matched control subjects (0.61%) (Study GS-US-141-1478).

Following a single oral dose of [14C]BIC in healthy subjects, the blood-to-plasma ratio of [14C]-radioactivity ranged between 0.50 and 0.55 through 120 hours post-dose, indicating that BIC was

predominantly distributed to plasma rather than the cellular components of blood (Study GS-US-141-1481).

Elimination and metabolism

Average T1/2 in studies was observed between 15.6 h and 20.88 h (ranging between 12.14 h and 14.47h in first and 4th quartiles). In population PK modelling, terminal half-life was estimated at 17.2hr.

Average CL/F in studies was observed between 349.4 and 900 mL/h (CV between 15.3% and 74.2%). In population PK modelling, CL/F was estimated at 504 mL/h, with variability 27.4%, and at extreme weights (5th and 95th percentiles) it ranged from 428 to 601 ml/h.

Bictegravir is primarily metabolized by cytochrome P450 (CYP)3A and uridine glucuronosyltransferase (UGT)1A1 with each enzyme playing an approximately equal role in the clearance of BIC.

Following a single oral dose of 100-mg [14C]BIC in healthy male subjects, 95.3% of the [14C]BIC dose was recovered with 60.3% of the dose from faeces and 35.0% of the dose from urine (Study GS-US-141-1481). M20 (hydroxy-BIC-sulphate, 20.1%) and M15 (BIC-glucuronide, 8.6%) were the major metabolites identified in plasma.

Unchanged drug accounted for 31% to 34% of the radioactive dose in the faeces that likely represents a combination of both unabsorbed drug and deconjugated BIC glucuronide. Desfluoro-hydroxy- BIC-cysteine-conjugate (10%–13% of dose) and other minor oxidative metabolites were identified in faeces. Radioactivity in urine consisted primarily of M15/M58 (BIC-glucuronide; 21% of dose) and other minor oxidative metabolites and their conjugates. Renal clearance of the unchanged parent was minimal (1.3% of dose).

Figure 7. Bictegravir metabolism pathway

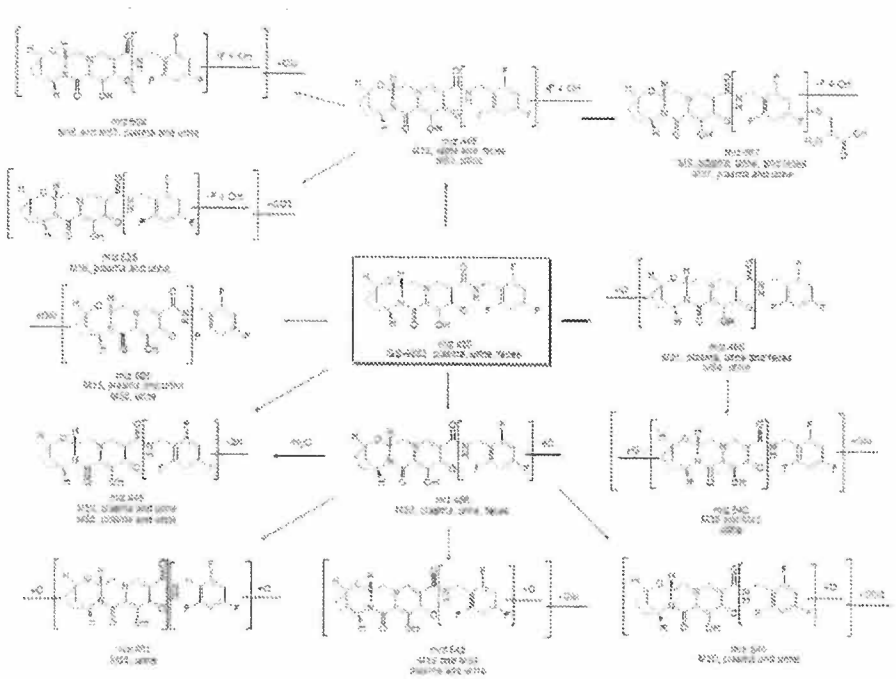


Table 12. M20 (hydroxy-BIC-sulphate) and M15 (BIC-glucuronide) were the major metabolites identified in plasma:

PK Parameter	BIC	M15	M20
AUC_{0-144} (µg•h/mL)	166	21.1	49.3
C_{max} (µg/mL)	8.22	0.669	1.42
T_{max} (h)	4	24	8
T_{last} (h)	72	72	72

Dose proportionality and time dependency

Dose proportionality is mainly explored in study GS-US-141-1218. Bictegravir exposure is dose-proportional over the dose range of 25 to 100 mg; Less than dose-proportional increases in BIC exposure were observed at doses greater than 100 mg, presumably limited by solubility. In study GS-US-141-1219, mean BIC AUC0-24 and Cmax were approximately dose proportional following single-dose administration of 5 to 50 mg dose administration, with decreasing dose proportionality at the 100

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mg dose. Following multiple-dose administration, dose proportionality was observed in AUC_{tau}, C_{max}, and C_{tau} over the dose range of 5 to 100 mg using the 50-mg dose as a reference.

Steady state levels of BIC were achieved between Study Days 4 to 6 of dosing and maintained through Day 14. Accumulation rate was around 1.6 fold.

Inter and intra-individual variability

Interindividual variability in the population study was 27.4 for CL/F and 1.1 for Vc/F. Intra individual variability may be estimated by the remaining residual variability (as CV) at 29.2%

PK in target populations

In the population PK analysis, healthy subjects exhibited 7.3% lower Vc/F compared to HIV-infected subjects. This seemed to be the only variation, and is not considered clinically relevant.

Special populations

Impaired renal function

Study GS-US-141-1479: Study Title: *A Phase 1, Open-Label, Parallel-Group, Adaptive Single-dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Renal Function*

Impaired renal function was studied in GS-US-141-1479. Severe renal impairment decreased BIC AUCs and C_{max} by 0.73 and 0.80 fold respectively; this was considered not clinically significant.

Table 13. Plasma PK parameters for GS-9883 and statistical comparisons

GS-9883 PK Parameter	Mean (%CV)		GLSM Ratio % (90% CI)
	Severe Renal Impairment (Test) (N = 10)	Normal Renal Function (Reference) (N = 8)	
Total AUC_{inf} (h·ng/mL)	138,169.7 (44.4)	170,105.6 (24.8)	72.63 (48.80, 108.10)
Total AUC_{last} (h·ng/mL)	136,956.4 (44.2)	168,876.8 (24.7)	72.45 (48.54, 108.07)
Total C_{max} (ng/mL)	5977.0 (34.8)	7227.5 (29.5)	80.32 (59.56, 108.30)
Free AUC_{inf} (h·ng/mL)[a]	830.6 (32.1)	824.5 (24.7)	99.29 (79.49, 124.04)
Free AUC_{last} (h·ng/mL)[a]	822.5 (32.0)	818.6 (24.6)	99.62 (79.24, 123.74)
Free C_{max} (ng/mL)[a]	37.7 (21.6)	35.0 (28.4)	109.80 (87.46, 137.85)

a Free AUClast, free AUCinf, and free Cmax were calculated based on unbound plasma GS-9883 (PK parameter × percentage unbound GS-9883 ÷ 100 for each subject).

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Impaired hepatic function

Study GS-US-141-1478 – Study Title: *A Phase 1, Open Label, Parallel Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of GS-9883 in Subjects with Normal and Impaired Hepatic Function*

Impaired hepatic function was studied in GS-US-14-1478. Moderate hepatic impairment decreased bic AUCs and Cmax by 0.58 and 0.63 fold respectively; percent of unbound fraction of BIC increases to 0.8% instead of 0.6%.

Table 14. Plasma PK parameters for BIC and statistical comparisons

BIC PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI)
	Moderate Hepatic Impairment (Test) (N = 10)	Healthy Control (Reference) (N = 10)	
AUC_{inf} (h*ng/mL)	115,086.2 (50.7)	172,883.6 (23.4)	58.71 (41.28,83.50)
C_{max} (ng/mL)	5013.0 (29.1)	7849.0 (27.8)	63.50 (49.80,80.96)
C_{24} (ng/mL)	1643.6 (47.5)	2660.0 (24.9)	51.56 (30.96,85.87)
Free AUC_{inf} (h*ng/mL)	880.9 (55.7)	1054.2 (22.7)	76.54 (56.48,103.71)
Free C_{max} (ng/mL)	39.6 (27.7)	48.1 (28.2)	82.78 (64.98,105.45)

GLSM = geometric least-squares mean

Free PK parameter is calculated as: Mean unbound fraction (%) * PK Parameter /100 for a single subject.

Other

No clinically relevant PK differences due to gender and race were identified.

Weight was a significant factor in the population PK study, impacting CL/F and Vd/F. Subjects corresponding to the 5th and 95th percentile of body weight (58 kg and 113 kg, respectively) demonstrated a -15.1 % and 19.2 % difference in CL/F, respectively, and a - 21.5 % and 29.7 % difference in Vc/F, respectively, as compared to the typical 80 kg subject. This was considered clinically not significant.

Age was tested as a potential covariate in both the BIC and TAF population PK analyses for B/F/TAF, but was determined to be not significant for both analytes. As such, age is not expected to substantially affect exposure of BIC or TAF.

No data are available in children.

Pharmacokinetic interaction studies

In vitro

BIC is a substrate of UGT1A1 and CYP3A4. Clinically relevant interaction with inhibitors and inducers of these enzymes has been carried out with darunavir/cobicistat (DRV/RTV) or with atazanavir/ritonavir (ATV/RTV) for CYP and UGT inhibition, and with rifampicin (RIF) for induction.

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BIC is not a direct or TDI of all tested CYPs up to 100µM. However, even though with CYP3A4, TDI by bictegravir is observed but with a KI>100 µM, the Applicant performed a DDI study with midazolam that allow to consider BIC as a weak CYP3A inhibitor.

BIC inducing effect has been demonstrated in vitro on CYP3A4, 2B6, P-gp and UGT1A1 but no clinical consequences are expected.

With an IC50=176 µM, BIC is not expected to affect exposure of drugs the metabolism of which is UGT1A1-dependant.

BIC is both a P-gp and BCRP substrate. Bictegravir (1 µM) is not a substrate of OATP1B1 or OATP1B3.

Up to 100µM, BIC does not exhibit in vitro inhibition of P-gp, BCRP, BSEP, OATP1B1, 1B3, OCT1, OAT1. Therefore, clinically relevant interactions related to this transporter inhibition are not expected at the expected systemic and intestinal concentrations.

With OAT3, BIC IC50=55 µM that is higher the worst concentration expected at the systemic level (5 µM), then, clinically relevant interaction related to the inhibition of this transporter can be ruled out.

With OCT2 and MATE1 IC50=0.42 µM and 8 µM respectively. Risk of DDI is, then, not excluded with OCT2 and borderline with MATE1.

FTC and TAF

FTC is predominantly eliminated by the kidney. TAF is primarily hydrolyzed by carboxylesterase 1 (CES) and Cat A (cathepsin A) and not recommended in combination with inhibitor of this enzyme such as boceprevir. Tenofovir alafenamide was slowly metabolized by CYP3A4.

Clinically relevant interactions related to any inhibition or induction of CYPs by emtricitabine are not expected. Likewise, in vitro, TAF did not show any inducing or inhibition potential towards main CYP450 enzymes, excepted with CYP3A4. Nonetheless, a DDI study with midazolam (study GS-US-1538) and rilpivirine (GS-US-120-0117), both CYP3A4 substrates, discard any significant induction or inhibition of CYP3A4 by TAF in vivo.

No UGT1A1 inhibition is expected by FTC and TAF. Likewise, no induction of UGTs is expected by FTC or TAF.

FTC is not expected to be a substrate and inhibitor of uptake and efflux transporters according to its extensive and high absorption.

TAF is a substrate of the efflux transporters P-gp and BCRP and, also, of the uptake transporters OATP1B1 and 1B3. Therefore, inhibition of these transporters may alter TAF exposure and then of TFV. TAF is neither a substrate of the hepatic uptake transporter OCT1 nor of the renal uptake transporters OAT1 and OAT3.

As regards inhibition of P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, BSEP, OCT1, and MATE1 by TAF, IC50 values are > 100 µM far higher the estimated cut-off values at the intestinal, hepatocyte and systemic level (21 µM, 18.5 µM and 4.5 µM respectively). Therefore, clinically relevant interactions related to any inhibition of these transporters by TAF are unlikely.

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In vivo

B/F/TAF

Interactions between the components BIC and FTC/TAF was explored in study GS-US-141-1218. TAF and FTC do not alter BIC absorption. BIC does not alter FTC absorption. Only TAF exposure is changed by coadministration of BIC and F/TAF, but TFV is by far more relevant and shows no DDI impact.

	GLSM		GLSM Ratio (90% CI), %
	Test	Reference	
GS-9883 PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. GS-9883 (Reference) (N = 34)			
AUC_{inf} (hr*ng/mL)	212,852.8	210,816.0	100.97(98.22,103.79
C_{max} (ng/mL)	14,693.24	14,761.70	99.54 (96.41,102.76)
C_{tau} (ng/mL)	5681.53	5553.18	102.31(98.48,106.29)
FTC PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{inf} (hr*ng/mL)	9545.74	9368.40	101.95 (100.13,103.80)
C_{max} (ng/mL)	1759.89	1773.33	99.24 (94.19,104.55)
C_{tau} (ng/mL)	67.04	63.33	105.86 (101.26,110.67)
TAF PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{inf}(hr*ng/mL)	352.61	272.28	129.50 (123.67,135.61)
C_{max} (ng/mL)	277.95	203.10	136.86 (116.09,160.09)
TFV PK Parameter: GS-9883+F/TAF (Test) (N = 34) vs. F/TAF (Reference) (N = 33)			
AUC_{inf} (hr*ng/mL)	299.66	263.52	113.72 (110.07,117.49)
C_{max} (ng/mL)	17.66	16.01	110.30 (105.27,115.56)
C_{tau} (ng/mL)	10.46	9.09	115.04 (110.79,119.46)

FTC = emtricitabine; F/TAF = emtricitabine/tenofovir alafenamide (coformulated); GLSM = geometric least-squares mean; TFV = tenofovir

Studies GS-US-380-1761 and GS-US-380-1999 with the FDC **ledipasvir/sofosbuvir (LDV/SOF)** and **sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)** did not highlight significant PK interaction between studied drugs.

In study GS-US-380-3908, B/F/TAF significantly increases **metformin** AUC_t about 39% with an 90%CI [131%-148]. However, the lack of significant changes on PD parameters (plasma glucose, active glucagon-like peptide 1 (GLP-1) and lactate levels) brings a reassuring information and could allow to conclude that no dose adjustment of metformin is needed when it is combined with B/F/TAF.

Interaction between B/F/TAF and **antacids, calcium carbonate and ferrous fumarate** was explored in study GS-US-380-3909:

BIC PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	B/F/TAF Under Test Conditions (N = 14)	B/F/TAF Alone (Fasted) (Reference) (N = 14)	
B/F/TAF (fasted) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	27,960.7 (52.5)	121,887.9 (24.4)	21.23 (17.57, 25.65)
C_{24} (ng/mL)	427.0 (57.4)	1795.7 (26.3)	21.94 (17.80, 27.04)
C_{max} (ng/mL)	1199.8 (52.0)	5635.0 (18.8)	19.59 (16.46, 24.02)
B/F/TAF (fasted) with calcium carbonate (Test)			
AUC_{inf} (ng•h/mL)	85,037.3 (43.1)	121,887.9 (24.4)	66.67 (56.67, 78.42)
C_{24} (ng/mL)	1222.9 (43.9)	1795.7 (26.3)	64.89 (54.47, 77.31)
C_{max} (ng/mL)	3442.1 (36.9)	5635.0 (18.8)	58.31 (50.72, 67.04)
B/F/TAF (fasted) with ferrous fumarate (Test)			
AUC_{inf} (ng•h/mL)	46,148.7 (32.9)	121,887.9 (24.4)	37.11 (32.95, 41.80)
C_{24} (ng/mL)	674.8 (32.8)	1795.7 (26.3)	36.92 (32.59, 41.83)
C_{max} (ng/mL)	1657.1 (27.1)	5635.0 (18.8)	29.10 (25.87, 32.72)
B/F/TAF (fasted) 2 hours before 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	115,968.1 (30.3)[a]	132,814.0 (27.0)	86.70 (81.01, 92.78)
C_{24} (ng/mL)	1699.2 (27.0)[a]	2009.3 (28.3)	85.46 (79.92, 91.38)
C_{max} (ng/mL)	5616.2 (22.7)[a]	5920.0 (16.5)	93.40 (87.53, 99.66)
B/F/TAF (fasted) 2 hours after 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	67,704.6 (47.0)[a]	132,814.0 (27.0)	47.66 (38.26, 59.35)
AUC_{last} (ng•h/mL)	63,447.0 (45.8)[a]	124,721.4 (28.0)	47.34 (37.91, 59.12)
C_{max} (ng/mL)	2735.0 (48.3)[a]	5920.0 (16.5)	41.51 (33.25, 51.83)
B/F/TAF (fed) with 20 mL maximum-strength antacid (Test)			
AUC_{inf} (ng•h/mL)	50,813.5 (34.8)	93,658.3 (27.2)	53.25 (44.21, 64.14)
C_{24} (ng/mL)	803.6 (36.4)	1410.1 (29.7)	56.01 (46.21, 67.88)
C_{max} (ng/mL)	2446.4 (31.4)	4700.7 (23.6)	51.46 (42.69, 62.03)
B/F/TAF (fed) with calcium carbonate (Test)			
AUC_{inf} (ng•h/mL)	94,892.8 (21.2)	93,658.3 (27.2)	103.29 (88.96, 119.93)
AUC_{last} (ng•h/mL)	91,454.0 (20.1)	91,204.9 (26.5)	102.36 (88.07, 118.98)
C_{max} (ng/mL)	4105.0 (13.7)	4700.7 (23.6)	89.58 (77.88, 103.10)
B/F/TAF (fed) with ferrous fumarate (Test)			
AUC_{inf} (ng•h/mL)	77,307.9 (24.8)	93,658.3 (27.2)	83.84 (74.07, 94.89)
C_{24} (ng/mL)	1228.7 (25.0)	1410.1 (29.7)	88.93 (78.12, 101.24)
C_{max} (ng/mL)	3485.0 (28.2)	4700.7 (23.6)	75.12 (64.82, 87.05)

a N = 13 for Test treatment

With antacids containing magnesium or aluminium, under fasted conditions, and given simultaneously, BIC AUC and C_{24h} substantially decrease, more than with RIF, about 79%. This interaction can be compensated by staggered the administration of BIC 2 hours before antacids (based on results from cohort 2) or alternatively, B/F/TAF can be taken with food 2 hours after antacids containing magnesium or aluminium.

With calcium carbonate and ferrous fumarate, under fasted conditions and given simultaneously, BIC AUC and C_{min} decrease about 33% and 42%, respectively, with calcium carbonate, and about 63% with ferrous fumarate. Even though the effect of calcium carbonate or ferrous fumarate has not been studied with staggered doses of the FDC, one can take B/F/TAF at least 2 hours before ferrous fumarate and can take B/F/TAF together with calcium-containing supplements without regard to food.

- Results from study GS-US-380-4270 show that B/F/TAF significantly, but weakly, increases **midazolam** exposure about 15% with a 90%CI [99.7-131]. This effect is likely driven by BIC the in vitro data of which demonstrate the ability of BIC to be a time-dependant inhibitor at high concentrations. The mild increase observed with midazolam is not expected to be clinically meaningful.

BIC alone

In study GS-US-311-1790, no significant effect of BIC and FTC/TAF on **ethinylestradiol, norgetromine and norgestrel** PK was observed. Therefore no dose adjustment of combined oral contraception is needed when co-administered with B/F/TAF.

Study GS-US-141-1485: A Phase 1 Adaptive Study to Evaluate Transporter, Cytochrome (CYP) 450-Mediated and UGT1A1 Drug-Drug Interactions Between GS-9883 and Probe Drugs. This study assessed the interaction of BIC with **ATV/COBI, rifampicin, ATV alone, voriconazole, rifabutin and DRV/COBI.**

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GS-9883 PK Parameter	Test[a]	Reference[a]	%GLSM Ratio (90% CI) (Test/Reference)
Cohort 1: GS-9883 75 mg SD + ATV 300 mg QD + COBI 150 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15): fed			
AUC_{inf} (h*ng/mL)	628,290.3 (17.4)	154,433.7 (16.0)	405.62 (376.07, 437.49)
C_{max} (ng/mL)	9033.3 (12.2)	6890.0 (12.3)	131.11 (122.71, 140.08)
$t_{1/2}$ (h)	59.99 (52.94, 63.10)	18.62 (15.87, 20.96)	
Cohort 2: GS-9883 75 mg SD + RIF 600 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15): fed			
AUC_{inf} (h*ng/mL)	36,398.0 (21.5)	155,986.3 (41.8)	24.52 (22.90, 27.33)
C_{max} (ng/mL)	5131.5 (35.7)	7118.7 (17.0)	72.21 (67.06, 77.75)
$t_{1/2}$ (h)	5.65 (5.36, 6.18)	18.09 (14.47, 20.75)	
Cohort 3: GS-9883 75 mg SD + ATV 400 mg QD (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15): fed			
AUC_{inf} (h*ng/mL)	638,857.0 (20.5)	154,253.8 (21.8)	414.51 (381.02, 450.94)
C_{max} (ng/mL)	9110.7 (16.6)	7078.7 (13.3)	128.10 (122.95, 133.47)
$t_{1/2}$ (h)	56.86 (50.70, 66.90)	17.47 (15.26, 19.81)	
Cohort 4: GS-9883 75 mg SD + VORI 300 mg BID (Test; N = 15) vs GS-9883 75 mg SD (Reference; N = 15); fasted			
AUC_{inf} (h*ng/mL)	160,519.3 (26.9)	101,659.4 (37.2)	161.14 (141.07, 184.06)
C_{max} (ng/mL)	5442.7 (33.6)	4844.0 (21.5)	108.94 (96.14, 123.43)
$t_{1/2}$ (h)	25.45 (18.65, 28.08)	15.92 (15.12, 19.76)	
Cohort 5: GS-9883 75 mg QD + RBT 300 mg QD (Test; N = 13) vs GS-9883 75 mg QD (Reference; N = 15); fasted			
AUC_{tau} (h*ng/mL)	86,164.3 (37.4)	196,486.2 (37.2)	62.01 (53.06, 72.47)
C_{max} (ng/mL)	6140.0 (36.0)	7624.7 (35.5)	80.37 (66.93, 96.50)
C_{tau} (ng/mL)	1212.2 (43.0)	2782.9 (40.7)	43.98 (37.14, 52.07)
Cohort 6: GS-9883 75 mg QD + DRV/COBI 800/150 mg QD (Test; N = 13) vs GS-9883 75 mg QD (Reference; N = 15); fed			
AUC_{tau} (h*ng/mL)	265,249.0 (19.3)	152,356.1 (16.2)	173.60 (161.55, 186.54)
C_{max} (ng/mL)	17,360.0 (15.6)	11,402.0 (15.2)	151.56 (140.15, 163.90)
C_{tau} (ng/mL)	8486.9 (24.9)	4017.3 (21.6)	211.43 (195.18, 229.03)

BID = twice daily; QD = once daily; SD = single dose

a Mean (%CV) for AUClast, AUCinf, AUCtau, Cmax, and Ctau; median (Q1, Q3) for t1/2

There was a substantial increase of BIC exposure, about 4-fold, with ATV/COBI (cohort 1) similar to the increase exposure of BIC with ATV alone (cohort 3) and suggesting that this effect is mainly driven by UGT1A1 inhibition by ATV. This assumption is corroborated by results obtained with two strong CYP3A4 inhibitors, VORI and DRV/COBI, with which BIC exposure increases about 61% and 74%, respectively. This highlights the moderate involvement of CYP3A4 in the overall hepatic clearance of BIC. Rifampicin substantially decreases BIC exposure about 75% whereas with rifabutin AUC decrease about 38% and C_{min} about 56%.

The following is reflected in the SmPC:

- no dose adjustment is recommended with VORI
- with rifabutin, BIC is not recommended
- with rifampicin, BIC is contra-indicated

2.4.3. Pharmacodynamics

Mechanism of action

The INSTI BIC and the N(t)RTIs FTC and TAF are potent and selective inhibitors of HIV-1 and HIV-2. Emtricitabine and TAF are also potent and selective inhibitors of HBV. All 3 drugs show potent ARV activity against diverse subtypes of HIV-1 in vitro. Emtricitabine and TAF are phosphorylated intracellularly through non-overlapping pathways, and in combination show no antagonism for the formation of their active metabolites. Bictegravir does not require metabolic modification for activity. Two- and 3-drug combinations of BIC, FTC, and TAF consistently show synergistic anti-HIV-1 activity in vitro and no evidence of antagonism or cytotoxicity.

The resistance profiles for the individual agents BIC, FTC, and TAF have been well characterized. There is no known cross-resistance between the NRTI and INSTI classes.

Bictegravir, FTC, and TAF have no pharmacologically significant off-target binding affinity to the receptors tested. Bictegravir, FTC, and TAF have low in vitro cytotoxicity in a variety of human cell types. Both FTC and TAF have shown a low potential for mitochondrial toxicity in long-term toxicity studies and there was no evidence of toxicity to mitochondria in vitro and in vivo.

Primary pharmacodynamics

BIC is a novel strand transfer inhibitor of HIV-1 integrase (INSTI) with high potency and selectivity in antiviral assays and does not require metabolic modification to exert ARV activity. BIC inhibited the strand transfer activity with an IC50 value of 7.5 nM, an activity comparable to those of EVG and DTG.

Table 15. Inhibitory Activity in HIV-1 Integrase Strand Transfer and 3'-Processing Assays

	Inhibition of Strand Transfer[a]		Inhibition of 3'-Processing[b]	
Compound	IC50 (nM)	Maximum Inhibition (%)[c]	IC50 (nM)	Maximum Inhibition (%)[c]
GS-9883	7.5 ± 0.3	99.4 ± 0.7	241 ± 51	106 ± 4
DTG	2.4 ± 0.6	100.3 ± 0.6	282 ± 33	115 ± 3
EVG	8.4 ± 0.7	99.9 ± 0.3	556 ± 40	93 ± 2

a The data represent the mean ± SD of 3 independent experiments done in triplicates.
b The data represent the mean ± SD of 5 independent experiments done in triplicates
c Maximum inhibition was determined by curve fitting.

Thus, the integration of HIV in cell was inhibited. This inhibition of HIV-1 DNA integration was evaluated by assessing the quantity of aborted circular HIV DNA species containing 1 or 2 long terminal repeats (2-LTR circles), as well as the quantity of authentic HIV-1 integration products in infected MT-2 cells. BIC enhanced the accumulation of 2-LTR circles, a product of integration failure. BIC profoundly decreased integration junctions but did not affect viral DNA synthesis as measured by

the late reverse transcription products, demonstrating an authentic inhibition of HIV-1 integration. As expected, DTG exhibited a similar effect on the integration junctions.

The dissociation kinetics of ^{3}H-labelled INSTIs BIC, DTG, RAL, and EVG were measured using wild-type HIV integrase/DNA complexes and a scintillation proximity assay. By both data analysis methods, BIC had a longer dissociation half-life from HIV-1 integrase/DNA complexes compared to DTG, RAL, and EVG; the long dissociation half-life has been proposed to contribute to a high barrier to resistance.

Against HIV

Using lymphoblastoid T-cell lines and primary human T-lymphocytes in HIV-1 antiviral assays, the estimated concentration of drug for half-maximal effective concentration (EC50) of BIC ranged from 1.5 to 2.4 nM and the selectivity indices ranged from 1500 to 8800.

Table 1. Antiviral Activity of BIC in T-Cell Lines

	EC_{50} (nM)	
Compound	MT-2 Cells[a]	MT-4 Cells[a]
BIC	1.5 ± 0.2	2.4 ± 0.4
DTG	1.5 ± 0.2	1.5 ± 0.3

a EC_{50} values represent the mean ± SD of at least 4 independent measurements performed in triplicate.
Source: PC-141-2032.

Table 2. Antiviral Activity of BIC in Primary Cells

	EC_{50} (nM)	
Compound	CD4^{+} T Lymphocytes[a]	Monocyte-derived Macrophages[a]
BIC	1.5 ± 0.3	6.6 ± 4.1
DTG	1.0 ± 0.3	3.1 ± 2.5

a EC_{50} values represent the mean ± SD of 4 independent donor determined in triplicate
Source: PC-141-2034.

When tested in primary human PBMCs against clinical isolates of all HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G, BIC displayed similar antiviral activity across all clinical isolates with mean and median EC50 values of 0.60 and 0.55 nM, respectively, based on a range of EC50 values between < 0.05 and 1.71 nM. DTG tested in parallel exhibited a similar potency with mean and median EC50 values of 0.61 nM and 0.68 nM, respectively, and a range of EC_{50} values from 0.09 to 1.13 nM against the same tested isolates. HIV-2 was similarly susceptible to both BIC and DTG with EC50 values of 1.1 nM and 2.1 nM, respectively.

Against other viruses

BIC and DTG were tested against hepatitis B and C viruses, influenza A virus, human rhinovirus (HRV), and RSV in cell-based assays. For both drugs, no antiviral activity against these viruses was observed.

Effect of serum proteins on BIC

The antiviral EC50 of BIC was determined in MT-2 cells in the presence of two key human serum components, human serum albumin (HSA) and α1-acid glycoprotein (α1-AGP) or in the presence of complete human serum.

The presence of the two serum components reduced the antiviral activity of BIC by 20-fold, compared to 11-fold reduction of the potency of DTG. These data indicate that the two tested components of human serum are capable of binding BIC as well as DTG.

In the presence of human serum, the shift in EC50 for both BIC and DTG exhibited similar trends as observed with the serum protein components: the BIC EC50 value, extrapolated to 100% human serum, shifted 74-fold and was comparable to the 39-fold shift extrapolated for DTG.

Viral resistance to BIC in clinical studies

Analyses were performed for HIV-infected subjects with clinical virology data from 4 B/F/TAF Phase 3 studies (GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878). An integrated virology analysis was performed for HIV-infected subjects with clinical virology data from Studies GS-US-380-1489 and GS-US-380-1490. All of the previously identified drug resistance mutations by antiretroviral drug class is shown in Table 16.

Table 16. Resistance Substitutions by Antiretroviral Class for the B/F/TAF Program

Resistance Associated Substitutions[a]	
Mutation Groups	**Codon Mutations**
Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance (-R) substitutions	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI-R substitutions	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/P/K/L, V151I/L/A, S153A/F/Y, E157K/Q, G163K/R, E170A
Primary Nucleoside and Nucleotide Reverse Transcriptase Inhibitor (N(t)RTI)-R substitutions	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine Analogue Mutations (TAMs)	M41L, D67N, K70R, L210W, T215Y/F, K219Q/N/E/R
Tenofovir (TFV) resistance associated substitutions	K65R/E/N, K70E
Emtricitabine (FTC) and lamivudine (3TC) resistance associated substitutions	M184V/I
Abacavir (ABC) resistance associated substitutions	K65R/E/N, K70E, L74V, Y115F, M184V/I
Secondary NRTI-R substitutions	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V[b]
Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)-R substitutions	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I
Secondary NNRTI-R substitutions	V90I, A98G, K101H, V106L, V179D/F/T
Primary Protease Inhibitor (PI)-R substitutions	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Atazanavir (ATV) or Darunavir (DRV) resistance associated substitutions	I47V, I50L/V, I54M/L, L76V, I84V, N88S

a Adapted from the current IAS-USA list with some modifications (Wensing 2017)

b Reversion mutations at RT codon T215 including T215A/C/D/E/G/H/I/L/N/S/V have not been definitively shown to be associated with reduced response to either emtricitabine or tenofovir DF.

Studies GS-US-380-1489 and GS-US-380-1490:

Both studies were performed in ART-naive patients: Study GS-US-380-1489 compares B/F/TAF vs ABC/DTG/3TC and study GS-US-380-1490 compares B/F/TAF vs DTG+F/TAF. At baseline, the INSTI-RAM detected are as follows:

Mutation Class[a]	Number of Subjects, n (%)			
	B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	All (N = 1274)
Primary INSTI-R	6 (1.0)	4 (1.3)	6 (1.9)	16 (1.3)
Average Number of Primary INSTI-R Mutations	1.0	1.0	1.0	1.0
T97A	5 (0.8)	4 (1.3)	6 (1.9)	15 (1.2)
Q148H	1 (0.2)	0	0	1 (0.1)
Secondary INSTI-R	325 (51.5)	152 (48.4)	158 (49.1)	635 (50.1)
Average Number of Secondary INSTI-R Mutations	1.2	1.2	1.2	1.2
M50I	124 (19.7)	47 (15.0)	60 (18.6)	231 (18.2)
H51Y	0	1 (0.3)	1 (0.3)	2 (0.2)
L68I/V	4 (0.6)	2 (0.6)	2 (0.6)	8 (0.6)
V72T	3 (0.5)[b]	1 (0.3)	3 (0.9)	7 (0.6)[b]
L74M	1 (0.2)	5 (1.6)	2 (0.6)	8 (0.6)
Q95K	1 (0.2)	0	0	1 (0.1)
S119P/R/T	197 (31.2)	103 (32.8)	99 (30.7)	299 (31.5)
A128T	3 (0.5)	0	0	3 (0.2)
E138A/K	1 (0.2)	2 (0.6)	2 (0.6)	5 (0.4)
G140S	1 (0.2)	0	0	1 (0.1)
Q148R	1 (0.2)	0	0	1 (0.1)
S153A	3 (0.5)	1 (0.3)	2 (0.6)	6 (0.5)
E157K/Q	35 (5.5)	12 (3.8)	12 (3.7)	59 (4.7)
G163K/R	6 (1.0)	5 (1.6)	6 (1.9)	17 (1.3)

There is no impact of pre-treatment RAMs or subtype to reach HIV-1 RNA < 50 copies/mL at Week 48 or virologic failure (HIV-1 RNA ≥ 50 copies/mL) for all treatment groups ($p > 0.05$ for all comparisons). In the B/F/TAF group, all 5 subjects with T97A and the one subject with Q148H + G140S in IN at baseline achieved HIV-1 RNA < 50 copies/mL at Week 4 and maintained HIV-1 RNA < 50 copies/mL through Week 48.

Of the 1274 FAS subjects in Studies GS-US-380-1489 and GS-US-380-1490, 17 subjects experienced virologic failure during the first 48 weeks and comprised the resistance analysis population (RAP). The final RAP (which did not include subjects who re-suppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs) was comprised of 8 subjects in the B/F/TAF group, 2 subjects in the ABC/DTG/3TC group and 3 subjects in the DTG + F/TAF group:

Table 17. Integrated Summary: HIV-1 Genotypic Resistance through Week 48 for Studies GS-US-380-1489 and GS-US-380-1490

	Number of Subjects, n (%)			
Resistance Category[a]	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)	P-Value[b]
RAP (% of FAS)	8 (1.3)	4 (1.3)	5 (1.5)	1.00, 0.77
Subjects with Data (Any Gene)	8 (100)	3 (75)	5 (100)	
Subjects who Resuppressed HIV-1 RNA < 50 copies/mL	0	2 (50)	2 (40)	
Final RAP[c] (% of FAS)	8 (1.3)	2 (0.6)	3 (0.9)	0.51, 0.76
Subjects with Data (Any Gene)	8 (100)	1 (50)	3 (100)	
Developed Resistance Mutations to Study Drugs (% of FAS)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Developed Resistance Mutations to Study Drugs (% of Final RAP)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Developed Any INSTI-R	0	0	0	
Developed Primary NRTI-R	0	0	0	
Developed Primary NNRTI-R	0	0	0	
Developed Primary PI-R	0	0	0	

3TC = lamivudine; ABC = abacavir; B/F/TAF = bidegravir/emtricitabine/tenofovir alafenamide, DTG = dolutegravir;
FAS = full analysis set; INSTI = integrase strand transfer inhibitor; INSTI = integrase strand transfer inhibitor;
NA = not applicable; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/tide reverse transcriptase
inhibitor; PI = protease inhibitor; -R = resistance
a Drug resistance mutations are defined in Table 2.
b P-value determined using Fisher's exact test; (B/F/TAF vs ABC/DTG/3TC; B/F/TAF vs DTG + F/TAF)
c Does not include subjects who resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs.

None of the subjects had resistance mutations emerge. Other substitutions in IN and/or RT that developed were at polymorphic sites; none of these changes were associated with a phenotypic change to BIC, FTC, or TFV.

Secondary pharmacology

Effect of BIC on cardiac conduction

Study GS-US-141-1489 was a partially-blinded, randomized, placebo- and positive-controlled, 4-period, single-dose, crossover study evaluating the effects of BIC (at therapeutic and supra-therapeutic doses) on ΔΔQTcF in healthy subjects. Forty-eight subjects completed 4 dosing periods; each period consisted of 1 day of dosing with 75 mg BIC, 300 mg BIC, placebo-to-match BIC, or moxifloxacin (400 mg) according to randomized sequence. Dosing in the first 3 periods was followed by a washout period of 7 days. Moxifloxacin was administered open label.

BIC was concluded to have no QTcF prolongation effect as the upper bounds of the 2-sided 90% CIs for the mean difference between therapeutic or supra-therapeutic doses of BIC and placebo were below 10 msec at all time points after dosing. No subject had a QTcF interval change from predose baseline > 30 or > 60 msec at any time point during any treatment (BIC 75 and 300 mg, placebo, and

moxifloxacin). Treatment-emergent absolute QTcF intervals > 450, > 480, or > 500 msec were not observed for any subject following BIC 75 and 300 mg, or moxifloxacin. One subject had treatment-emergent absolute QTcF interval > 450 msec following placebo administration.

2.4.4. Discussion on clinical pharmacology

The PK/PD properties of FTC and TAF have been evaluated throughout their respective development programs. Therefore, we will focus on discussing the BIC PK/PD properties as part of the B/F/TAF application.

Analytical methods:

Analytical methods are well described and acceptable. In particular, analytical method validation for BIC in plasma for the main studies was provided. PK parameters calculation was classical and well explained.

Bioavailability:

The absorption of BIC in humans is expected to be > 61% based on the results of the human ADME study in healthy subjects. This is not enough to classify BCS as a molecule with sufficient permeability (>85% of absorption), therefore we disagree with the Applicant's suggestion that BIC be a BCS Class II compound, and we consider a BCS Class IV classification.

Bioequivalence and food effect:

Relative bioavailability study GS-US-141-1233 showed higher than expected BIC exposures when BIC was administered as the B/F/TAF 75/200/25 mg FDC (BIC AUC and Cmax increased by 1.27 and 1.31 fold, out of the 80-125 acceptance range for the confidence interval). The dose of BIC was therefore reduced from 75 mg to 50 mg and a new B/F/TAF 50/200/25 mg FDC tablet was developed, showing lower BIC exposures (BIC AUC and Cmax decreased by 0.78 fold as compared to the 75 mg BIC + FTC/TAF) but within the confidence interval that was enlarged (70-143%) to take into account the different BIC doses. An enlarged CI could be accepted given the lack of lower boundary of BIC therapeutic window and the clinical efficacy results.

GS-US-141-1233 showed that after a high-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.13 fold, and after a moderate-fat meal, BIC AUC and Cmax were increased by 1.24 and 1.20 fold. This food effect was larger with the 75 mg FDC (1.45 fold increase in AUC and 1.27 fold increase in Cmax). GS-US-141-1218 also provided results on food effect of BIC alone, with the largest food effect: Cmax increased 2 fold and AUCs 1.8 fold after a high-fat meal. However, given the efficacy and PK values (and notably IQ values) of B/F/TAF administered with or without food in the Phase 3 studies, there is no evidence of loss of efficacy when B/F/TAF is administered without food.

Metabolism:

BIC has three stereo-centres and is produced as a single stereoisomer, but stability data and routine manufacturing data did not show a risk of epimerization. Therefore, there is no risk of inter-conversion.

M20 (hydroxy-BIC-sulphate) and M15 (BIC-glucuronide) were the major metabolites identified in plasma. Considering the high proportion of M20 (>20%), further in-vitro interaction studies are needed

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notably on the effect of M20 on CYP1A2, 2C9, 2C19, 2C8, 2B6, 2D6 and transporters, such as P-gp and BCRP.

PK in subjects with impaired renal function:

In subjects with severe renal impairment, BIC AUC and Cmax were decreased by 0.73 and 0.80 fold respectively. This decrease of exposure seems paradoxical in case of renal impairment, and was unexpected given the PK profile of BIC (renal excretion of intact bictegravir is a minor pathway, ~1% of dose). However, unbound BIC exposure was similar between the 2 groups. As explained by the Applicant, the fractions of BIC plasma protein binding in individual subjects overlapped between the 2 groups, with the percentages of unbound plasma BIC ranging from 0.43% to 0.63%, except in 1 subject with severe renal impairment. This subject showed an unexpectedly higher percentage of unbound plasma BIC (2.28%), which may have led to lower BIC exposure and shorter BIC half-life compared with the other subjects in the study, despite no medical history or concomitant medications explaining this anomaly. When data from this subject were excluded, GLSM ratios for AUClast, AUCinf, and Cmax were 87.44%, 87.51%, and 90.12%, respectively, when subjects with severe renal impairment were compared with subjects with normal renal function. The lack of clinical relevance of such BIC decrease of exposure is endorsed.

PK in subjects with impaired hepatic function:

In subjects with moderate hepatic impairment, BIC AUC and C_{max} were decreased by 0.58 and 0.63 fold respectively. This decrease of exposure seems paradoxical in case of hepatic impairment, notably given that BIC is primarily eliminated by hepatic metabolism.

The higher percentage of unbound fraction of BIC in subjects with hepatic impairment may be due to the decreased production of albumin in these subjects, resulting in lower plasma protein binding of BIC, which is highly protein bound.

Based on the mean (%CV) BIC C_{tau} value of 2610 (35.2) ng/mL following administration of B/F/TAF to HIV-infected subjects (N = 1193) in the Phase 3 clinical studies (representing an IQ of 16.1), a potential decrease of approximately 23% in subjects with moderate hepatic impairment would represent a C_{tau} value 12.4-fold above the paEC95 (162 ng/mL) against wild type HIV-1 virus. Additionally, the lack of an exposure-efficacy relationship for BIC over an IQ range of 4.7 to 40.1 following administration of B/F/TAF in the Phase 3 clinical studies confirms that this small decrease in BIC exposure in subjects with moderate hepatic impairment is not deemed significant. In accordance to the Applicant, the small difference in free BIC exposure is not clinically relevant, and subjects with moderate hepatic impairment may take B/F/TAF with or without food.

Interactions

In vitro, BIC is a substrate of UGT1A1, CYP3A4, P-gp and BCRP. BIC is not a substrate of OATP1B1, OATP1B3. BIC is a weak CYP3A4, OCT2 and MATE1 inhibitor, and has demonstrated in vitro inducing effect on CYP3A4, 2B6, P-gp and UGT1A1, without relevant clinical consequences in vivo. BIC is not expected to affect exposure of drugs the metabolism of which is UGT1A1-dependant. In vitro, BIC is not an inhibitor of P-gp, BCRP, BSEP, OATP1B1, 1B3, OCT1, OAT1.

In study GS-US-380-3908 (ddi metformin), B/F/TAF significantly increases metformin AUC_t about 39% with an 90%CI [131%-148]. Beyond the PD effect of metformin regardless the HIV patient status, the safety profile of the biguanide could be impacted due to renal impaired function that frequently occurs

in HIV- and diabetic patients. In this clinical situation, metformin exposure could be more pronounced increasing the risk of metformin related adverse events. Caution, and eventually a dose adjustment is, then, advised in patients having a moderate renal function.

When B/F/TAF is given simultaneously with antacids under fasted conditions, BIC AUC and C24h substantially decrease, more than with rifampicin, about 79%. This interaction can be compensated by staggering the administration of BIC 2 hours before antacids. When administered 2 hours after, about a half of BIC exposure decreases, in a same magnitude as rifabutin combination. Consequently, B/F/TAF should not begiven simultaneously and in fasted conditions with magnesium or aluminium-containing antacids; B/F/TAF is recommended 2 hours before, or with food 2 hours after magnesium or aluminium-containing antacids.

No DDI study has been performed on the effect of H2-antagonists (e.g. ranitidine) or proton-pump inhibitors (e.g. omeprazole) on BIC pharmacokinetics, because BIC absorption, unlike that of other INSTIs, is not pH dependent under physiologically relevant conditions. This is confirmed by population PK analyses indicating that the extent of BIC absorption was unaffected by PPIs:

	Mean (%CV)		
BIC PK Parameter	B/F/TAF With PPI Usage (Test) (N = 109)	B/F/TAF Without PPI Usage (Reference) (N = 1084)	GLSM Ratio (%) (90% CI)
AUC_{tau} (ng•h/mL)	97,971.9 (29.3)	102,406.2 (26.7)	95.2 (90.8, 99.8)
C_{max} (ng/mL)	5643.8 (25.4)	6196.3 (22.5)	90.6 (87.0, 94.4)
C_{tau} (ng/mL)	2581.0 (38.0)	2612.8 (34.9)	98.0 (92.0, 104.4)

Pharmacodynamics/antiviral activity:

The antiviral properties of BIC and DTG were compared.

In vitro data suggest that BIC is better than RAL and EVG and at least equivalent to DTG in terms of antiviral activity and resistance profile. In addition, some particularities might contribute to improve its properties against HIV strains with INSTI-RAM:

BIC has a longer dissociation T1/2 from HIV-1 integrase/DNA complexes than DTG, which may be associated to a higher barrier to resistance.

The antiviral activity of BIC against several HIV strains with INSTI-RAM is at least similar to DTG but also less impacted than DTG by some primary mutations (notably for the mutations G140S + Q148R ± additional INSTI mutation).

On the other hand, a study has shown a higher level of resistance to BIC (susceptibility decreased by 44-fold) than DTG (susceptibility decreased by 26-fold) with the mutations T66I + E138K + Q148K.

Finally, because BIC and F/TAF have a high genetic barrier to the development of resistance, the emergence of resistance with the combination B/F/TAF is expected to be low in clinical practice.

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Overall, despite pharmacodynamics properties, the clinical development of BIC has been confined to patients with viral strains not harbouring INSTI-R. As for DTG, if BIC were to be developed in patients with INSTI-R testing a higher dose would have to be considered.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of BIC/F/TAF has been sufficiently characterized.

2.5. Clinical efficacy

Primary studies that support the efficacy of the B/F/TAF (50/200/25 mg) FDC are two Phase 3 studies in HIV-infected, ART-naive adults (Studies GS-US-380-1489 and GS-US-380-1490) and two Phase 3 studies in HIV-infected, virologically suppressed adults (Studies GS-US-380-1844 and GS-US-380-1878). These are supported by a Phase 2 study of BIC 75 mg + F/TAF in HIV-infected, ART-naive adults (Study GS-US-141-1475).

2.5.1. Dose response study

Dose selection

The 50-mg dose of BIC was selected for the B/F/TAF FDC based on the following studies:

Study GS-US-141-1218 was a single-ascending doses (5, 25, 50, 100, 300, or 600 mg) and multiple-ascending doses (5, 25, 50, 100, or 300 mg once daily for 7 days) of single-agent BIC were well tolerated in healthy subjects, and a lack of drug-drug interaction was confirmed between BIC and F/TAF.

- the dose-ranging proof-of-concept study GS-US-141-1219. Once-daily doses of single-agent BIC (5, 25, 50, or 100 mg) administered for 10 days were also well tolerated, and led to dose-dependent decreases in HIV-1 viral load:

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Table 18. GS-US-141-1219: Time Weighted Average Change from Baseline up to Day 11 (DAVG11) in Plasma HIV-1 RNA (log10 copies/mL) (PP Analysis Set)

	GS-9883 5 mg (N=3)	GS-9883 25 mg (N=4)	GS-9883 50 mg (N=4)	GS-9883 100 mg (N=4)	Placebo (N=4)
$DAVG_{11}$[a]					
N	3	4	4	4	4
Mean (SD)	-0.92 (0.104)	-1.33 (0.174)	-1.37 (0.310)	-1.61 (0.256)	-0.01 (0.144)
95% CI	(-1.18 , -0.66)	(-1.61 , -1.06)	(-1.87 , -0.88)	(-2.01 , -1.20)	(-0.24 , 0.22)
Median	-0.87	-1.33	-1.45	-1.57	0.02
Q1, Q3	-1.04, -0.85	-1.46, -1.20	-1.61, -1.13	-1.77, -1.44	-0.11, 0.10
Min, Max	-1.04, -0.85	-1.54, -1.13	-1.63, -0.96	-1.85, -1.34	-0.21, 0.12
Pairwise p-values[b]					
vs. Placebo	<.001	<.001	<.001	<.001	
vs. GS-9883 100 mg	<.001	0.097	0.15		
vs. GS-9883 50 mg	0.016	0.81			
vs. GS-9883 25 mg	0.026				

a One subject in 5 mg group was excluded from the Per-Protocol (PP) Analysis Set as this subject's baseline HIV-1 RNA value was 173 copies/mL.
b P-value was calculated from two-sided t test.

The plasma exposure-response relationship was well characterized by an E_{max} model. Inhibitory quotient (IQ) was estimated by dividing pre-dose concentration on Day 11 (C_{tau}) by the in vitro protein-adjusted concentration that results in 95% inhibition (paIC95, 162 ng/mL - from study PC-141-2032). BIC doses of 25, 50, and 100 mg once daily yielded median protein-adjusted IQ of 95% (paIQ95) values of 4.9, 13.4, and 25.9, respectively. Based on PK/PD analyses, exposure associated with a 75 mg dose of single agent BIC is expected to provide near-maximal virologic response, with a predicted paIQ95 of approximately 20, providing considerable coverage above the target concentration of 162 ng/mL (paIC95).

The Phase 2 safety and efficacy study GS-US-141-1475 was a randomized, double-blinded study of the safety and efficacy of BIC 75 mg + F/TAF versus DTG 50 mg + F/TAF in HIV-1 infected antiretroviral treatment-naive adults. Treatments were administered without regard to food.

Baseline demographic and disease characteristics were similar between the 2 treatment groups. Efficacy outcomes are as follows:

Table 19. GS-US-141-1475: Overall Summary of Virologic Outcomes at Week 12, 24 and 48 Using the US FDA-Defined Snapshot Algorithms

			BIC+F/TAF vs DTG+F/TAF	
	BIC+F/TAF	DTG+F/TAF	p-value[a]	Difference in Percentages (95% CI)[b]
Full Analysis Set	N = 65	N = 33		
HIV-1 RNA < 50 copies/mL Week 12	61 (93.8%)	31 (93.9%)	0.79	−1.3% (−12.9% to 10.2%)
HIV-1 RNA < 50 copies/mL Week 24	63 (96.9%)	31 (93.9%)	0.50	2.9% (−8.5% to 14.2%)
HIV-1 RNA < 50 copies/mL Week 48	63 (96.9%)	30 (90.9%)	0.17	6.4% (−6.0% to 18.8%)
Per Protocol Analysis Set	N = 63	N = 30		
HIV-1 RNA < 50 copies/mL Week 24	62 (98.4%)	30 (100.0%)	0.40	−2.0% (−10.0% to 5.9%)
HIV-1 RNA < 50 copies/mL Week 48[a]	61[a] (100.0%)	29 (96.7%)	0.14	3.3% (−6.2% to 13.1%)

a N = 61 at Week 48.

b Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the baseline HIV-1 RNA stratum-adjusted MH proportion.

For each of the subgroups analysed (age, race, baseline HIV-1 RNA, baseline CD4 cell count, and study drug adherence), there was no difference between the 2 treatment groups in the percentage of subjects with HIV-1 RNA < 50 copies/mL.

At Week 48, mean changes from baseline in HIV-1 RNA and CD4 cell count were similar in both groups.

Based on this study, a BIC dose at 75 mg was selected.

The relative bioavailability study GS-US-141-1233 evaluated two FDC tablet formulations (B/F/TAF [50/200/25 mg] FDC and B/F/TAF [75/200/25 mg] FDC) compared with BIC 75 mg + F/TAF (200/25 mg). According to these results, the FDC containing BIC 50 mg instead of BIC 75 mg was selected for further evaluation in Phase 3 studies, in order to achieve equivalent BIC exposure than with BIC 75 mg single component.

2.5.2. Main studies

Studies in ART-naïve patients

Study GS-US-380-1489: *A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naive Adults.*

Patients were generally treated in ambulatory environment and were enrolled and treated at a total of 122 study centers: 2 in Belgium, 8 in Canada, 1 in the Dominican Republic, 6 in France, 3 in Germany, 3 in Italy, 10 in Spain, 8 in the United Kingdom (UK), and 81 in the United States (US).

Study GS-US-380-1490: *A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naive Adults.*

Subjects were ambulatory patients that were enrolled and treated at a total of 126 study centers: 6 in Australia, 2 in Belgium, 6 in Canada, 1 in the Dominican Republic, 4 in France, 8 in Germany, 3 in Italy, 8 in Spain, 11 in the United Kingdom (UK), and 77 in the United States (US).

Main inclusion criteria

Eligible subjects for studies 1489 and 1490 were ART-naive (≤ 10 days of prior therapy with any antiretroviral agent except the use for pre-exposure prophylaxis [PrEP] or postexposure prophylaxis [PEP], up to 1 month prior to screening); HLA-B*5701-negative, HIV- infected adults with plasma HIV-1 RNA levels ≥ 500 copies/mL; a screening genotype showing sensitivity to FTC, tenofovir (TFV), 3TC, and ABC; an estimated glomerular filtration rate (eGFR) ≥50 mL/min (≥ 0.83 mL/sec) according to the Cockcroft-Gault formula (eGFRCG); and the absence of chronic hepatitis B virus (HBV) infection.

Objectives

The primary objective for studies 1489 and 1490 is as follows:

- To evaluate the efficacy of B/F/TAF versus ABC/DTG/3TC or DTG + F/TAF in HIV-1 infected, ART-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objective of studies 1489 and 1490 is:

- To evaluate the efficacy, safety, and tolerability of the 2 treatment groups through Weeks 48, 96, and 144.

Study 1489 has the additional secondary objective

- To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Weeks 48, 96, and 144.

Results

There were 4 Phase 3 studies. The following tables summarise the efficacy results from these main studies supporting the present application:

Table 20. Summary of efficacy for trial GS-US-380-1489

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1 Infected, Antiretroviral Treatment-Naive Adults		
Study identifier	GS-US-380-1489	
Design	Randomized, double-blinded, multicenter, active-controlled study	
	Duration of main phase:	144 weeks
Hypothesis	Non-inferiority	
Treatments groups	B/F/TAF	B/F/TAF 50/200/25 mg QD N = 314

	ABC/DTG/3TC		ABC/DTG/3TC (ABC/DTG/3TC) 600/50/300 mg QD N = 315
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA <50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 96
		% subjects with HIV-1 RNA <20 c/mL	At Week 48 and 96
		Change from baseline in plasma HIV-1 RNA	
		Change from baseline in CD4 cell count	
Database lock	09 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	ABC/DTG/3TC
	Number of subject	314	315
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	290 (92.4%)	293 (93.0%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	275 (87.6%)	275 (87.3%)
	Mean change from Baseline in HIV-1 RNA (log10 c/ml at Week 48)	-3.11	-3.08
	SD	0.660	0.719
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	233	229
	SD	185.2	188.8
Effect estimate per comparison	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	Adjusted difference in proportion	-0.6%
		95% CI	-4.8% to 3.6%

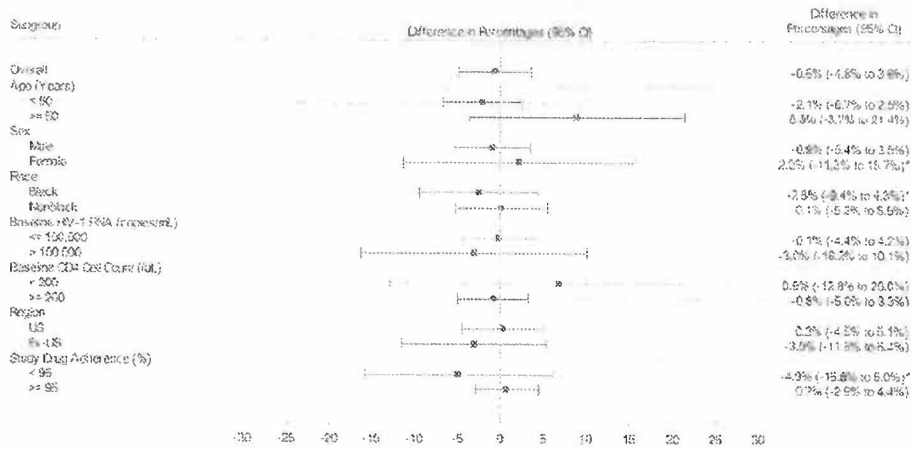
This primary endpoint was supported by the PP analysis, with virologic success rates of B/F/TAF and ABC/DTG/3TC groups at respectively 99.3% and 98.6% (difference in percentages: 0.7%, 95.002% CI: −1.4% to 2.8%). No subject developed treatment-emergent resistance to any study drug.

Subgroups analyses of study GS-US-380-1489:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analyzed (age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence):

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Figure 8. GS-US-380-1489: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window was between Day 295 and 378 (inclusive).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (< 100,000 or ≥ 100,000 copies/mL), and region stratum (US or ex-US) (if not the subgroup factor).

Study drug adherence subgroup analyses were based on the adherence up to the Week 48 visit for active study drugs.

Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the ABC/DTG/3TC group.

* Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum adjusted MH method.

Table 21. Summary of efficacy for trial GS-US-380-1490

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9883/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults			
Study identifier	GS-US-380-1490		
Design	Randomized, double-blinded, multicenter, active-controlled study		
	Duration of main phase:		144 weeks
Hypothesis	Non-inferiority		
Treatments groups	B/F/TAF		B/F/TAF 50/200/25 mg QD N = 320
	DTG+F/TAF		DTG 50 mg + FTC/TAF 200 mg/25 mg QD N = 325
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA <50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 96
		% subjects with HIV-1 RNA <20 c/mL	At Week 48 and 96
		Change from baseline in plasma HIV-1 RNA	
		Change from baseline in CD4 cell count	
Database lock	12 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		

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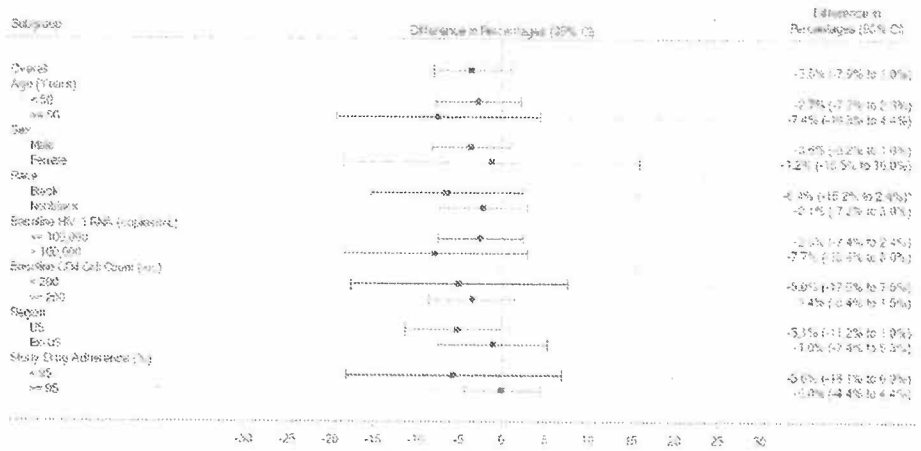
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	DTG+F/TAF
	Number of subject	320	325
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	286 (89.4%)	302 (92.9%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	263 (82.2%)	283 (87.1%)
	Mean change from Baseline in HIV-1 RNA (log10 c/ml at Week 48)	-3.08	-3.12
	SD	0.716	0.671
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	180	201
	SD	166.6	166.4
Effect estimate per comparison	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	Adjusted difference in proportion	-3.5%
		95% CI	-7.9% to 1.0%

This primary endpoint was supported by the PP analysis, with virologic success rates of B/F/TAF and DTG+F/TAF groups at respectively 98.9% and 99.7% (difference in percentages: −0.7%, 95.002% CI: −2.6% to 1.2%). No subject developed treatment-emergent resistance to any study drug.

Subgroups analyses of study GS-US-380-1490:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analyzed (age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence):

Figure 9. GS-US-380-1490: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window is between Days 295 and 378 (inclusive).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA (≤ 100,000 or > 100,000 copies/mL) and region stratum (US or ex-US) (if not the subgroup factor).

Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.

Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the DTG+F/TAF group.

* Proportion difference and 95% CI from normal approximation without stratification as they were not calculable by stratum adjusted MH method.

Studies in virologically suppressed patients

Study GS-US-380-1844: *A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed.*

Outpatient subjects were enrolled and treated at a total of 96 study centers: 3 in Australia, 1 in Belgium, 5 in Canada, 4 in France, 8 in Germany, 1 in Italy, 7 in Spain, 3 in the United Kingdom (UK), and 64 in the United States (US; including Puerto Rico).

Main inclusion criteria

Eligible subjects were HIV-1 infected adults who were virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen with the comparator ARV combination for ≥ 3 consecutive months prior to screening, with no documented resistance to any of the study agents at any time in the past; an estimated glomerular filtration rate (eGFR) ≥ 50 mL/min according to the Cockcroft-Gault formula (eGFRCG); and the absence of chronic hepatitis B virus (HBV) infection.

Objectives

The primary objective of this study was as follows:

- To evaluate the efficacy of switching from a regimen of dolutegravir (DTG) and abacavir/lamivudine (ABC/3TC) or an FDC of ABC/DTG/3TC to an FDC of bictegravir (BIC, B; previously referred to as GS 9883)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (B/F/TAF) versus continuing DTG and ABC/3TC as the FDC ABC/DTG/3TC in virologically suppressed HIV-1 infected subjects as determined by the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of the 2 treatment groups through Week 48
- To evaluate the bone safety of the 2 treatment groups as determined by the percentage change from baseline in hip and spine bone mineral density (BMD) through Week 48

Study GS-US-380-1878: *A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults.*

Outpatient subjects were enrolled and treated at 121 study centers in the United States (68), United Kingdom (UK) (14), Germany (12), Australia (7), Canada (6), France (6), Spain (3), Belgium (2), Italy (2), and the Dominican Republic (1).

Main inclusion criteria

Eligible subjects were medically stable HIV-1 infected adults who met the following criteria: on a stable once daily ARV regimen consisting of RTV- or COBI-boosted ATV or DRV plus either FTC/TDF or ABC/3TC with documented HIV-1 RNA < 50 copies/mL for ≥6 months preceding and at the screening visit; estimated glomerular filtration rate (eGRF) ≥ 50 mL/min according to the Cockcroft-Gault formula for creatinine clearance (eGRFCG); no previous use of any approved or experimental integrase strand transfer inhibitor (INSTI); and no documented or suspected resistance to FTC, tenofovir (TFV), ABC, or 3TC, including but not limited to the reverse transcriptase resistance mutations K65R and M184V/I. Subjects with chronic hepatitis B infection (unless receiving a non-TDF-containing regimen) or chronic hepatitis C infection were permitted to enter the study.

Objectives

The primary objective of this study was as follows:

To evaluate the efficacy of switching to a fixed-dose combination (FDC) of bictegravir (BIC, B; previously referred to as GS-9883)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (B/F/TAF) versus continuing on a regimen consisting of boosted atazanavir (ATV) or darunavir (DRV) plus either emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or abacavir/lamivudine (ABC/3TC) in HIV-1 infected adult subjects who were virologically suppressed, as determined by the proportion of subjects with HIV-1 RNA ≥50 copies/mL at Week 48

The secondary objective of this study was as follows:

To evaluate the safety and tolerability of the 2 treatment groups through Week 48

Results

Table 22. Summary of efficacy for trial GS-US-380-1844

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Switching from a Regimen of Dolutegravir and ABC/3TC, or a Fixed Dose Combination (FDC) of ABC/DTG/3TC to a FDC of GS-9883/F/TAF in HIV-1 Infected Subjects who are Virologically Suppressed			
Study identifier	GS-US-380-1844		
Design	Randomized, double-blinded, multicenter, active-controlled study		
	Duration of main phase:		48 weeks
Hypothesis	Non-inferiority		
Treatments groups	B/F/TAF		B/F/TAF 50/200/25 mg QD N = 282
	ABC/DTG/3TC		ABC/DTG/3TC 600/50/300 mg QD N = 281
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA ≥50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 48
		% subjects with HIV-1 RNA <20 c/mL	At Week 48
		Change from baseline in CD4 cell count	
Database lock	26 April 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	ABC/DTG/3TC
	Number of subject	282	281
	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)	3 (1.1%)	1 (0.4%)
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	264 (93.6%)	267 (95.0%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	254 (90.1%)	257 (91.5%)
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	-31	4
	SD	181.3	191.0
Effect estimate per comparison	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)	Adjusted difference in proportion	0.7%
		95% CI	-1.0% to 2.8%

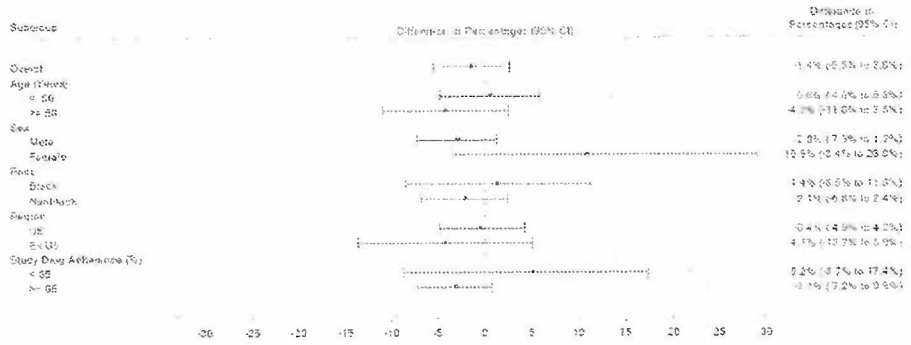
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This primary endpoint was supported by the PP analysis, with virologic failure rates of B/F/TAF and DTG+F/TAF groups at respectively 0.4% and 0.0% (difference in percentages: 0.4%, 95.002% CI: −1.1% to 2.2%). No subject developed treatment-emergent resistance to any study drug.

Subgroups analyses of study GS-US-380-1844:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analyzed (age, sex, race, region, and study drug adherence):

Figure 10. GS-US-380-1844: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



The Week 48 window is between Days 295 and 378 (inclusive).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

Study drug adherence subgroup analyses are based on the adherence up to Week 48 visit for active study drug.

Relative to the vertical line at 0, differences on the right favor the B/F/TAF group and differences on the left favor the ABC/DTG/3TC group

Table 23. Summary of efficacy for trial GS-US-380-1878

Title: A Phase 3, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir plus either Emtricitabine/Tenofovir or Abacavir/Lamivudine to GS-9883/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1 Infected Adults			
Study identifier	GS-US-380-1878		
Design	Randomized, open-labelled, multicenter, active-controlled study		
	Duration of main phase:		48 weeks
Hypothesis	Non-inferiority		
Treatments groups	B/F/TAF		B/F/TAF 50/200/25 mg QD N = 290
	SBR (stay on baseline regimen)		Boosted ATV or DRV + FTC/TDF or ABC/3TC N = 287
Endpoints and definitions	Primary endpoint	% subjects with HIV-1 RNA ≥50 c/mL	At Week 48, using FDA Snapshot algorithm
	Secondary efficacy endpoints	% subjects with HIV-1 RNA <50 c/mL	At Week 48

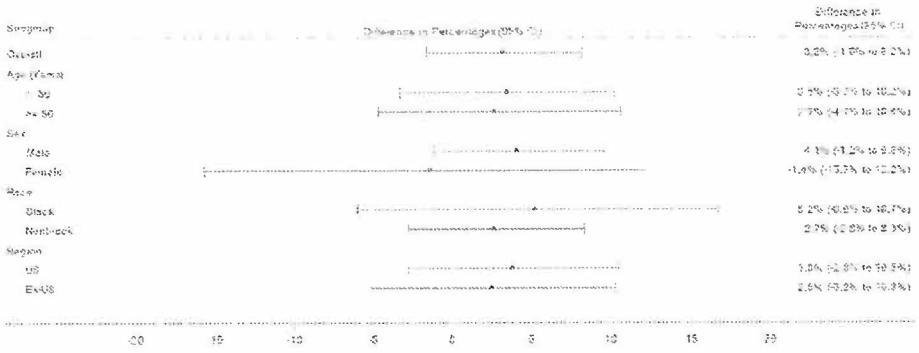
		% subjects with HIV-1 RNA <20 c/mL	At Week 48
		Change from baseline in CD4 cell count	
Database lock	15 May 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Time point: Week 48		
Descriptive statistics and estimate variability	Treatment group	B/F/TAF	SBR
	Number of subject	290	287
	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)	5 (1.7%)	5 (1.7%)
	Subjects with HIV-1 RNA <50 c/mL at W48 (%)	267 (92.1%)	255 (88.9%)
	Subjects with HIV-1 RNA <20 c/mL at W48 (%)	249 (85.9%)	243 (84.7%)
	Mean change from Baseline in CD4+ cell counts (cells/mm3 at Week 48)	25	0
	SD	151.2	159.4
Effect estimate per comparison	Subjects with HIV-1 RNA ≥50 c/mL at W48 (%)	Adjusted difference in proportion	-0.0%
		95% CI	-2.5% to 2.5%

This primary endpoint was supported by the PP analysis, with virologic failure rates of B/F/TAF and DTG+F/TAF groups at respectively 1.1% and 0.8% (difference in percentages: 0.3%, 95.002% CI: −1.9% to 2.5%). No subject developed treatment-emergent resistance in the B/F/TAF group. One subject in the SBR group (on a regimen of RTV-boosted DRV plus ABC/3TC) developed L74V in reverse transcriptase.

Subgroups analyses of study GS-US-380-1878:

The percentage of subjects with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm based on the FAS was similar between the 2 treatment groups for all of the subgroups analysed (age, sex, race and region):

Figure 11. GS-US-380-1878: Forest Plot of Treatment Difference in HIV-1 RNA < 50 copies/mL by Subgroup at Week 48 Using the US FDA-Defined Snapshot Algorithm (FAS)



Week 48 window was between Day 295 and 378 (inclusive).
The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

Regardless of prior treatment regimen (FTC/TDF vs ABC/3TC), the response rates in Study GS US-380-1878 were high and similar between both treatment groups:

- Baseline FTC/TDF-containing regimen: B/F/TAF 92.2%; SBR 89.3%

- Baseline ABC/3TC-containing regimen: B/F/TAF 91.1%; SBR 86.4%

Clinical studies in special populations

There was no clinical study performed in special populations (notably paediatric subjects, HIV/HBV-co-infected subjects or renal impaired HIV-infected subjects).

The number of elderly subjects in the B/F/TAF clinical development program was limited. Age was tested as a potential covariate in both the BIC and TAF population PK analyses for B/F/TAF, but was determined to be not significant for both analytes. As such, age is not expected to substantially affect exposure of BIC or TAF.

Supportive studies

The week 48 results of study GS-US-380-1961 became available during the evaluation.

Study GS-US-380-1961 is an ongoing, Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching to B/F/TAF in HIV-infected, virologically suppressed women on a regimen consisting of GEN, STB, or ATV+RTV+FTC/TDF for ≥ 12 weeks prior to screening.

Subjects were enrolled and treated at a total of 58 study centers in 5 countries: Uganda (27.0%, 127 subjects), Russia (23.8%, 112 subjects), Thailand (21.5%, 101 subjects), US (15.3%, 72 subjects), and the Dominican Republic (12.3%, 58 subjects). Overall, 470 subjects (B/F/TAF 234, SBR 236) who were randomized and received at least 1 dose of study drug were included in both the Safety Analysis Set and FAS.

As of the Week 48 data cut date, 98.1% of randomized and treated subjects (461 subjects; B/F/TAF 98.7%, 231 subjects; SBR 97.5%, 230 subjects) had completed study drug in the randomized phase

and 0.2% of subjects (1 subject in the SBR group) were continuing study drug in the randomized phase. Overall, 1.7% of subjects (8 subjects; B/F/TAF 1.3%, 3 subjects; SBR 2.1%, 5 subjects) prematurely discontinued study drug in the randomized phase prior to the Week 48 data cut date. Reasons for premature discontinuation of study drug were generally comparable between treatment groups.

Demographic and baseline characteristics were similar between the 2 treatment groups. Most of the women were not Hispanic/Latino (84.3%), and most were black (37.0%), white (28.3%), or Asian (21.7%). Median age was 39 years (range: 20 to 63 years). Median (Q1, Q3) body mass index was 25.6 (22.1, 30.5) kg/m2. Baseline disease characteristics were generally similar between the 2 treatment groups: the median (Q1, Q3) baseline CD4 cell count was 686 (541, 867) cells/μL, with 83.2% of subjects having a baseline CD4 count ≥ 500 cells/μL. The median (Q1, Q3) baseline CD4% was 36.7% (31.1%, 42.6%). Most subjects were receiving GEN (53.0%, 249 subjects) or STB (41.9%, 197 subjects) at baseline. The most common HIV risk factor was heterosexual sex (98.3% of subjects). Most subjects had asymptomatic HIV-1 infection (90.4%); 7.0% had symptomatic HIV-1 infection, and 2.6% were diagnosed with AIDS. The median (Q1, Q3) eGFRCG at baseline was 100.8 (84.0, 119.8) mL/min.

The percentages of subjects in the FAS with HIV-1 RNA ≥ 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm (primary endpoint) were similar between the 2 treatment groups (B/F/TAF 1.7%; SBR 1.7%; difference in percentages: 0.0%, 95.001% CI: −2.9% to 2.9%). Because the upper bound of the 2-sided 95.001% CI of the difference between treatment groups (B/F/TAF − SBR) was less than the pre-specified 4% margin, switching to B/F/TAF was determined to be non-inferior to maintaining baseline regimen. Similarly, the percentages of subjects in the FAS with HIV-1 RNA < 50 copies/mL and < 20 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were similar between the 2 treatment groups.

Table 24. GS-US-380-1961: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 copies/mL (Full Analysis Set)

	B/F/TAF (N = 234)	SBR (N = 236)	B/F/TAF vs. SBR	
			p-value	Difference in Percentages (95.001% CI)
HIV-1 RNA < 50 copies/mL	224 (95.7%)	225 (95.3%)	1.00	0.4% (−3.7% to 4.5%)
HIV-1 RNA >= 50 copies/mL	4 (1.7%)	4 (1.7%)	1.00	0.0% (−2.9% to 2.9%)
HIV-1 RNA >= 50 copies/mL in Week 48 Window	4 (1.7%)	4 (1.7%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA >= 50 copies/mL	0	0		
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA >= 50 copies/mL	0	0		
No Virologic Data in Week 48 Window	6 (2.6%)	7 (3.0%)		
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL	0	1 (0.4%)		
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	3 (1.3%)	4 (1.7%)		
Missing Data During Window but on Study Drug	3 (1.3%)	2 (0.8%)		

CD4 cell counts were maintained in both groups. Mean (SD) changes from baseline at Week 48 for the FAS were as follows: B/F/TAF 29 (159.4) cells/µL; SBR 26 (170.3) cells/µL; difference in least-squares mean: 3 cells/µL, 95% CI: −27 to 34 cells/µL.

Analysis performed across trials (pooled analyses and meta-analysis)

The pooled-results of the studies GS-US-380-1489 and GS-US-380-1490 in ART-naïve subjects are as follows:

Table 25. GS-US-380-1489 and GS-US-380-1490: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cut-off at 50 copies/mL – Pooled Data (Full Analysis Set)

	B/F/TAF 380-1489,1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG+F/TAF 380-1490 (N = 325)
HIV-1 RNA < 50 copies/mL	576 (90.9%)	293 (93.0%)	302 (92.9%)
B/F/TAF vs. ABC/DTG/3TC			
Difference in Percentages (95% CI)	-2.1% (-5.0% to 1.6%)		
p-value	0.26		
B/F/TAF vs. DTG + F/TAF			
Difference in Percentages (95% CI)	-1.9% (-5.6% to 1.8%)		
p-value	0.32		
HIV-1 RNA >= 50 copies/mL	17 (2.7%)	8 (2.5%)	4 (1.2%)
HIV-1 RNA >= 50 copies/mL in Week 48 Window	5 (0.8%)	6 (1.9%)	1 (0.3%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA >= 50 copies/mL	12 (1.9%)	2 (0.6%)	3 (0.9%)
No Virologic Data in Week 48 Window	41 (6.5%)	14 (4.4%)	19 (5.8%)
Discontinued Study Drug Due to AE/Death	3 (0.5%)	4 (1.3%)	3 (0.9%)
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA < 50 copies/mL	27 (4.3%)	9 (2.9%)	14 (4.3%)
Missing Data During Window but on Study Drug	11 (1.7%)	1 (0.3%)	2 (0.6%)

Week 48 window is between Day 295 and 378 (inclusive).

* Other reasons include subjects who discontinued study drug due to investigator's discretion, subject decision, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the CMH test stratified by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

The difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI was calculated based on the MH proportion adjusted by baseline HIV-1 RNA stratum (<= 100,000 vs. > 100,000 copies/mL) and region stratum (US vs. ex-US).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

There are 4 Phase 3 pivotal studies assessing B/F/TAF 50/200/25 mg: 2 in ART-naïve subjects, and 2 in virologically supressed subjects. The design, statistical method, outcomes and inclusion/exclusion criteria are acceptable. The choice of the comparators (DTG-based regimen in the 2 studies in ART-naïve subjects and in one switch study, PI-based regimen in the other switch study) is endorsed given DTG is the more effective and used INSTI, in comparison to raltegravir and elvitegravir. While this comparator has been used in both pivotal studies in TN patients, the backbone with DTG was different in both studies, ABC/3TC or F/TDF. The comparison of B/F/TAF to a PI-based regimen in a switch study provides additional data to reinforce the place of such INSTI with significant barrier of resistance into the HIV therapeutic strategy.

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Of note, the comparison with DTG is done in TN and in virologically suppressed patients.

Although a more stringent 10% non-inferiority margin would have been regarded as more appropriate than the 12% selected margin for the studies performed in ART-naive subjects, ultimately results are overall compatible with a more stringent non inferiority margin.

In these pivotal studies, enrolled subjects are predominantly white homosexual men with unaltered immune function and asymptomatic HIV infection, as for main of the Phase 3 studies in HIV clinical studies. The proportion of women and ART-naive subjects with VL >100,000 c/mL is low (10-15%) but an additional switch study only performed in women confirms this non-inferiority.

Efficacy data and additional analyses

The short-term monotherapy study suggested that 100 mg bictegravir might be slightly better than 50 mg. The Applicant initially chose 75 mg primarily based on the Emax model. The choice of this dose might be endorsed considering that the clinical development of BIC does not encompass patients with viral strains harbouring INSTI-RAM, where higher dose might have been required as for dolutegravir. Then, the dose of bictegravir was subsequently lowered to 50 mg when bictegravir was incorporated into the FDC with FTC and TAF based on PK data.

While it is clear that the BIC dose was to be different as part of the FDC vs outside the FDC, there might still be some room for maximizing the dose. Nevertheless, it can ultimately be acknowledged that the dose as selected has enabled to achieve non-inferiority of B/F/TAF vs DTG+2 NRTIs. However, it is expected that higher BIC dose would be required in the context of INI-RAM emergence.

Overall, the efficacy endpoints support the non-inferiority of B/F/TAF compared to DTG-based regimen (FTC/TAF or ABC/3TC) in ART-naive subjects and when switching from such regimen in virologically suppressed subjects. These results are supported by the Per Protocol analyses and other secondary endpoints, especially the changes from baseline in plasma HIV-1 RNA and CD4 cell count. In addition, the switch to B/F/TAF is non-inferior to the continuation of a DRV- or ATV-based regimen. This is consistent with the known efficacy of DTG in comparison to PI. The rates of virological success or lack of efficacy with B/F/TAF are consistent with the historical data from F/TAF-studies.

In the Phase 3 studies comparing B/F/TAF vs DTG+F/TAF or ABC/DTG/3TC in ART-naive subjects, there is a trend for lower response rate in the subgroup of patients with high viral load (>100,000 c/ml) treated with B/F/TAF. It is noteworthy that given that ABC/3TC is somewhat regarded as not maximizing efficacy in patients with high viral load, the trend for higher efficacy of DTG was more pronounced when DTG was combined with the same backbone as for BIC (i.e. FTAF) than when DTG was combined with ABC-3TC. Given that the subgroup of patients with high viral load is regarded as discriminatory, the results in patients with high viral load might translate a somewhat lower performance of BIC as compared to DTG which might be related to a non-maximized dose of BIC. While it can be acknowledged that in the subgroup of patients with adherence <95% the trend favouring dolutegravir might be driven by the missing data rather than virologic failure (which would otherwise have argued that limited adherence might be more pejorative for bictegravir than dolutegravir), this is not the case for the overall analysis in patients with high viral load. Overall, the trend in favour of dolutegravir in patients with high viral load as reflected in section 5.1 of the SmPC.

In studies GS-US-380-1490 (B/F/TAF vs DTG+F/TAF in ART-naive subjects) and GS-US-380-1844 (B/F/TAF vs ABC/DTG/3TC in virologically suppressed subjects), there is a slightly higher rate of subjects who discontinued from B/F/TAF treatment due to adverse events, although not statistically significant.

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Across all these studies, no INSTI-RAM had emerged in the B/F/TAF groups, as in the DTG groups. This is consistent with the favourable resistance profile of BIC, with a barrier to resistance development expected to be similar to DTG. However, as already stated the efficacy of B/F/TAF in subjects with history of virological failure under INSTI therapy was not evaluated.

2.5.4. Conclusions on the clinical efficacy

B/F/TAF 50/200/25 mg has been demonstrated to be overall non inferior to DTG + FTC/TAF or ABC/3TC in ART-naive or virologically suppressed subjects without history of INSTI resistance. High percentage of patients have achieved HIV RNA level <50 copies/ml at week 48 (≥90% at Week 48) and this demonstration is derived from three well-designed studies (double blind, large sample and primary endpoint in line with EU guidelines) with comparable populations enrolled. In addition, an additional switch study demonstrated the non-inferiority of B/F/TAF vs DRV- or ATV-based regimen, which is consistent with DTG. The clinical demonstration can support the use of BFTAF for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated *with resistance to the integrase inhibitor class*, emtricitabine or tenofovir.

2.6. Clinical safety

Patient exposure

A total of **1511 subjects** have received at least 1 dose of B/F/TAF in the Phase 2 and 3 studies, including 1206 subjects from the randomized phases of the Phase 3 studies. This population exposure to B/F/TAF exceeds the requirements of the ICH E1 guideline for the safety evaluation of drugs, but the number of subjects with high duration of treatment (≥72 weeks) is very limited. The duration of exposure was similar between groups within each study.

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Table 26. GS-US-380-1489, GS-US-380-1490, GS-US-141-1475, GS-US-380-1844, GS-US-380-1878: Duration of Exposure to Randomized Study Drug (Safety Analysis Set)

	ART-Naive Adult Subjects					Virologically Suppressed Adult Subjects			
	GS-US-380-1489/GS-US-380-1490			GS-US-141-1475[a]		GS-US-380-1844		GS-US-380-1878[b]	
	Pooled	380-1489	380-1490						
	B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG + F/TAF (N = 325)	BIC + F/TAF (N = 65)	DTG + F/TAF (N = 33)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Exposure Duration									
Mean (SD)	49.8 (11.97)	51.6 (10.60)	49.7 (10.88)	58.0 (8.69)	57.4 (10.43)	50.7 (10.59)	50.9 (10.20)	44.9 (7.09)	44.3 (8.92)
Median	49.2	51.3	48.6	59.9	60.0	49.9	50.3	46.7	46.7
Q1, Q3	45.6, 56.1	46.3, 57.6	45.6, 55.1	59.1, 60.0	59.7, 60.1	45.1, 56.3	45.1, 56.3	44.0, 48.0	44.0, 48.0
Min, Max	0.1, 74.3	0.6, 72.6	1.4, 74.4	0.1, 63.0	2.3, 61.1	0.1, 72.9	7.6, 72.4	1.3, 56.6	0.1, 56.7
Exposure Cutoffs									
≥ 4 Weeks (28 days)	631 (99.5%)	314 (99.7%)	324 (99.7%)	64 (98.5%)	32 (97.0%)	281 (99.6%)	281 (100.0%)	289 (99.7%)	285 (99.3%)
≥ 8 Weeks (56 days)	622 (98.1%)	312 (99.0%)	321 (98.8%)	64 (98.5%)	32 (97.0%)	279 (98.9%)	280 (99.6%)	287 (99.0%)	282 (98.3%)
≥ 12 Weeks (84 days)	615 (97.0%)	312 (99.0%)	317 (97.5%)	64 (98.5%)	32 (97.0%)	278 (98.6%)	280 (99.6%)	284 (97.9%)	277 (96.5%)
≥ 24 Weeks (168 days)	605 (95.4%)	307 (97.5%)	314 (96.6%)	63 (96.9%)	32 (97.0%)	273 (96.8%)	273 (97.2%)	281 (96.9%)	273 (95.1%)
≥ 36 Weeks (252 days)	595 (93.8%)	301 (95.6%)	310 (95.4%)	63 (96.9%)	32 (97.0%)	271 (96.1%)	269 (95.7%)	276 (95.2%)	265 (92.3%)
≥ 48 Weeks (336 days)	370 (58.4%)	201 (63.8%)	180 (55.4%)	63 (96.9%)	31 (93.9%)	169 (59.9%)	172 (61.2%)	98 (33.8%)	102 (35.5%)
≥ 60 Weeks (420 days)	102 (16.1)	63 (20.0%)	49 (15.1%)	29 (44.6%)	20 (60.6%)	46 (16.3%)	47 (16.7%)	—	—
≥ 72 Weeks (504 days)	5 (0.8%)	3 (1.0%)	3 (0.9%)	—	—	5 (1.8%)	5 (1.8%)	—	—

Duration of exposure to study drug was the number of weeks between the first dose and the last dose of randomized study drug.

For subjects who had prematurely discontinued randomized study drug, if the last dose date of randomized study drug was completely missing or only year was known, the latest of randomized study drug start and end dates or randomized clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date

For subjects who had not prematurely discontinued randomized study drug, the data cut date was used to impute the last dose date.

a Includes only double-blinded, randomized treatment

b Includes only randomized treatment

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Adverse events

The adverse event (AE) profile was generally similar in ART-naive and virologically suppressed adults, with similar rates of any AEs, Grade 3 or 4 AEs, SAEs, SAEs considered related to study drugs, and AEs leading to study drug discontinuation across the different treatment groups.

Table 27. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Any AE	529 (83.4%)	283 (89.8%)	272 (83.7%)	225(79.8%)	225 (80.1%)	233 (80.3%)	226 (78.7%)
Grade 3 or 4 AE	56 (8.8%)	24 (7.6%)	25 (7.7%)	16 (5.7%)	10 (3.6%)	13 (4.5%)	18 (6.3%)
Study Drug-Related AE	139 (21.9%)	127 (40.3%)	83 (25.5%)	23 (8.2%)	44 (15.7%)	54 (18.6%)	6 (2.1%)
Grade 3 or 4 Study Drug-Related AE	5 (0.8%)	4 (1.3%)	0	2 (0.7%)	0	2 (0.7%)	0
Any SAE	58 (9.1%)	25 (7.9%)	23 (7.1%)	15 (5.3%)	22 (7.8%)	17 (5.9%)	20 (7.0%)
Study Drug-Related SAE	3 (0.5%)	1 (0.3%)	0	1 (0.4%)	0	1 (0.3%)	0
AE Leading to Premature Study Drug Discontinuation	5 (0.8%)	4 (1.3%)	1 (0.3%)	6 (2.1%)	2 (0.7%)	2 (0.7%)	1 (0.3%)
Death	1 (0.2%)	0	2 (0.6%)	2 (0.7%)	0	1 (0.3%)	1 (0.3%)

The denominator for percentages was based on the number of subjects in the Safety Analysis Set

Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.

Relatedness to study drug is assessed by the investigator.

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Table 28. GS-US-380-1489 and GS-US-380-1490: Study Drug-Related Adverse Events by Preferred Term Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set)

	B/F/TAF 380-1489, 1490 (N = 634)	ABC/DTG/3TC 380-1489 (N = 315)	DTG + F/TAF 380-1490 (N = 325)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	139 (21.9%)	127 (40.3%)	83 (25.5%)
Nausea	26 (4.1%)	55 (17.5%)	17 (5.2%)
Headache	29 (4.6%)	15 (4.8%)	10 (3.1%)
Diarrhoea	29 (4.6%)	13 (4.1%)	11 (3.4%)
Fatigue	16 (2.5%)	10 (3.2%)	7 (2.2%)
Dizziness	13 (2.1%)	9 (2.9%)	2 (0.6%)
Insomnia	11 (1.7%)	9 (2.9%)	1 (0.3%)
Abnormal dreams	9 (1.4%)	8 (2.5%)	2 (0.6%)
Abdominal distension	7 (1.1%)	5 (1.6%)	4 (1.2%)
Flatulence	6 (0.9%)	2 (0.6%)	7 (2.2%)
Vomiting	6 (0.9%)	5 (1.6%)	2 (0.6%)
Constipation	7 (1.1%)	2 (0.6%)	3 (0.9%)
Abdominal discomfort	4 (0.6%)	4 (1.3%)	3 (0.9%)
Abdominal pain	3 (0.5%)	6 (1.9%)	2 (0.6%)
Dyspepsia	4 (0.6%)	4 (1.3%)	3 (0.9%)
Somnolence	4 (0.6%)	3 (1.0%)	2 (0.6%)
Decreased appetite	3 (0.5%)	3 (1.0%)	2 (0.6%)
Sleep disorder	3 (0.5%)	5 (1.6%)	0
Anxiety	1 (0.2%)	3 (1.0%)	1 (0.3%)

Adverse events were coded using MedDRA 19.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Relatedness to study drug is assessed by the investigator.

Serious adverse event/deaths

Across the Phase 2-3 studies, 7 deaths were reported: 4 in subjects receiving B/F/TAF (Studies GS-US-380-1490, GS-US-380-1844, or GS-US-380-1878), 2 in subjects receiving DTG+F/TAF (Study GS-US-380-1490), and 1 in a subject receiving boosted ATV + FTC/TDF (Study GS-US-380-1878). None of the deaths was considered related to study drug by the Applicant. No treatment-emergent deaths were reported in Phase 1 studies with single-agent BIC or regimens containing BIC and F/TAF.

The incidence of SAEs in Phase 2-3 studies was comparable between treatment groups within each study.

Adverse events of special interest

Hepatic safety

The hepatic safety results can be summarised as follows:

	B/F/TAF Group	Control Group	Studies
Hepatic AEs	1.4%	1.9% - 3.1 %	Pooled studies GS-US-380-1489-1490
	4.6%	0%	Phase 2 study GS-US-141-1475
	1.8%	0.4%	Switch study GS-US-380-1844

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	B/F/TAF Group	Control Group	Studies
	1.4%	3.5%	Switch study open label GS-US-380-1878
ALT increase	11.3%	12% -14%	Pooled studies GS-US-380-1489-1490
	25%	**9.4%**	Phase 2 study GS-US-141-1475
	18.4%	**9.6%**	Switch study GS-US-380-1844
	23.4%	**10.5%**	Switch study open label GS-US-380-1878
AST increase	13.1%	11.1%-15.2%	Pooled studies GS-US-380-1489-1490
	23.4%	**9.4%**	Phase 2 study GS-US-141-1475
	16.3%	**9.6%**	Switch study GS-US-380-1844
	14.8%	**10.2%**	Switch study open label GS-US-380-1878
Hyperbilirubinemia	**11.6%**	**4.1% - 5.8%**	Pooled studies GS-US-380-1489-1490
	14.1%	12.5%	Phase 2 study GS-US-141-1475
	7.4%	**3.6%**	Switch study GS-US-380-1844
	5.5%	33.7%	Switch study open label GS-US-380-1878
ALP increase	2.2%	2.2% -3.2%	Pooled studies GS-US-380-1489-1490
	0%	3.1%	Phase 2 study GS-US-141-1475
	2.5%	0.7%	Switch study GS-US-380-1844
	0.3%	3.5%	Switch study open label GS-US-380-1878

The incidence of non-infectious, non-congenital hepatic AEs was comparable between the B/F/TAF and comparator group within each Phase 3 study and within the pooled analysis.

No subject treated with B/F/TAF had a non-infectious, non-congenital hepatic SAE or discontinued study drugs due to hepatic AEs. No subject treated with B/F/TAF or a comparator met Hy's Law criteria.

No clinically relevant median changes from baseline were observed in alkaline phosphatase, ALT, AST, or total bilirubin for the B/F/TAF or comparator group in any of the Phase 3 studies. Transaminase elevations were reported in a higher proportion in virologically suppressed subjects who switched treatment to B/F/TAF than in subjects in the comparator groups. However, these transaminase elevations were mainly Grade 1 or 2, resolved without B/F/TAF discontinuation and were not associated with AEs.

Graded total bilirubin increases occurred in a higher percentage of subjects treated with B/F/TAF than the comparator in Studies GS-US-380-1489, GS-US-380-1490, and GS-US-380-1844; however, the increases were primarily Grade 1 or Grade 2 in severity and were not associated with hepatic AEs or other liver-related laboratory abnormalities.

The incidence of Grade 3 or 4 treatment-emergent liver-related laboratory abnormalities was comparable between treatment groups within each Phase 3 study and within the pooled analysis (with the exception of total bilirubin in Study GS-US-380-1878, due to ATV treatment in some subjects in the SBR group).

Bone safety

B/F/TAF demonstrated a bone safety profile comparable with that of ABC/DTG/3TC, a regimen that is not associated with bone toxicity. In both ART-naive (study GS-US-380-1489) and virologically suppressed subjects (GS-US-380-1844), mean (SD) percentage changes from baseline in hip and spine BMD were comparable between the B/F/TAF and ABC/DTG/3TC treatment groups.

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Renal safety

B/F/TAF demonstrated a renal safety profile comparable with that of ABC/DTG/3TC, a regimen that is not associated with renal toxicity, and an improved renal safety profile compared with a regimen consisting of boosted ATV or DRV plus FTC/TDF or ABC/3TC.

No subject had proximal tubulopathy (including Fanconi Syndrome) or discontinued study drugs due to a renal and urinary disorder or associated investigation AE.

Across the Phase 3 studies, changes from baseline in serum creatinine and $eGFR_{CG}$ were consistent with the known inhibitory effect of BIC or DTG on renal tubular secretion via OCT2 and/or MATE1. These changes were not clinically relevant and are not reflective of changes in actual glomerular filtration rate. Changes in serum creatinine and $eGFR_{CG}$ were observed by Week 4 and remained stable thereafter through Week 48:

Median (Q1, Q3) change from baseline to Week 48	**Serum creatinine**	**$eGFR_{CG}$**
Pooled studies GS-US-380-1489 and GS-US-380-1490	B/F/TAF: 0.10 (0.03, 0.17) mg/dL ABC/DTG/3TC: 0.11 (0.03, 0.18) mg/dL DTG+F/TAF: 0.11 (0.04, 0.19) mg/dL	B/F/TAF: −8.8 (−18.4, 0.1) mL/min ABC/DTG/3TC: −10.8 (−21.6, −2.4) mL/min DTG+F/TAF: −10.8 (−20.0, −1.7) mL/min
Switch study GS-US-380-1844	B/F/TAF: 0.00 (−0.07, 0.06) mg/dL ABC/DTG/3TC: 0.02 (−0.05, 0.09) mg/dL	B/F/TAF: 1.0 (−5.2, 9.4) mL/min ABC/DTG/3TC: −1.8 (−9.0, 4.8) mL/min
Switch study GS-US-380-1878	B/F/TAF: 0.06 (−0.03, 0.13) mg/dL SBR: 0.00 (−0.07, 0.07) mg/dL	B/F/TAF: −4.3 (−12.6, 4.8) mL/min SBR: 0.2 (−6.6, 7.6) mL/min

Ocular safety

Overall, the incidence of AEs in the eye disorders SOC and the incidence of AEs potentially related to uveitis were low and comparable between treatment groups in the 4 Phase 3 B/F/TAF studies. Clinically, none of the AEs potentially related to uveitis were considered representative of an actual case of posterior uveitis.

Table 29. GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878: Adverse Events in the Eye Disorders System Organ Class and Potential Uveitis Adverse Events (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Eye Disorders SOC	19 (3.0%)	10 (3.2%)	18 (5.5%)	9 (3.2%)	9 (3.2%)	7 (2.4%)	5 (1.7%)
Potential Uveitis AEs[a]	4 (0.6%)	1 (0.3%)	8 (2.5%)	3 (1.1%)	3 (1.1%)	1 (0.3%)	1 (0.3%)

a Based on the list of terms used for the GEN development program, which was reviewed and edited by an external ophthalmologist for comprehensiveness.

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Psychiatric disorders

Adverse events based on the suicide/self-injury Standard MedDRA Query were infrequent in the 4 Phase 3 B/F/TAF studies through 48 weeks of treatment. Most subjects who experienced a suicide-related AE when receiving B/F/TAF had a pre-existing history of depression or mental illness.

Table 30. GS-US-380-1489, GS-US-380-1490, GS-US-380-1044, GS-US-380-1878: Suicide Events by Suicide/Self-Injury SMQ (Safety Analysis Set)

	ART-Naive Adult Subjects			Virologically Suppressed Adult Subjects			
	380-1489, 1490	380-1489	380-1490	GS-US-380-1844		GS-US-380-1878	
	Pooled B/F/TAF (N = 634)	ABC/DTG/ 3TC (N = 315)	DTG +F/TAF (N = 325)	B/F/TAF (N = 282)	ABC/DTG/ 3TC (N = 281)	B/F/TAF (N = 290)	SBR (N = 287)
Suicide Events	7 (1.1%)	3 (1.0%)	2 (0.6%)	3 (1.1%)	1 (0.4%)	0	1 (0.3%)
Depression suicidal	1 (0.2%)	0	0	1 (0.4%)	0	0	0
Intentional overdose	0	0	0	1 (0.4%)	0	0	0
Suicidal ideation	3 (0.5%)	3 (1.0%)	1 (0.3%)	2 (0.7%)	1 (0.4%)	0	0
Suicide attempt	3 (0.5%)	0	1 (0.3%)	1 (0.4%)	0	0	1 (0.3%)

Laboratory findings

B/F/TAF demonstrated a clinical laboratory safety profile similar to that of comparator regimens. There were no clinically relevant changes from baseline in the B/F/TAF group or differences between the B/F/TAF and comparator groups in median values for hematology or clinical chemistry parameters (including metabolic parameters), and median values were generally within reference ranges. Of note, higher rates of minor transaminase increases were observed in the B/F/TAF groups than in the DTG-containing groups, but were not considered clinically significant.

Safety in special populations

The AE profile for subjects receiving B/F/TAF was not affected by sex, age and race.

Renal impairment

In study GS-US-141-1479, BIC 75 mg was administered in subjects with severe impaired renal function (n=10) compared with control subjects with normal renal function (n=8). One AE in each renal function group was considered related to study drug by the investigator (nausea in a subject with severe renal impairment and headache in a subject with normal renal function). The safety profile of BIC was similar between the 2 renal function groups.

Hepatic impairment

In study GS-US-141-1478, BIC 75 mg was administered in subjects with normal (n=10) or moderate (n=10) hepatic impairment. The AEs considered related to study drug by the investigator were reported in 3 subjects (30%) with moderate hepatic impairment and in none of the normal matched control subjects. These events were headache (2 subjects) and somnolence (1 subject).

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HBV/HCV-coinfection

In HIV/HBV-co-infected subjects (14 subjects in study GS-US-380-1490 and 14 subjects in study GS-US-380-1878), the safety profile of B/F/TAF was similar to that in patients with HIV mono-infection. In study GS-US-380-1490, 1 subject in the B/F/TAF group had a confirmed on-treatment ALT flare (defined as ALT > 10 x ULN and ALT > 2 x baseline on 2 consecutive occasions) at Week 12. The ALT flare was reported as a Grade 2 AE of immune reconstitution inflammatory syndrome that was not considered related to study drug. No hepatic AEs were reported for this subject. Another HIV/HBV co-infected subject in the B/F/TAF group, with normal ALT (30 U/L) and AST (24 U/L) at baseline, experienced Grade 3 ALT (316 U/L) and Grade 2 AST (136 U/L) at Week 8, both of which resolved to within the normal range by Week 24. One additional subject (DTG+F/TAF group) experienced Grade 1 ALT and AST elevations. In study GS-US-380-1878, 3 subjects in the B/F/TAF group experienced treatment-emergent Grade 1 ALT elevation, one of whom also experienced Grade 1 AST elevation. One subject in the SBR group experienced Grade 2 total bilirubin abnormality.

In HIV/HCV-co-infected subjects (n=25), elevations in AST and ALT occurred more frequently than in the subjects without viral hepatitis infection. The incidence of graded AST and ALT elevations for HIV/HCV baseline-co-infected subjects was similar between the 2 treatment groups.

Pregnancy

No adequate and well-controlled studies of B/F/TAF or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of BIC, FTC, or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. B/F/TAF should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. No clinically relevant concerns are apparent from review of available pregnancy data in clinical studies (11 pregnancies reported in the Phase 3 studies, including 5 subjects treated with B/F/TAF) or from Antiretroviral Pregnancy Registry (APR) data for FTC and from the limited data for TAF.

Discontinuation due to adverse events

The rate of discontinuation due to AE with B/F/TAF is low (≤2%), similarly to the comparators groups. These AEs are generally gastro-intestinal, neuropsychiatric or allergic disorders.

2.6.1. Discussion on clinical safety

As expected, the safety profile of B/F/TAF is similar to DTG+FTC/TAF. The more frequent AEs are gastrointestinal disorders (diarrhoea, nausea, vomiting), headache, fatigue and insomnia (<5% of subjects). It has to be underlined that only 48 weeks data from the ongoing longer term pivotal phase 3 studies have been made available.

The relevant aspects of the safety profile of B/F/TAF are:

Hepatotoxicity: Although no liver hypersensitivity reaction or severe drug-induced liver occurred in subjects treated with B/F/TAF, higher rates of transaminases elevations and hyperbilirubinemia were observed compared to DTG-based regimen. These elevations were mild and transient. Considering the available data in monkeys which showed bile duct hyperplasia a at the higher doses of B tested (1000 mg/kg/day) not always reversible and the cases of increased ALT activities also reported at the highest doses and the potential competition of B for the UGT1A1 enzyme with unconjugated bilirubin, the risk of hepatobiliary disorders is a potential concern for bictegravir-containing regimen. Of note, an

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amendment to the study protocols GS-US-380-1489 and GS-US-380-1844 was made to include recommendations for the management of potential hepatobiliary toxicity. The recommendation was to highlight the potential hepatobiliary toxicity of bictegravir based on data available in monkeys at the highest dose tested (biliary hyperplasia and hepatocyte hypertrophy) and that further investigations might be necessary in case of signs/ laboratory abnormalities suggestive of hepatobiliary disorders. Hepatotoxicity will be actively monitored through PSURs.

Renal disorders: as DTG, BIC also increases serum creatinine level within the first weeks of treatment and remained stable thereafter, due to the inhibition of the transporters OCT2 and MATE-1. This is not considered to be clinically relevant since do not reflect a change in glomerular filtration rate, but should be considered for the biological monitoring of renal impaired subjects treated with B/F/TAF.

Psychiatric disorders: depression, suicidal ideation and suicidal behaviour (particularly in patients with pre-existing history of psychiatric illness) are a class-effect of integrase inhibitors and listed in the SmPC of dolutegravir, raltegravir and elvitegravir. The rate of suicide events is ~1% across the different study groups, and seems not increased with B/F/TAF compared to the other INSTI. However, considering the limited number of patients included in all the studies, it is difficult to draw any conclusion. At least, the level of risk might be similar with BIC than with DTG. Outside the suicide events, a number of other psychiatric AEs have been reported with B/F/TAF. Based on the data provided on psychiatric disorders, 1/3 of patients included in the pivotal studies had "medical history of psychiatric disorders". Overall, similar patterns of psychiatric disorders (qualitative and quantitative aspects) were observed in comparative studies versus DTG. The CHMP requested the inclusion of psychiatric disorders in section 4.8 of the SmPC in line with other integrase inhibitors.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Based on safety data provided it can be concluded that no new risks or safety issues have been identified for the FDC of BIC/F/TAF.

2.7. Risk Management Plan

Safety concerns

Important Identified Risks	None
Important Potential Risks	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness
Missing Information	Long term safety information

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	Safety in pregnancy and lactation

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC Ongoing	To evaluate the efficacy, safety, and tolerability of B/F/TAF and ABC/DTG/3TC through 144 weeks in HIV-infected, ART-naive adults.	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) Long-term safety (missing information)	Submission of final study report	Q2 2020
GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF Ongoing	To evaluate the efficacy, safety, and tolerability of B/F/TAF and DTG+F/TAF through 144 weeks in HIV-infected, ART-naive adults.	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (important potential risk) Long-term safety (missing information)	Submission of final study report	Q2 2020
Antiretroviral Pregnancy Registry (APR) Ongoing	To collect information on the risk of birth defects with antiretroviral drugs, including B/F/TAF, to which pregnant women are exposed.	Safety in pregnancy (missing information)	Submission of interim reports	In the B/F/TAF PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs).

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Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None	N/A	N/A
Important potential risk(s)		
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness.	Routine risk communication: SmPC section 4.8 PL section 4	*Additional pharmacovigilance activities:* GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF
Missing information		
Long term safety information	No risk minimization measures are considered necessary for this missing information.	*Additional pharmacovigilance activities:* GS-US-380-1489 – Long term safety and efficacy study comparing B/F/TAF to ABC/DTG/3TC GS-US-380-1490 – Long term safety and efficacy study comparing B/F/TAF to DTG+F/TAF
Safety in pregnancy and lactation	Routine risk communication: SmPC section 4.6 PL section 2	*Additional pharmacovigilance activities:* Antiretroviral Pregnancy Registry

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR

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cycle with the international birth date (IBD). The IBD is 7 February 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of bictegravir with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers bictegravir to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Descovy (emtricitabine/ tenofovir alafenamide). The bridging report submitted by the applicant has been found acceptable.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Biktarvy (bictegravir / emtricitabine / tenofovir alafenamide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

While untreated HIV-1 infection remains a life threatening disease, for years it has become a chronic disease with combined antiretroviral therapy being early introduced to prevent pejorative impact of immune deficiency (notably including opportunistic infections in patients with CD4<200/mm3).

The goal of ARV therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. Thanks to combined antiretroviral therapies nowadays available high level of viral suppression (>85% of patients with HIV RNA <50 copies/ml) can be achieved in HIV infected patients.

B/F/TAF is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the individual components. B/F/TAF is a FDC combining a novel INSTI, bictegravir (BIC), with the backbone emtricitabine (F)/tenofovir

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alafenamide (TAF), already available as Descovy. Therefore, no other ARV are expected to be coadministered with B/F/TAF, considered as a single-tablet regimen (STR) for the treatment of HIV-1 infection. B/F/TAF is intended to be administered in subjects infected with HIV-1 without any known mutations associated with resistance to the individual components (i.e. including patients in first line treatment and virologically suprassed patients).

3.1.2. Available therapies and unmet medical need

Multiple therapeutic options have become available over time notably in first line therapy. Other STR are already available on the market for first line therapy, combining 2 NRTI s + 1 NNRTI, 1 INSTI or 1 boosted-PI.

Overall, B/F/TAF is not aimed at responding to an unmet medical need, but rather as an alternative options to other first line antiretroviral regimens.

3.1.3. Main clinical studies

The clinical development of B/F/TAF is supported by 4 Phase 3 studies performed in ART-naive subjects (GS-US-380-1489 and GS-US-380-1490) or virologically-suppressed subjects (GS-US-380-1844 and GS-US-380-1878) and a small underpowered phase 2 study GS-US-1475 in treatment naive. In studies GS-US-380-1489, GS-US-380-1490 and GS-US-380-1844 the comparator was a dolutegravir-based regimen which is relevant given its potency and its wide use in clinical practice (through ABC/DTG/3TC). Study GS-US-380-1878 is aimed at substantiating the switch to Protease inhibitor (PI) based regimen. The design and methodology of these studies are endorsed (non-inferiority with standard primary endpoints).

In addition, the bioequivalence study GS-US-141-1233 is pivotal for the selection of a bictegravir dose as part of the FDC. Indeed, it was shown that a higher exposure of BIC was observed when BIC 75 mg was contained within the FDC as compared to BIC 75 mg+FTAF leading to select 50 mg of BIC for the FDC. The selected regimen of the FDC (BIC 50mg) FTAF is a once daily regimen with or without food as tested in the phase III studies.

It is important to underline that the clinical development of BIC encompassed patients without viral strains harbouring INSTI-RAM, despite its similarly enhanced pharmacodynamics properties as compared to other INSTI. A higher BIC dose (75 mg) might have to be considered in such situation. BIC-FTAF targets first line and virologically suppressed patients without viral strains harbouring mutations of resistance to any components of the FDC and to the INI class.

3.2. Favourable effects

Overall, the efficacy endpoints support the non-inferiority of B/F/TAF compared to DTG-based regimen (FTC/TAF or ABC/3TC) in ART-naive subjects and when switching from such regimen in virologically suppressed subjects. These results are supported by the Per Protocol analyses and other secondary endpoints, especially the changes from baseline in plasma HIV-1 RNA and CD4 cell count. In addition, the switch to B/F/TAF is non-inferior to the continuation of a DRV- or ATV-based regimen. This is consistent with the known efficacy of DTG in comparison to PI. High level of virologic suppression is achieved and in the B/F/TAF groups and the DTG-based regimen groups, no subject developed treatment-emergent resistance to any study drug.

In ART-naive subjects, B/F/TAF is non-inferior to DTG-based regimen (primary endpoint: percentage of subjects with HIV-1 RNA <50 c/mL at Week 48 non inferiority margin of 12%; difference in

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percentages: -0.6% [-4.8% to 3.6%] vs ABC/DTG/3TC; -3.5% [-7.9% to 1.0%] vs DTG+F/TAF). While disputable 12% large non inferiority margin was selected, results are compatible with more stringent margin.

In virologically-suppressed subjects (primary endpoint: percentage of subjects with HIV-1 RNA ≥ 50 c/mL at Week 48, non-inferiority margin of 4%), B/F/TAF is non-inferior to ABC/DTG/3TC (difference in percentages: 0.7% [-1.0% to 2.8%]) and PI-based regimen (difference in percentages: 0.0% [-2.5% to 2.5%]).

The efficacy results were similar between the treatment groups for all of the subgroups analysed (by age, sex, race, baseline CD4 cell count, region and study drug adherence).

Adherence is required to prevent loss of virologic suppression and potential development of drug resistance. The adherence to ARV regimen is expected to be improved by reducing the pill burden and dosing frequency. Thus, the use of this once-daily single-tablet regimen such as B/F/TAF is expected to favour adherence and consequently optimise virologic outcomes.

3.3. Uncertainties and limitations about favourable effects

In the Phase 3 studies comparing B/F/TAF vs DTG+F/TAF or ABC/DTG/3TC in ART-naive subjects, there is a trend for lower response rate in the subgroup of patients with high viral load (>100,000 c/ml) treated with B/F/TAF. It is noteworthy that given that ABC/3TC is somewhat regarded as not maximizing efficacy in patients with high viral load, the trend for higher efficacy of DTG was more pronounced when DTG was combined with the same backbone as for BIC (i.e. FTAF) than when DTG was combined with ABC-3TC. Given that the subgroup of patients with high viral load is regarded as discriminatory, the results in patients with high viral load might translate a somewhat lower performance of BIC as compared to DTG which might be related to a non-maximized dose of BIC. The results of the subgroup analyses in patients with high viral load at baseline are reflected in section 5.1.

Due to the high level of virologic suppression achieved the resistance pattern of BIC remains to be established. Possibility of rescue therapy with dolutegravir (with higher dose for INSTI-R strain) is unlikely given the overlap of resistance profile, but there are several options for rescue therapy with other cARTs.

3.4. Unfavourable effects

The safety profile of B/F/TAF appears similar to that DTG+F/TAF. The more frequent AEs are gastrointestinal disorders (diarrhea, nausea, vomiting), headache, fatigue and insomnia (<5% of subjects). The rates of Grade 3 or 4 related AE and AE leading to discontinuation are low (≤ 2%).

No liver hypersensitivity reaction or severe drug-induced liver were observed, but the rates of transaminases elevations and hyperbilirubinemia were higher with B/F/TAF compared to DTG-based regimen. These elevations were mainly minor and transient.

Similarly to DTG, increases of creatinine level were observed within the first weeks of treatment by B/F/TAF. These increases remained stable thereafter and are due to the inhibition of the transporters OCT2 and MATE-1. There was no relevant renal AE, including tubulopathy.

Psychiatric disorders are a class-effect of integrase inhibitors and therefore were scrutinized within B/F/TAF application. The rate of suicide events is ≈ 1% across the different studies and is not different between B/F/TAF and DTG groups. Most subjects with a suicide-related AE while receiving B/F/TAF had a history of depression or mental illness.

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3.5. Uncertainties and limitations about unfavourable effects

Only 48 weeks data from the ongoing longer term pivotal phase 3 studies have been made available which carries some level of uncertainties on the long term safety of bictegravir

Given the non-clinical findings in favour of hepatobiliary impact [based on data available in monkeys at the highest dose tested (biliary hyperplasia and hepatocyte hypertrophy)], and the particular awareness of physicians through a dedicated amendment across the clinical studies to recommend further investigations in case of signs/ laboratory abnormalities suggestive of hepatobiliary disorders (notably appropriate imaging consultation with a specialist), such a safety issue should be kept under scrutiny for the future use of the drug in the real life setting.

Moreover, as for other TAF containing regimen, attention of physicians should be warranted on the potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Virologic success in ART-naive subjects, Week 48 (FAS)	HIV-1 RNA <50 copies/mL	n/N (%)	576/634 (90.9%)	ABC/3TC: 293/315 (93%) DTG+F/TAF: 302/325 (92.9%)	Difference in percentages (95% CI): Vs ABC/3TC: -2.1% (-5.9% to 1.6%) Vs DTG+F/TAF: -1.9% (-5.6% to 1.8%) Trend to lower rate of virologic success in subjects with baseline VL >100,000 c/ml	Pooled studies GS-US-380-1489 and -1490
Virologic failure in virologically-suppressed subjects, Week 48 (FAS)	HIV-1 RNA ≥50 copies/mL	n/N (%)	3/282 (1.1%)	1/281 (0.4%)	Difference in percentages (95% CI): 0.7% (-1.0% to 2.8%)	GS-US-380-1844
			5/290 (1.7%)	5/287 (1.7%)	Difference in percentages (95% CI): 0.0% (-2.5% to 2.5%) Open-label study	GS-US-380-1878
Unfavourable Effects						
AEs related to study drug	According to investigator	%	Diarrhoea (4.6%) Headache (4.6%) Nausea (4.1%)	DTG+F/TAF: Nausea (5.2%) Diarrhoea (3.4%) Headache (3.1%)	Duration of treatment no longer than 72 weeks, no information in elderly subjects, low number of subjects with HBV or HCV-coinfection, lack of HIV-infected subjects with renal or hepatic impairment	Pooled studies GS-US-380-1489 and -1490
			Headache (2.5%) diarrhoea (0.7%)	Headache (2.8%) abnormal dreams, flatulence, and nausea (each 1.8%)	As above.	GS-US-380-1844
			Headache (4.8%) flatulence and nausea (each 2.4%)	Proteinuria (0.7%)	As above. Open-label study.	GS-US-380-1878

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Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Hepatic AEs	Graded hyperbilirubinemia	%	11.6%	DTG+F/TAF: 5.8% ABC/DTG/3TC: 4.1%	Mainly Grade 1 or 2. No difference in the rates of Grade 3 or 4. Similar rates of graded ALT/AST increases. No Hy's law criteria.	Pooled studies GS-US-380-1489 and -1490
Psychiatric AEs	Suicide events	n/N (%)	7/634 (1.1%)	DTG+F/TAF: 2/325 (0.6%) ABC/DTG/3TC: 3/315 (1.0%)	Class effect of INSTI. One suicide attempt in the B/F/TAF group considered related to study drug.	Pooled studies GS-US-380-1489 and -1490
			3/282 (1.1%)	1/281 (0.4%)	Class effect of INSTI.	GS-US-380-1844
			0/290	1/287 (0.3%)	As above. In addition, 1 case of schizophrenia considered related to study drug in the B/F/TAF group.	GS-US-380-1878

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Bictegravir is a potent new integrase inhibitor close to dolutegravir as regards its enhanced pharmacodynamics properties as compared to raltegravir and elvitegravir. A high level of virologic suppression has been achieved in the two phase 3 studies versus dolutegravir, although a trend for somewhat lower performance of BIC as compared to DTG in the discriminatory high viral load strata (>100 000 copies/ml) is observed and is shown in section 5.1. No emergence of resistance has been observed across the development programme.

BIC safety profile is similar to that of other components of the INSTI class, with mainly potential psychiatric disorders.

3.7.2. Balance of benefits and risks

BFTAF represents a new potent once daily single tablet (STR) regimen. This STR do not address a high medical need, but provides a new option to the HIV therapeutic armamentarium with a different backbone to ABC/DTG/3TC (acknowledging the need for HLA testing for minimizing the risk of hypersensitivity reactions with abacavir contained in ABC/DTG/3TC).

The clinical demonstration can support the use of BFTAF for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.

3.8. Conclusions

The overall B/R of Biktarvy is positive.

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4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Biktarvy is favourable in the following indication:

Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that bictegravir is a new active

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substance as it is not a constituent of a medicinal product previously authorised within the European Union.

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Full Length Article

Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate

Pavan Kommavarapu [a,*], Arthanareeswari Maruthapillai [a], Kamaraj Palanisamy [a], Manasvi Sunkara [b]

[a] Department of Chemistry, SRM University, SRM Nagar, Kancheepuram District, Kattankulathur, 603203, Tamilnadu, India

[b] Department of Pharmaceutical Chemistry, KMCH College of Pharmacy, Coimbatore, 641 048, Tamilnadu, India

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ABSTRACT

Rilpivirine (RPV) is a pharmaceutical drug used for the treatment of HIV infection. The drug is characterised with poor aqueous solubility and dissolution rate leading to low bioavailability of the drug. Hence, there is a need for the improvement of the solubility and dissolution of such drugs. In this aspect, enhancement of the solubility and dissolution of the practically water insoluble drug rilpivirine was achieved by solid dispersion (SD) preparation using solvent evaporation method which eventually leads to bioavailability enhancement. SDs were formed using Kollidon VA 64 which is a water soluble copolymer and varying copolymer ratio to Avicel PH-101, Celucire 50/13 and lecithin soya. Solubility studies were carried out to establish the solubility enhancing property of the SDs. To support solubility analysis results, powder dissolution studies were carried out. The SDs were characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray powder diffraction studies, scanning electron microscopy. It was found that the SDs formed showed the absence of crystalline nature of the drug and its conversion to amorphous state. The solubility and dissolution of the rilpivirine SDs were enhanced. There is a 14.9 fold increase in solubility for Drug: Kollidon VA 64: Celucire 50/13 (1:4:1). For Drug: Kollidon VA 64 (1:5), Drug: Kollidon VA 64: lecithin soya (1:4:1) and Drug: Kollidon VA 64: Avicel PH-101 (1:4:1) it was 5.9, 5.4 and 4.2 respectively. In-vitro drug release kinetics was investigated. This study demonstrates the use of solvent evaporation method for the preparation of SDs in solubility and dissolution enhancement.

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* Corresponding author. Tel.: +91 8056791313.
E-mail address: kommavarapu.pavan@gmail.com (P. Kommavarapu).

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1. Introduction

Rilpivirine, 4-[[4-[[(E)-2-cyanovinyl]-2, 6-dimethylphenyl] amino] pyrimidin-2-yl] amino] benzonitrile is a pharmaceutical drug used for the treatment of HIV infection. It is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with higher potency, longer half-life and reduced side-effect profile compared with older NNRTIs, such as efavirenz (Guillorink, 2007, Goebel et al., 2006). Although rilpivirine has gained acceptance in the treatment of HIV infection, it is characterized with poor solubility which limits its absorption and dissolution rate which delays onset of action (Bheri et al., 2009; Sharma and Garg, 2014). The chemical structure of rilpivirine is shown in Fig. 1.

According to the Biopharmaceutical Classification System (BCS), most of the drugs exhibiting insolubility belong to BCS class II. This class includes drugs having low water solubility with high membrane permeability. For this reason dissolution will be the rate-limiting step in drug absorption from the oral solid dosage forms of this class (Amidon et al., 1995). Current statistics report that about 40% of new chemical entities (NCEs) are known to belong to the biopharmaceutics classification systems (BCS) class II type of molecules with poor solubility and high permeability properties (Singaraju et al., 2007; Amidon et al., 1995). Rilpivirine is classified as a BCS class II compound (Anita, 2012). Different solubility and dissolution enhancement techniques are applied such as inclusion complexation (Veiga et al., 1996), drug micronization in to amorphous form (Hancock and Zografi, 1997), prodrug formation (Rautio et al., 2008) and solid dispersion (Serno et al., 2008; Vasconcelos et al., 2007; Chiou and Riegelman, 1971; Serajuddin, 1999; Gumaa and Dressman, 2000). Among these methods, solid dispersion technique is most frequently used.

Solvent evaporation method involves preparation of a solution containing both matrix material and drug, and the removal of the solvent resulting in the formation of the solid mass. Nature of the solvent and the rate of evaporation of the solvent are the critical factors which can affect the formed mass (Xie et al., 2005). The most important advantage of this method is that thermal decomposition of the drugs can be avoided as low temperature is required for the evaporation of the organic solvents. Preparation of solid dispersions using solvent evaporation method has been utilized successfully for the improvement of dissolution rate and stability of SDs of poor aqueous soluble drugs (Gumaa and Dressman, 2000; Patel and Patel, 2006; Sethia and Squillante, 2004; Khan, 2013). In the present study Kollidon VA 64 which is a water soluble copolymer is used as matrix material and the solvent system constitutes methanol and ethanol in the ratio 1:1.

The aim of this work was to improve the aqueous solubility and dissolution of rilpivirine using solid dispersion technique using hydrophilic carrier Kollidon VA 64. Powder X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were used to characterize the solid-state properties of rilpivirine, the physical mixture and solid dispersions. The aqueous solubility and dissolution behaviour of rilpivirine SDs were evaluated further. Surface morphology study was carried out using scanning electron microscopy (SEM).

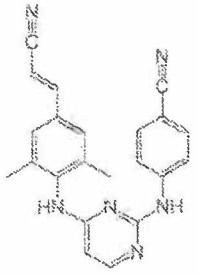


Fig. 1 – Chemical structure of Rilpivirine.

2. Materials and methods

2.1. Materials

Rilpivirine (RPV) was a gift from PharmaTrain (Hyderabad, India). Kollidon VA 64 was procured from BASF (Germany), Soya lecithin was from VWR International Ltd (Poole, England), Avicel PH-101 was from Sigma–Aldrich (Saint Louis, USA), Gelucire 50/13 was provided by Gattefosse (Cedex, France), Ethanol Absolute 99.9% was from Commercial Alcohols (Brampton, Canada) and methanol HPLC grade (merck). All the chemicals used were analytical reagent grade and used without further purification.

2.2. Methods

2.2.1. Preparation of physical mixture

Physical mixtures (PMs) of RPV in the ratio RPV: Kollidon VA 64 (1:5) (PM1), RPV: Kollidon VA 64: Lecithin soya (1:4:1) (PM2), RPV: Kollidon VA 64: Avicel PH-101 (1:4:1) (PM3) and RPV: Kollidon VA 64: Gelucire 50/13 (1:4:1) (PM4) were prepared by blending them by triturating for about 10 min and sieved through 500 micron mesh sieve.

2.2.2. Preparation of solid dispersion

SDs of RPV was prepared by solvent evaporation method. Prepared PMs of RPV were transferred into a beaker containing ethanol and methanol in the ratio 1:1. The solvent was then evaporated under vacuum (Roots vacuum pump-WZJPVC, Hyderabad India) and the resulting solid dispersions were collected and stored in desiccators until they attained constant weight. The solidified masses were crushed, pulverized and passed through sieve-60 mesh (Fertech, Verder Scientific India Pvt. – India).

2.2.3. Powder X-ray diffraction (XRD)

The XRD patterns of pure RPV, PMs and all binary systems of RPV with Kollidon VA 64 were recorded using a Bruker D8 advance X-ray diffractometer (Bruker AXS GmbH, Germany)

with Cu anode and Lynx eye detector over the interval 3° 2θ to 45° 2θ, with step size 0.01° 2θ and time per step of 0.6 s. The instrument was operated at 40 kV generator voltage and 40 mA generator current. Variable divergent slit and Anti scattering slit were used of V_____mm. Nickel filter was used in secondary beam path. Eva software (which is also available in online version for free) was used for data processing and evaluation.

2.2.4. *Differential scanning calorimetry (DSC)*

DSC (Mettler Toledo DSC 821e, Switzerland) with STARe software was used for recording and processing DSC thermograms of RPV, PMs and binary systems of RPV with Kollidan VA 64. The accurately weighed sample (3–5 mg) was placed in an aluminium pan. An empty aluminium pan was used as a reference. The experiment was carried out in nitrogen atmosphere at a flow rate 40 mL per min at a scanning rate of 20 °C/min in the range of 30–350 °C.

2.2.5. *Fourier transform infrared spectroscopy (FTIR) studies*

Infrared spectra were obtained using a PerkinElmer Spectrum-one FTIR spectrometer (Shelton, CT, USA) using universal Attenuated Total Reflectance (UATR) accessory. The scanning range was kept from 4000 to 650 cm^{-1} and the accumulations were 4.

2.2.6. *Scanning electron microscopy (SEM)*

The morphology of the RPV and SDs were investigated by scanning electron microscopy (SEM, JOEL, JSM-6380) at an accelerating voltage of 1.0 kV. Double coated carbon conductive tabs are mounted on SEM sample stubs and samples were stick uniformly and coated by Platinum Sputter Coater vacuum coater (JEOL, JFC 1600, Auto fine Coater) to minimize electrostatic charging.

2.2.7. *Solubility determination*

The equilibrium solubility of the pure drug and the prepared SDs were determined in Ultra-pure water (Millipore®, USA) by adding excess amount of sample in water and the samples were shaken for 24 h at 37 °C in a horizontal shaker (n = 3). After the supernatant is filtered through 0.45 μm filters the filtrate was assayed spectrophotometrically at 306 nm.

2.2.8. *Drug release rate studies*

USP apparatus II (paddle) method using electrolab dissolution apparatus was used to study the drug release profile. Dissolution studies were carried out using 900 mL 0.5% Polysorbate 20 in 0.01 N HCl (pH = 2.0) at 37 ± 0.5 °C and stirred at 75 rpm. Amount of samples equivalent to twenty-five mg of RPV were added to dissolution medium and five mL samples were withdrawn after 10, 20, 30, 45 and 60 min and replaced each time with 5 mL fresh 0.5% Polysorbate 20 in 0.01 N HCl. The solutions were immediately filtered through 0.45 μm membrane filter, diluted and the concentration of RPV determined spectrophotometrically. Different mathematical models were applied to dissolution data to study the drug release kinetics.

3. Results and discussion

Fig. 2 shows the overlaid XRD patterns of pure RPV (a), Kollidan VA 64 (b), Lecithin soya (c), Avicel PH-101 (d), Gelucire 50/13 (e) and f, g and h represents PMs PM1, PM2, PM3 and PM4 respectively. RPV showed characteristic diffraction peaks at two theta positions mentioned in Table 1 along with their d values and peak intensities. From these values it is evident that input RPV is in crystalline nature. Kollidan VA 64 (b) and Lecithin soya (c) are amorphous in nature and Avicel PH-101 (d) is crystalline and Gelucire 50/13 (e) is mostly amorphous in nature. Since the Physical mixtures (PMs) of RPV have no additional peaks other than RPV and respective constituents they are compatible. The crystallinity of RPV was significantly reduced in the physical mixture but to a much greater extent in the latter, as almost all intense peaks of pure RPV had completely disappeared. The absence of peaks indicated that the drug was uniformly dispersed in the matrix material. Fig. 3

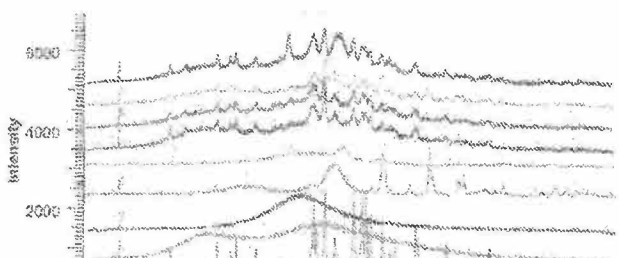


Fig. 2 – XRD patterns of single components and binary systems of RPV (a) and Kollidan VA 64 (b), Lecithin soya (c), Avicel PH-101 (d), Gelucire 50/13 (e), PM1 (f), PM2 (j), PM3 (g) and PM4 (h).

Table 1 – X-ray diffraction characteristic 2θ° peak positions, d value and intensities of pure rilpivirine hydrochloride.

Angle (2-Theta)	d value (Angstrom)	Intensity (counts)
8.059	9.818	170
9.676	9.135	628
10.777	8.203	197
10.953	8.072	348
13.435	6.585	3863
14.533	6.089	1118
14.959	5.917	1926
15.262	5.800	320
15.959	5.550	193
16.415	5.396	852
16.562	5.346	1043
16.923	5.235	200
17.356	5.104	146
18.081	4.904	583
18.462	4.807	567
19.211	4.616	526
19.580	4.577	385
19.829	4.474	358
20.693	4.288	847
21.077	4.211	2556
21.279	4.172	1348
21.618	4.106	294
22.257	4.064	2275
22.761	3.904	1067
22.986	3.866	586
23.645	3.760	486
24.281	3.663	2657
24.471	3.635	776
25.269	3.556	2859
25.615	3.525	2156
25.953	3.475	1636
27.082	3.381	259
27.382	3.348	1788
27.596	3.295	659
28.252	3.278	587
28.702	3.229	961
28.950	3.193	388
29.980	3.055	1295

represents the overlaid diffraction pattern of SDs. Here a, d, b and c correspond to SD's of RPV: RPVSD1, RPVSD2, RPVSD3 and RPVSD4 respectively. From Fig. 3 it could be concluded that the drug might have transferred to the amorphous state, as no peaks were visible.

The DSC thermogram of RPV alone (Fig. 4) shows an endothermic Tmax of 248.49 °C, corresponding to the melting point of the crystalline form of RPV. RPV melts with decomposition which starts at about 248.49 °C. In the DSC thermograms of physical mixtures and solid dispersions of RPV with Kollidon VA 64 the sharp melting point peak of pure RPV at 248.49 °C was not visible (Fig. 5) in all the cases. The characteristic features of the RPV peak were lost. This indicated that RPV was molecularly dispersed and no longer present as a crystalline material, but was converted into the amorphous state.

Fig. 6 illustrates the FTIR spectra of RPV, physical mixture and solid dispersions. The IR spectrum of RPV is characterized by typical absorption bands at about 2217 cm^{-1} (C≡N), 2852 cm^{-1} (C=O stretch), 1597 cm^{-1} (aromatic >C = C), 1435 cm^{-1} (C–H bending), 1330 cm^{-1} (-CH wagging) and 1185 cm^{-1}(symmetric C–N stretching). Additional absorption bands are observed at 1631 cm^{-1}, 1586 cm^{-1}, 1557 cm^{-1}, 1504 cm^{-1}, 1249 cm^{-1}, 1214 cm^{-1}, 1179 cm^{-1}, 1152 cm^{-1} and 1070 cm^{-1}. There is a reduction of peak intensities is observed in PMs and SDs and all other peaks of RPV were smoothened indicating strong physical interaction of the drug with carrier materials. However, no additional peaks were observed in any of the binary systems, indicating absence of any chemical interaction between RPV and the carriers.

Fig. 7 display SEM photographs for RPV physical mixtures and Fig. 8 represents SEM micrographs of RPV and SDs. The RPV crystals seemed to be irregular in shape and size. SEM images of SDs clearly indicated the interaction of drug with respective carrier material and concluded the incorporation of drug in matrix material. While examining PMs no specific interaction observed between drug and matrix material. In case of SDs it was difficult to distinguish the presence of RPV crystals. The RPV crystals appeared to be incorporated in the matrix material. From SEM images it can be deduced that the

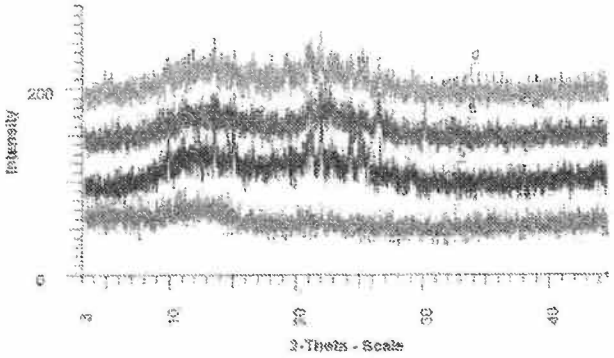


Fig. 3 – XRD patterns of solid dispersions (SDs) of RPV: RPVSD1 (a), RPVSD2 (d), RPVSD3 (b), RPVSD4 (c).

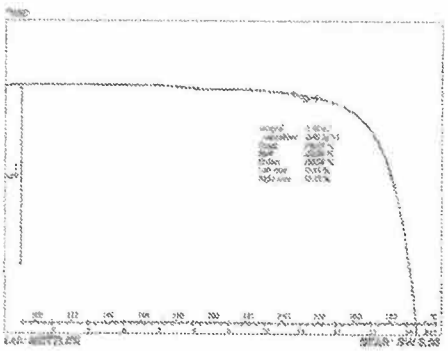


Fig. 4 – DSC thermogram of Rilpivirine.

drug is successfully dispersed in the carrier material by solvent evaporation method.

The aqueous solubility of RPV is found to be 0.0385 ± 0.0011 mg/ml which can be considered as practically insoluble drug in water. The solubility of RPV increased markedly in water in presence of matrix material. There was an enhancement of 14.9 fold in solubility for RPVSD2 and for RPVSD1, RPVSD3 and RPVSD4 it is about 5.9, 5.4 and 4.2 fold i.e. the corresponding solubility values are 0.275 ± 0.005, 0.110 ± 0.009, 0.099 ± 0.002 and 0.078 ± 0.014 respectively. The solubility of physical mixtures PM1, PM2, PM3 and PM4 was found to be 0.027 ± 0.011, 0.025 ± 0.011, 0.035 ± 0.012 and 0.029 ± 0.013 mg/ml respectively which are greater than pure drug but not significant increase as compared with SDs. The enhancement in aqueous solubility of RPV SDs can be explained in terms of wetting property and hydrophilicity nature of carriers with simultaneous reduction in the crystallinity of the drug. All solid dispersion systems displayed higher solubility of RPV than pure drug. Enhancement in solubility was observed in the following order: (Kollidan VA 64: Gelucire 50/13)> (Kollidan VA 64)> (Kollidan VA 64: Lecithin soya)> (Kollidan VA 64: Aerosil PR-101).

The dissolution curves of RPV, RPV physical mixtures and RPV solid dispersions in 0.5% Polysorbate 20 in 0.01 N HCl (pH = 2.0) at 37 ± 0.5 °C are shown in Fig. 5 and the corresponding values are tabulated in Table 2. From the obtained results it is perceptible that all the binary systems of RPV have superior dissolution rates than pure drug and its corresponding physical mixtures. The physical mixtures also showed improved dissolution rate as compared with RPV but the highest drug release is observed for SDs prepared by solvent evaporation method. It was observed that more than 85% of the drug is released in 30 min though there are differences in release mechanism in the initial 20 min. After 60 min almost about 98% of the drug is released in all the cases. It is evident that the solid dispersions improved the dissolution rate of RPV to the greatest extent. Enhanced dissolution from the solid dispersions is due to greater hydrophilicity and higher wetting effect which increased the contact between the drug and the carrier. The rapid dissolution of RPV from solid dispersions may be attributed to a decrease in the crystallinity of drug and its molecular and colloidal dispersion in the hydrophilic carrier matrix. As the soluble carrier dissolves, the insoluble drug gets out in the open to dissolution medium in the form of very fine particles for quick dissolution. The dissolution profiles of RPV SDs were used to evaluate the kinetics of drug release. Six different kinetic models were applied to understand the drug release characteristics. In order to select the appropriate mathematical model to describe drug release kinetics Coefficient of determination (R^2) and root mean square error (RMSE) were evaluated for model

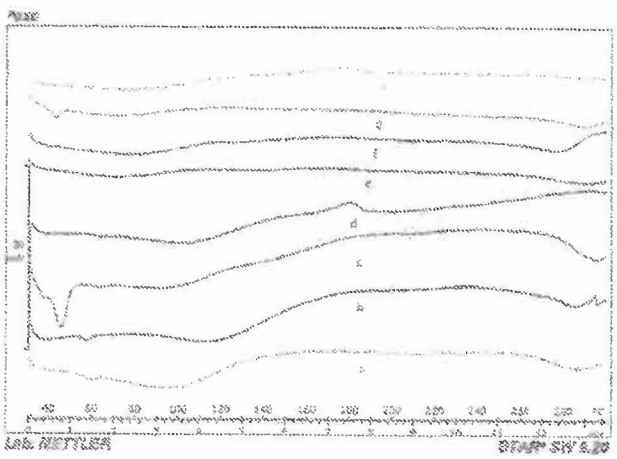


Fig. 5 – DSC curves of PMs of RPV: PM1 (a), PM2 (d), PM3 (b) and PM4 (c) and SDs: RPVSD1 (e), RPVSD2 (g), RPVSD3 (h) and RPVSD4 (f).

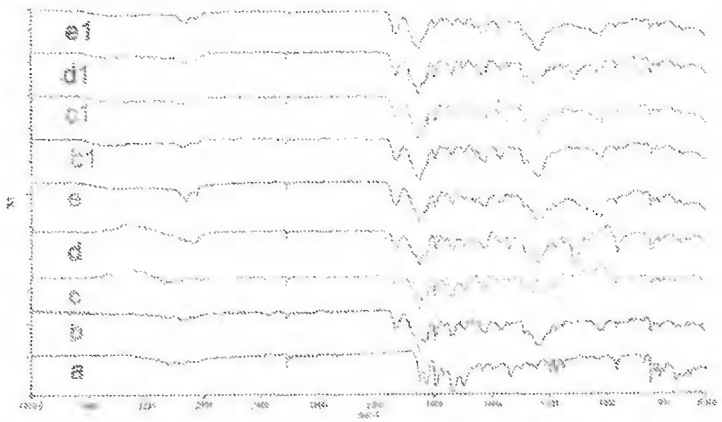


Fig. 6 – FT-IR spectra of RPV (a), PMs of RPV : PM1 (b), PM2 (c), PM3 (d) and PM4 (e) and SDs: RPVSD1 (b1), RPVSD2 (d1), RPVSD3 (e1) and RPVSD4 (c1).

selection. The closer the value of Coefficient of determination (R^2) to unity and smaller the value of root-mean-square error (RMSE) we opt to choose that model as appropriate model which best describes the drug release profile. Coefficient of determination (R^2) and root-mean-square error (RMSE) values tabulated in Table 2 and used to select appropriate model that describes drug release characteristics. From the obtained results it is observed that for RPVSD1, RPVSD3 and RPVSD4 drug release mechanism is best described by Weibull model for which obtained Coefficient of determination values are 0.9512, 0.9774 and 0.9564 and root-mean-square error values are 3.8, 3.0 and 3.6 respectively. Since this is an empiric model, it presents some deficiencies like there is no kinetic fundament and could only describe, but does not adequately characterize the dissolution kinetic properties of the drug and it is of limited use for establishing in vivo in vitro correlations.

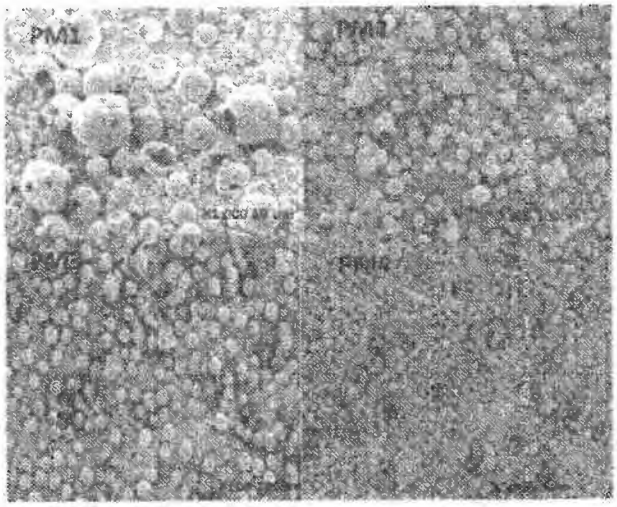


Fig. 7 – SEM micrographs of RPV physical mixtures PM1, PM2, PM3 and PM4.

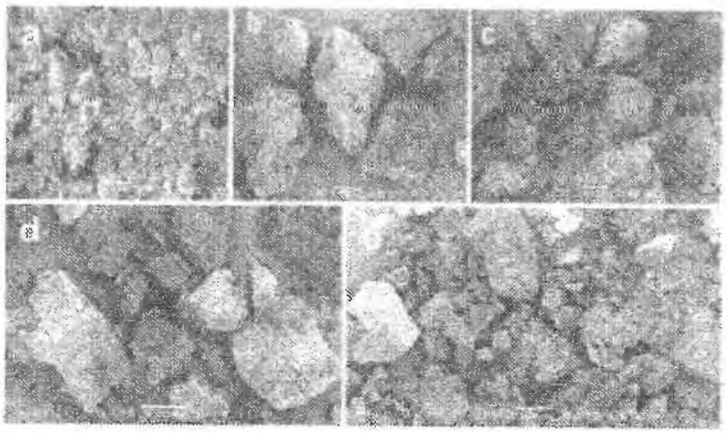


Fig. 8 – SEM micrographs for RPV (a), SDs: RPVSD1 (b), RPVSD2 (d), RPV RPVSD3 (e) and RPVSD4 (c).

RPVSD2 is best described by Korsmeyer-Peppas model and the obtained coefficient of determination and root-mean square error values are 0.9560 and 8.2 respectively. This model is a semi-empirical model, relating exponentially the drug release to the elapsed time. This model is used to analyse the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

Dissolution efficiency (%DE) is the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period and is expressed by the following expression:

$$\text{Dissolution efficiency (DE)} = \frac{\int_{t_1}^{t_2} y\,dt}{y_{100}(t_2 - t_1)} \times 100$$

DE values of RPVSD1, RPVSD2, RPVSD3 and RPVSD4 are found to be 76.3, 78.8, 75.8 and 77.2 respectively. DE values are related with the real amount of drug dissolved in the dissolution medium and thus, lead to a better extrapolative for in vivo performance.

The solid dispersion systems prepared by solvent evaporation method showed a greater extent of dissolution rate and solubility as compared to pure drug and physical mixtures. The increased solubility and dissolution rate may be

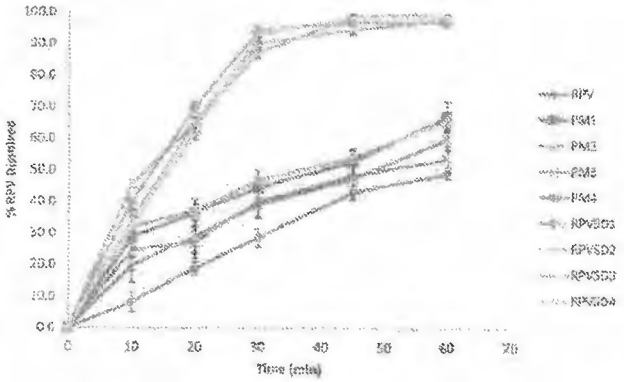


Fig. 9 - Dissolution profiles for RPV, Physical mixtures (PMs) of RPV and RPV solid dispersions (SDs) in 0.5% Polysorbate 20 in 0.01 N HCl (pH = 2.0) at 37 ± 0.5 °C stirred at 75 rpm (n = 3).

Table 2 – The dissolution time of RPV, RPV Physical mixtures and Rilpivirine solid dispersions in 0.5% Polysorbate 20 in 0.01 N HCl (pH – 2.0) at 37 ± 0.5 °C stirred at 75 rpm, mean ± SD (n = 3).

Time (min)	Percentage of drug dissolved								
	RPV	PM1	PM2	PM3	PM4	RPVSD1	RPVSD2	RPVSD3	RPVSD4
10	5.2 ± 3.6	28.7 ± 6.3	32.1 ± 5.6	24.5 ± 5.2	19.8 ± 5.0	40.0 ± 0.9	43.7 ± 1.2	34.2 ± 2.8	32.6 ± 1.9
20	18.9 ± 2.2	36.4 ± 6.3	36.8 ± 2.0	27.2 ± 3.0	29.0 ± 3.1	64.8 ± 1.7	64.9 ± 1.8	64.6 ± 2.1	63.5 ± 2.0
30	36.5 ± 2.9	44.5 ± 5.2	46.8 ± 3.2	40.0 ± 4.9	39.0 ± 4.2	94.0 ± 1.8	87.3 ± 1.8	90.2 ± 2.0	91.6 ± 2.5
45	48.1 ± 2.1	52.8 ± 6.4	54.2 ± 2.3	48.4 ± 4.2	47.5 ± 3.9	97.1 ± 0.8	98.8 ± 0.9	94.7 ± 1.5	98.8 ± 0.6
60	54.2 ± 1.9	57.2 ± 4.8	66.0 ± 1.9	53.7 ± 4.7	58.9 ± 5.2	97.1 ± 0.5	100.4 ± 0.8	98.1 ± 0.8	98.9 ± 0.7

Table 3 – Model dependent mathematical kinetic models for the evaluation of drug release mechanism of RPV solid dispersions.

Kinetic Models	Coefficient of determination (R^2)				Root-mean-square error (RMSE)			
	RPVSD1	RPVSD2	RPVSD3	RPVSD4	RPVSD1	RPVSD2	RPVSD3	RPVSD4
Zero order	0.7148	0.8582	0.7734	0.7575	11.9	7.9	11.3	13.0
First order	0.8640	0.9100	0.9082	0.8083	10.7	10.4	15.3	17.4
Second order	0.5065	0.7508	0.6374	0.6245	12.4	13.9	22.6	23.6
Korsmeyer-Peppas	0.8736	0.9568	0.8568	0.8942	10.2	5.7	10.2	11.9
Weibull	0.9312	0.8230	0.9774	0.9564	3.8	9.4	3.6	5.5
Hixson–Crowell	0.6822	0.8275	0.7247	0.7206	13.5	9.8	15.5	15.4

attributed to the weight fraction of the polymer, decreased crystallinity of drug and molecular dispersion of the drug in carrier matrix (Karavas et al., 2007). The insoluble drug in carrier matrix when out in the open to dissolution media the soluble drug carrier dissolves in media and the drug will make contact with dissolution media as very fine particles which is responsible for speedy dissolution. Other important factor responsible for faster dissolution is increased amorphicity of the drug in SDs which is confirmed by diffraction and thermal studies. The surfactant property f polymer which results in increased surface available for dissolution which is also responsible for faster dissolution. While performing the dissolution studies it was observed the pure drug is floating on the media. As compared with pure drug little amount is observed for physical mixtures and the SDs sink immediately.

Data Analysis Tools for scientific data analysis provided in Microsoft excel is used for statistical evaluation of data. Statistical assessment of dissolution data of RPV and RPV SDs is done by ANOVA: Single Factor. When compared the dissolution profile of RPV with RPV SDs it is found that the F value for RPVSD1, RPVSD2, RPVSD3 and RPVSD4 is 13.709, 14.735, and 10.835 respectively which are well above the F critical value 5.318. The P-value of RPVSD1, RPVSD2, RPVSD3 and RPVSD4 is 0.0059, 0.0050, 0.011 and 0.014 respectively which reflects these findings by being significantly smaller than 0.05. From these findings we conclude that there is a significant difference between the groups and from ANOVA test we say that RPV SDs outperforms RPV. Further comparison of drug release is done by t-Test: Paired Two Sample for Means between RPV and RPV SDs dissolution profiles. The absolute t Stat values for RPVSD1, RPVSD2, RPVSD3 and RPVSD4 is found to be 9.131, 13.232, 8.017 and 5.968 respectively which are greater than t Critical two-tail value 2.776. Hence we conclude from these finding that there is significant difference between RPV and RPV SDs. The formation of RPV SDs improved the dissolution rate as compared with RPV.

4. Conclusions

In the binary systems of rilpivirine prepared with different hydrophilic carriers showed superior performance in enhancing aqueous solubility and the dissolution of Rilpivirine. XRD, FTIR and DSC studies of the binary systems of rilpivirine showed that the crystallinity of rilpivirine was decreased to a greater extent in solid dispersions, which markedly increased the aqueous solubility and dissolution rate of rilpivirine. The main factors contributed for higher solubility and release rate are such as increased wettability and conversion to amorphous state. The dissolution efficiency for all the solid dispersions is greater than 70%. Thus, the study provided a way to enhance solubility and understand the release mechanism.

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Fax: +49 89 2399 4465

Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA
ROYAUME-UNI

Formalities Officer
Name: Feeney, Karen
Tel: +49 89 2399 - 7914
or call
+31 (0)70 340 45 00

Application No. / Patent No	Ref	Date
16 798 063.0 - 1112 / 3 346 995 /	O008281EP:CJH/ PAK/HEB	23.12.2022

Proprietor
Gilead Sciences, Inc.

Interlocutory decision in Opposition proceedings (Art. 101(3)(a) and 106(2) EPC)

The Opposition Division - at the oral proceedings dated 27.10.2022 - has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.

The reasons for the decision are enclosed.

Documents for the maintenance of the patent as amended:

Auxiliary Request 1

Description, Paragraphs

1-367 of the patent specification

Claims, Numbers

1-7 filed in electronic form on 26-05-2022

Drawings, Sheets

1/6-6/6 of the patent specification

Possibility of appeal
This decision is open to appeal according to Article 106(2) EPC. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Registered letter
EPO Form 2327 07.13TRI

Opposition Division:

Chairman:	Büttner, Ulf
2nd Examiner:	Collura, Alessandra
1st Examiner:	Trifilieff, Sylvie



Penney, Karen
Formalities Officer
Tel. No.: +49 89 2399-7914

Enclosure(s): 16 page(s) reasons for the decision (Form 2916)
Wording of Art. 106 - 108 and R. 97 - 98 EPC (Form 2019)
Documents relating to the amended text
Minutes of oral proceedings

to EPO postal service: 20.12.22

Registered letter
EPO Form 2527 07.19TR

I. Summary of facts and submissions

1. European patent 3 346 995 having the title "THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS " is based upon European patent application No.16 798 063.0 filed on 08-11-2016. It claims priority of US 201562253042 filed on 09-11-2015 and US 201662399999 filed on 26-09-2016.

The mention of the grant of the patent has been published in the European Patent Bulletin of 28-08-2019 . Proprietor of the patent (hereinafter P) is
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
US.

2. Notices of opposition has/have been filed by
Opponent 1 (hereinafter O1):
Teva Pharmaceutical Industries Ltd
5 Basel Street
49131 Petach-Tikva
IL
on 27-05-2020

Opponent 2 (hereinafter O2):
Cooke, Richard
Elkington and Fife LLP
Patents Department
3-4 Holborn Circus
London EC1N 2HA
GB
on 28-05-2020

Opponent 3 (hereinafter O3):
Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
AT
on 28-05-2020 .

The opponents request revocation of the patent in its entirety on the following grounds:

. the granted subject-matter extends beyond the content of the application as originally filed (A. 100(c) and A. 123(2) EPC): O1, O2 and O3.

. the granted subject-matter lacks novelty (A. 100(a); A. 54 EPC): O2 and O3.

. the granted subject-matter lacks inventive step (A. 100(a); A. 56 EPC): O1, O2 and O3.

. O2 and O3 further dispute the validity of the priority.

All opponents request oral proceedings as an auxiliary measure.

3. With the submission dated 11-01-2021, P requests that the oppositions be dismissed and that the patent be maintained as granted or on the basis of one of the 29 auxiliary requests (AR1 to AR29) filed with the same submission.

P requests oral proceedings as an auxiliary measure.

4. The opponents react as follows:

O2 submits further arguments on 04-03-2021.

O3 submits further arguments on 24-03-2021.

O1 submits D38 and D39 together with further arguments on 26-03-2021.

All Os request oral proceedings as an auxiliary measure.

5. On 24-06-2021 the opposition division (OD) sends summons for oral proceedings to be held on 18 and 19-01-2022 by videoconference together with their preliminary opinion.

6.1. Requests for postponement of the oral proceedings are submitted:

by O3 on 28-06-2021

by O1 on 05-07-2021

by P on 08-07-2021 and 12-07-2021

6.2. On 05-08-2021 summons for holding oral proceedings on 24 and 25-03-2022 are sent.

7. On 23-12-2021 O3 sends submissions together with experimental reports D40.

8. On 24-01-2022 P sends submissions together with further documents D41 and D42.

9. Following O3's request from 22-03-2022 oral proceedings are postponed to 27 and 28-10-2022.

10. On 25-08-2022 O1 files submissions together with documents D43 and D44.

11. On 26-08-2022 O2 and O3 file submissions.

On the same day P sends submissions together with a new main request and ten auxiliary requests (AR1 to AR10) as well as documents D45 and D46.

12. On 13-10-2022 P sends coloured versions of D41 and D42 (already filed on 24-01-2022).

13. On 27-10-2022 oral proceedings are held by videoconference in the presence of all parties. Following the parties' requests, interpretation from German to English is provided.

At the end of the proceedings the OD announces their decision.

The documents cited by the parties during the proceedings are:

		P	O1	O2	O3
PRIO 1	US 2015/62253042				TM1
PRIO 2	US 2016/62399999				TM2
D1	WO 2015/196116			D1	TM14

D1a	Evidence of D1 entry to European Regional phase			D1a	
D2	WO 2015/196137			D2	TM15
D3	WO 2014/100323		D1	D3	TM3
D4	WO 2013/116720		D3	D4	
D5	WO 2015/022351		D2	D5	TM17
D6	Gilead Sciences Finalizes Agreement with Tibotec Pharmaceuticals to Develop and Commercialize a Single-Tablet Regimen of Prezista® with Emtriva®, GS 7340 and Cobicistat, 15 November 2011			D6	
D7	British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy, 2015, pages 13-14			D7	
D8	BNF 2015, Emtricitabine with tenofovir, pages 557-558 and 566			D8	
D9	Fernando, S., Butterworth, A., Choices, choices: the rapidly evolving HIV treatment landscape, pmlive.com, 15 March 2015			D9	
D10	Business Wire, 5 November 2015, "U.S. Food and Drug Administration Approves Gilead's Single Tablet Regimen Genvoya® (Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide) for treatment of HIV-1 infection"			D10	

D11	Centre for Drug Evaluation and Research, first page of approval package, Odefsey®			D11	
D12	Business Wire, 1 July 2015, "Gilead Submits New Drug Application to U.S. Food and Drug Administration for Single Tablet Regimen for HIV Containing Rilpivirine, Emtricitabine and Tenofovir Alafenamide (R/F/TAF)"			D12	
D13	Business Wire, 4 April 2016, "U.S. Food and Drug Administration Approves Descovy® (Emtricitabine, Tenofovir Alafenamide), Gilead's Third TAF-Based HIV Therapy			D13	
D14	Business Wire, 28 May 2015, "European Medicines Agency Validates Gilead's Marketing Application for Fixed-dose Combination of Emtricitabine and Tenofovir Alafenamide for HIV treatment"			D14	
D15	Aulton, Pharmaceutics: The Science of Dosage Form Design, 2nd Edition, 2002, pages 411-412			D15	
D16	P. Shende et al., "Multi-layer Tablet: Current scenario and recent advances", International Journal of Drug Delivery 4 (2012) 418-426;		D4		
D17	WO 2017/083304 A1		D5		
D18	WHO Drug Information 29(2), July 2015				TM4

D18 a	Publication date of TM4				TM4a
D19	Guidance on the establishment of new INN stems, 2007				TM5
D20	WHO, The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances, 2013				TM6
D20 a	WHO, Pre-Stems: Suffixes used in the selection of INN, 2012				TM6a
D20 b	WHO, Pre-Stems: Suffixes used in the selection of INN, June 2014				TM6b
D21	Yoshinaga et al., Antiviral Characteristics of GSK.1265744, an HIV Integrase Inhibitor Dosed Orally or by Long-Acting Injection, Antimicrobial Agents and Chemotherapy, January 2015, Vol. 51, Nr. 1, p. 397-406				TM7
D21 a	Park et al., Review of integrase strand transfer inhibitors for the treatment of human immunodeficiency virus infection, Expert Rev. Anti Infect. Ther. 13(10), 2015				TM7a
D21 b	Shah et al., Dolutegravir: A New Integrase Strand Transfer Inhibitor for the Treatment of HIV, Pharmacotherapy, Vol. 34, No. 5, 2014				TM7b
D22	WO 02/08241 A2				TM8
D23	Clayden et al., 2015 Pipeline Report, HCV, HCV, TB, July 2015				TM9

D24	FDA, Drug Approval Package Viread				TM10
D25	EMA, Viread, Authorization details				TM11
D26	Press Release Gilead dated November 5, 2015				TM12
D27	Experimental Report dated May 15, 2020				TM16
D28	US 2014/0221356 A1				TM18
D28 a	Submission in the Examination Proceedings of TM18 dated August 26, 2015				TM18 a
D29	Kulkarni et al., The Combined Anti-HIV-1 Activities of Emtricitabine and Tenofovir plus the Integrase Inhibitor Elvitegravir or Raltegravir Show High Levels of Synergy In Vitro, Antimicrobial Agents and Chemotherapy, October 2014, Vol. 58, Nr. 10, p. 6145-6150				TM19
D30	Analyzing Gilead Sciences' Research and Development in 3Q15, October 23, 2015				TM20
D31	EudraCT number 2015-003988-10 dated November 19, 2015				TM21
D32	USAN statement dated February 24, 2016				TM22
D33	WO 2010/091197 A2				TM23

D34	WO 2013/115916 A1				TM24
D35	Phase I study into the potency, safety and pharmacokinetics of multiple doses of BIC	D35			
D36	Biktarvy EPAR Scientific Discussion	D36			
D37	Phase II study comparing BIC (75 mg) + FTC/TAF (200/25 mg) vs DTG (50 mg) + FTC/TAF (200/25 mg)	D37			
D38	P. Kommavarapu et al., "Preparation and characterization of rilpivirine solid dispersions with the application of enhanced solubility and dissolution rate", Beni-Suef University Journal of Basic and Applied Sciences 4 (2015) 71-79.		D38		
D39	European Medicines Agency, Assessment report "Genvoya", 24 September 2015, extract (pp.1-20).		D39		
D40	Experimental Report dated December 22, 2021				D40
D41	Smith S. et al. (2018)	D41			
D42	Acosta R. et al. (October 2021)	D42			
D43	Lozano A.B et al., Antivir. Res. 2020, 179, 104717		D43		
D44	Chamberlain N. et al., Open Forum Infect. Dis. 2021, 8(6)		D44		
D45	Song poster IAS 2009	D43			

D46	Eron report IAS 2009	D44			

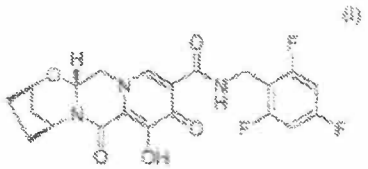
II. Grounds for the decision:

The oppositions meet the requirements of Art. 99(1) and 100 EPC and Rules 3(1), 76(1) and 76(2) EPC and are thus admissible.

A. MAIN REQUEST (MR; filed on 26-08-2022):

It comprises 8 claims among which 2 independent claims which read:

1. A tablet comprising 50 mg of the compound of Formula I:



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

8. A tablet according to any one of the preceeding claims for use in the therapeutic treatment of an HIV infection.

It is noted that the name of the compound of Formula I is bictegravir (BIC).

1. No objection is raised with respect to the requirements of R. 80 (admissibility) or A. 84 EPC (clarity).

The OD sees no reason to differ.

2. Extension of the claimed subject-matter beyond the content of the application as filed (A. 123.2 EPC):

According to Os the application as filed does not disclose the tablet of claim 1. Such a specific tablet would neither be disclosed in the claims nor in the description of the original application. The passages of the original application (claims and/or description)

which could be relied upon for basis, in particular because they would recite the emtricitabine pharmaceutically acceptable salts, would comprise additional limitations such as coatings or a particular tablet weight which are not present in claim 1.

P is of the opinion that claim 1 finds basis in the following different passages of the original application: § 8, 10, 12, 16, 34, 37, 48, 50, 53, 77 to 85, 90 to 98, 103 to 111, 264, claims 6 to 9. In particular, claim 1 would be described in §8 combined with the teaching found throughout the application stating that emtricitabine is present either as such or as a pharmaceutically acceptable salt (§10, 12, 16, 48, 50, 53, 77).

P also argues that the subject-matter of claim 1 is not an unallowable intermediate generalisation because the application as filed would not describe an inextricable link between the doses of the active compounds and the other limitations found in the different paragraphs of the original application such as total weight of the tablet or presence of a coating.

Reading §8 of the original application, the OD notes that it describes a solid oral dosage form (1st sentence) which in certain embodiments (2nd sentence) comprises 50 mg of the compound of formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

This passage does neither specify that the dosage form is a tablet nor that emtricitabine can be in the form of a salt.

Concerning the feature of claim 1 relating to the "tablet" specific form, the OD observes that it is the only galenic form specifically mentioned in the original application and is recited throughout the original application. Hence its presence in claim 1 does not present the skilled person with any new teaching with respect to the original application.

As for the feature relating to the "emtricitabine salt", all paragraphs which mention the solid dosage form of claim 1 comprise further additional technical features such as "a total weight of less than 850 mg" (§10), "a coated tablet" (§12), segregation of BIC and tenofovir alafenamide (§16) or a specific plasma C_{max} to be achieved (§77). The other paragraphs referred to by P, i.e. §48, 50, 53 are not specifically directed to a solid dosage form as in claim 1.

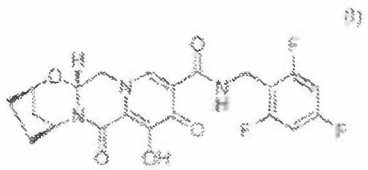
The OD thus considers that introducing the feature "emtricitabine salt" in original §8 to arrive at claim 1 represents subject-matter which extends beyond the content of the application as filed.

The main request does not meet the requirements of A. 123.2 EPC.

B. **AUXILIARY REQUEST 1** (AR1, filed on 26-08-2022):

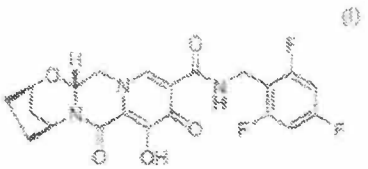
It comprises 7 claims among which 3 independent claims which read:

1. A tablet comprising 50 mg of the compound of Formula I:



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the tablet comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.

4. A tablet comprising 50 mg of the compound of Formula I:



or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the tablet is a coated tablet.

7. A tablet according to any one of the preceeding claims for use in the therapeutic treatment of an HIV infection.

1. Admissibility (R. 80 EPC):

O1 points out that AR1 includes a new independent claim 4 to replace previous dependent claim 5 and that this amendement is not caused by a ground for opposition and leads to two independent claims of the same category.

P answers that this amendment is a reaction to the objection according to A. 123.2.

The OD considers that this amendment is a fair attempt to answer to an objection under A. 123.2 EPC towards the MR.

AR1 is admissible.

2.1. No objection is raised with respect to the requirements of A. 84 EPC (clarity), A. 123.2 EPC (extension of the subject-matter beyond the application as filed) or A. 123.3 EPC (extention of the protection).

The OD sees no reason to differ.

2.2. No opponent contested the validity of the priority for AR1.

The OD considers that the priority is valid.

3. Novelty (A. 54 EPC):

Os object that claim 1 lacks novelty over D1.

D1 was filed on 10-06-2015 and validly entered the European regional phase so that it represents prior art according to A. 54.3 EPC.

Os contend that D1 §96 teaches a combination of 50 to 500 mg of sodium bictegravir with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate or tenofovir alafenamide and 200 mg emtricitabine. D1 would further disclose that tablets are the preferred pharmaceutical compositions (§65 and claim 21). D1 would hence anticipate the subject-matter of claim 1.

P answers that multiple selections/combinations are required to arrive at the subject-matter of claim 1.

§96 of D1 does not disclose *expressis verbis* the tablet of claim 1. The closest specific embodiment in this paragraph recites "a compound disclosed herein (which is either BIC or its sodium salt) is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate or tenofovir alafenamide and 200 mg emtricitabine". The next sentence states that "a compound disclosed therein (e.g. a compound of formula II

-which is BIC sodium salt-) may be combined with the agents provided therein in any dosage amount of the compound (e.g. from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed".

It is observed that §96 does not specifically mention a tablet. Further, to arrive at the subject-matter of claim 1 the following selections must be made: select tenofovir alafenamide among the three possible tenofovir salts, select the amount of 50 mg of BIC or BIC sodium salt. The last part of the last sentence (of §96) does not change this fact.

For these reasons, the OD concludes that D1 does not anticipate the subject-matter of claim 1.

AR1 meets the requirements for novelty.

4. Inventive step (A. 56 EPC):

The opponents regard D5 as the closest prior art document.

D5 would disclose a composition comprising 50 mg dolutegravir (which is an integrase inhibitor), 200 mg emtricitabine and 25 mg tenofovir alafenamide (p. 19-20). The most preferred composition would be a tablet (p. 23).

The distinguishing feature between this teaching and the subject-matter of claim 1 would be the use of 50 mg bictegravir as integrase inhibitor instead of 50 mg dolutegravir.

The patent would not disclose any technical effect linked to this difference.

Hence the problem would be the provision of a fixed-dose combination in form of a tablet comprising an alternative integrase inhibitor, emtricitabine and tenofovir alafenamide.

Since the combination tenofovir alafenamide + emtricitabine would represent a fixed "backbone" in HIV tri-therapy the skilled person would have changed the integrase inhibitor, i.e. dolutegravir.

To this end the skilled person would have turned to D3 which describes integrase inhibitors and would have selected bictegravir because it would stand out as one of the best compounds according to several passages of D3 (ex. 1, 7, table 4 p. 224, claim 42). Its dosage would be described on p. 35 of D3 and would anyway be a matter of routine development.

D18, D28 or D28a could be used as an alternative to D3 since they would also hint to the preferred use of BIC.

Comments are also submitted concerning P's post-filed data of D41 and D42 allegedly demonstrating the existence of a technical effect of BIC over dolutegravir (D41) and of the claimed tablet over a tablet of D5 (D42).

P considers that in view of D5 the objective technical problem would be the provision of an effective therapy to treat HIV which provides near-maximal virologic response, can be formulated as a single tablet, provides minimised food effects, and which has an improved resistance profile and improved forgiveness and barrier to resistance under conditions of suboptimal adherence. The food effects would be described in ex. 3 and 9 of the patent and confirmed by D36, the improved resistance would be described in D41 and the improved forgiveness in D42.

In P's view there would firstly be no reason for the skilled person to replace dolutegravir rather than any of the other two active compounds, i.e. emtricitabine or tenofovir alafenamide.

Further selecting BIC from the many active compounds described in D3 would imply hindsight. D18 and D28a would not provide any specific technical information hinting at a specific selection of BIC.

Moreover it would be unrealistic to simply switch the 50 mg of dolutegravir for the exact same amount of BIC.

D5 describes compositions to treat HIV infection which comprise dolutegravir, emtricitabine and tenofovir. Several examples of such compositions are disclosed among which one comprising 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir, in particular tenofovir alafenamide (p. 20, l. 1-2). D5 further states that tablet is the preferred dosage form (p. 23, l. 8).

As admitted by all parties, the difference with the subject-matter of claim 1 lies in the presence of 50 mg BIC in the latter instead of 50 mg dolutegravir in the example of D5.

It is not disputed that the patent itself does not contain any experiment comparing the composition of D5 and a tablet as in claim 1.

As stated by P however, the patent shows that the composition of claim 1 has improved food effects over the same composition which comprises 75 mg BIC instead of 50 mg.

Hence the problem with respect to the teaching of D5 is to provide an alternative composition (to that of D5) with good food effects to treat HIV infection.

The solution is the composition of claim 1.

Examples 3 and 9 of the patent demonstrate that it possesses good food effects. The anti-HIV effect is not actually shown in the patent but there is no reason to doubt that it exists. This has not been contested by the opponents.

Having defined the problem as above, the question to be answered is whether it would have been obvious for the skilled person to replace 50 mg of dolutegravir by 50 mg of BIC.

The composition of D5 comprises three active compounds so that theoretically any of these three compounds could be changed. In view of D7 however the Os' argument according to which the combination tenofovir/emtricitabine is a "backbone" in the anti-HIV therapy can be accepted.

Thus the skilled person would have been led to replace dolutegravir rather than tenofovir and/or emtricitabine. Dolutegravir being an integrase inhibitor, the skilled person would have turned to D3 which describes such compounds (p. 3, l. 11-12).

BIC corresponds to compound 42 in D3. Although D3 describes a great number of possible integrase inhibitors, it is noted that BIC (compound 42) seems to possess adequate properties as can be seen in examples 106 (table 3, p. 221 giving a fair IC_{50} of 487 nM) and 107 (table 4 p. 224 giving the oral bioavailability, C_{max} and AUC after oral administration). BIC is also specifically recited in claim 32 of D3. Thus even if BIC is not actually singled out and mentioned as being the best integrase inhibitor among those of D3, it certainly represents a good possible alternative integrase inhibitor to dolutegravir of D5.

Notwithstanding, it must also be assessed whether it would have been obvious to use the same amount of BIC as that of dolutegravir in the anti-HIV composition.

The OD cannot follow the Os' arguments according to which the skilled person would have simply used the same amount of integrase inhibitor. It is noted that D5 itself indicates (p. 16, l. 15-18) that the daily dose of dolutegravir can vary from 20 to 75 mg per day, i.e. leading to tablets possibly comprising amounts of dolutegravir different from 50 mg.

Similarly, other integrase inhibitors are administered at other various daily doses: elvitegravir 150 mg (D10), raltegravir administered at 800 mg or 1600 mg daily depending on co-administered agents (D21a, p. 1195) which also leads to tablets comprising amounts different from 50 mg.

From the above, it cannot be concluded that integrase inhibitors are generally administered at the same amount.

Consequently the skilled person would have had no reason to simply replace the 50 mg of dolutegravir of the tablet of D5 by 50 mg of BIC.

In summary, even if the skilled person would have considered replacing dolutegravir of the tablet of D5 by BIC, he would not have had any hint concerning the adequate daily dose and consequently the amount of BIC to be put in the tablet.

More importantly and as explained above and illustrated in the patent, it is shown that a tablet of claim 1, i.e. comprising 50 mg of BIC has better food effects than the same tablet comprising 75 mg of BIC. Thus an amount of 50 mg of BIC leads to a specific unexpected beneficial effect which was not to be foreseen.

Hence not only would the skilled person have had no hint as to which amount of BIC was to be put into the tablet, he would also not have been directed to use precisely 50 mg of BIC.

For these reasons, the OD is convinced that the tablet subject-matter of claim 1 meets the requirements for inventive step.

AR1 meets the requirements for inventive step.

Conclusion:

The opposition division therefore concludes that, taking into consideration the amendments made by the patent proprietor during opposition proceedings, the patent and the invention to which it relates meet the requirements of the EPC. The patent will be maintained in amended form pursuant to Article 101(3)(a) EPC, provided that the requirements of Rule 82(2) EPC are fulfilled.

Article 106
Decisions subject to appeal

(1) An appeal shall lie from decisions of the Receiving Section, Examining Divisions, Opposition Divisions and the Legal Division. It shall have suspensive effect.

(2) A decision which does not terminate proceedings as regards one of the parties can only be appealed together with the final decision, unless the decision allows a separate appeal.

(3) The right to file an appeal against decisions relating to the apportionment or fixing of costs in opposition proceedings may be restricted in the Implementing Regulations.

Rule 97
Appeal against apportionment and fixing of costs

(1) The apportionment of costs of opposition proceedings cannot be the sole subject of an appeal.

(2) A decision fixing the amount of costs of opposition proceedings cannot be appealed unless the amount exceeds that of the fee for appeal.

Rule 98
Surrender or lapse of the patent

The decision of an Opposition Division may be appealed even if the European patent has been surrendered in all the designated Contracting States or has lapsed in all those States.

Article 107
Persons entitled to appeal and to be parties to appeal proceedings

Any party to proceedings adversely affected by a decision may appeal. Any other parties to the proceedings shall be parties to the appeal proceedings as of right.

Article 108
Time limit and form

Notice of appeal shall be filed, in accordance with the Implementing Regulations, at the European Patent Office within **two months** of notification of the decision. Notice of appeal shall not be deemed to have been filed until the fee for appeal has been paid. Within **four months** of notification of the decision, a statement setting out the grounds of appeal shall be filed in accordance with the Implementing Regulations.

Further information concerning the filing of an appeal

(a) Notice of appeal can be filed in accordance with Rule 1 and Rule 2(1) EPC, by delivery by hand, by post, or by technical means of communication. The filing has to comply with the details and conditions and, where appropriate, any special formal or technical requirements laid down by the President of the European Patent Office (R. 99(3) EPC).

(b) The addresses of the filing offices of the European Patent Office are as follows:

(i) European Patent Office D-80298 Munich Germany	(ii) European Patent Office Postbus 5818 NL-2280 HV Rijswijk (ZH) The Netherlands	(iii) European Patent Office D-10958 Berlin Germany
Fax: +49 89 2399-4465	Fax: +31 70 340-3016	Fax: +49 30 259 01-840

(c) The notice of appeal must contain the name and address of the appellant in accordance with the provisions of Rule 41(2)(c) EPC, an indication of the decision impugned, and a request defining the subject of the appeal. In the statement of grounds of appeal the appellant shall indicate the reasons for setting aside the decision impugned, or the extent to which it is to be amended, and the facts and evidence on which the appeal is based (R. 99(1) and (2) EPC). The notice of appeal and any subsequent submissions stating the grounds for appeal must be signed (R. 50(3) EPC).

(d) The fee for appeal is laid down in the Rules relating to Fees. The schedule of fees and expenses of the EPO or a reference to the current version is regularly published in the Official Journal of the European Patent Office under the heading "Guidance for the payment of fees, expenses and prices". Fee information is also published on the EPO website under www.epo.org/fees.

Description

TECHNICAL FIELD

[0001] Pharmaceutical formulations suitable for treating viral infections such as HIV are provided, in particular solid oral dosage forms including the compound of Formula I, emtricitabine and tenofovir alafenamide.

BACKGROUND

[0002] Human immunodeficiency virus, type 1 (HIV-1) infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide (Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic. 2013). Standard of care for the treatment of HIV-1 infection uses combination antiretroviral therapy (ART) to suppress viral replication to below detectable limits, increase CD4 cell counts, and halt disease progression.

[0003] There is also a need for medications to serve populations with limited treatment options (e.g., children, women, and the elderly). In certain situations, these populations may have difficulty maintaining treatment because of pill burden (number of pills to take each day, as well as different combinations of pills) or the size of the pills themselves, once they are coformulated into a multidrug composition. For example, there is currently no fixed dose combination registered for once a day dosing (i.e., QD) for very young children (e.g., younger than age 12 years).

[0004] A goal of antiretroviral therapy is to achieve viral suppression in the HIV infected patient. Treatment guidelines published by the United States Department of Health and Human Services provide that achievement of viral suppression requires the use of combination therapies, i.e., several drugs from at least two or more drug classes. In addition, decisions regarding the treatment of HIV infected patients are complicated when the patient requires treatment for other medical conditions (e.g., metformin, rifampin, HCV antivirals, hormonal contraceptives, etc.). Because the standard of care requires the use of multiple different drugs to suppress HIV, as well as to treat other conditions the patient may be experiencing, the potential for drug-drug interaction is a criterion for selection of a drug regimen. As such, there is a need for antiretroviral therapies having a decreased potential for drug-drug interactions (e.g., those that affect transporters (e.g., OCT-2) or activate receptors (e.g., PXR).

[0005] WO 2015/186116 relates to sodium (2R,5S,13aR)-7,9-dioxo-10 -((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazepin-8-olate.

[0006] WO 2015/196137 relates to crystalline forms and co-crystals of (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanpyrido[1 ',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamido, and pharmaceutical formulations, and therapeutic uses thereof. The cited document also relates to crystalline forms of sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate Form I.

[0007] WO 2014/100323 relates to compounds for use in the treatment of human immunodeficiency virus (HIV) infection.

[0008] WO 2013/116720 relates to the use of the hemifumarate form of (9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine)(tenofovir alafenamide hemifumarate) in combination with cobicistat.

[0009] WO 2015/022351 relates to a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir or a prodrug thereof, wherein the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, in treatment of viral infection/disease such as an HIV infection.

[0010] Thomson Reuters Drug News (2011) "Gilead and Tibotec finalize agreement on single-tablet HIV regimen" reported a licence agreement between Gilead Sciences and Tibotec Pharmaceuticals for the development and commercialization of a single-tablet regimen combining Prezista (darunavir) with Emtriva (emtricitabine), GS-7340 and cobicistat.

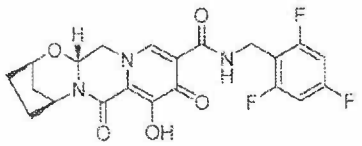
SUMMARY

[0011] The present invention is defined by the appended claims.

[0012] One embodiment of the invention provides a tablet comprising 50 mg of the compound of Formula I:

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(I)

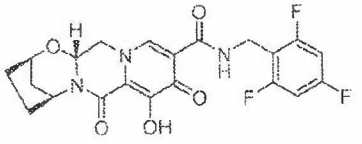


or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.

[0013] In another embodiment of the invention, a tablet of the invention is provided for use in the therapeutic treatment of an HIV infection.

[0014] All the compositions and oral dosage forms herein include a compound of Formula I, (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, having the following structure:

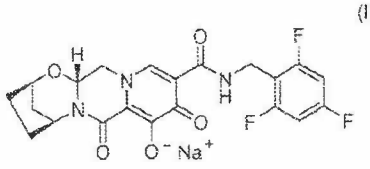
(I)



or a pharmaceutically acceptable salt thereof.

[0015] In certain embodiments, the pharmaceutically acceptable salt of the compound of Formula I is a compound of Formula II, sodium (2R,5S,13aR)-7,9-dioxo-10-((2,4,6-trifluorobenzyl)carbamoyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepin-8-olate, having the following structure:

(II)



[0016] The inventors have successfully formulated an oral dosage form containing the compound of Formula I, tenofovir alafenamide and emtricitabine. This oral dosage form is suitable for use in medicine, and in particular in treating viral infections such as HIV.

[0017] In one aspect, a solid oral dosage form comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof is provided. In certain embodiments, the dosage form comprises 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine. For instance, in certain embodiments, the dosage form comprises 50 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine. In certain embodiments, the dosage form comprises 52 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

[0018] In another aspect, a solid oral dosage form comprising 75 mg of the compound of Formula I as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine is provided. In certain embodiments, a solid oral dosage form comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine is provided. In certain embodiments, a solid oral dosage form comprising 78 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0019] The inventors have found that it is possible to formulate solid oral dosage forms that are pharmaceutically

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acceptable (i.e. pharmacologically efficacious and physically acceptable) while reducing the total amount of excipients necessary to achieve an acceptable pharmacokinetic profile. Accordingly, in one aspect a solid oral dosage form is provided, comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (e.g. less than 800 mg or less than 730 mg or less than 700 mg).

[0020] In another one aspect a solid oral dosage form is provided, comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (e.g. less than 800 mg or less than 700 mg).

[0021] In another aspect, a coated tablet comprising 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0022] In another aspect, a coated tablet comprising 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0023] In another aspect, a tablet comprising 62 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0024] In another aspect, a tablet comprising 78 mg of the compound of Formula II, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

[0025] In another aspect, a tablet comprising (a) 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g (e.g., less than about 1 g). Typically, (a) and (b) are present within separate layers in a multilayer tablet.

[0026] In another aspect, a tablet comprising (a) 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g (e.g., less than about 1 g). Typically, (a) and (b) are present within separate layers in a multilayer tablet.

[0027] In another aspect, a tablet comprising from 8.5-11.0 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 3.0-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 25-30 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the compound of Formula I is present as of the compound of Formula II and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate.

[0028] In another aspect, a tablet comprising from 9.5-11.5 % w/w of the compound of Formula I or a pharmaceutically acceptable salt thereof, 2.5-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 26-33 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the compound of Formula I is present as of the compound of Formula II and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate.

[0029] The inventors have found that the use of a fixed dose combination may assist in achieving appropriate pharmacokinetic parameters and/or adequate tablet stability. In addition, the use of a multilayer tablet as a particular type of fixed dose combination may also provide pharmacokinetic and/or stability benefits. Accordingly, in another aspect a fixed dose combination tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided. Additionally, multilayer tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided.

[0030] In another aspect, a kit comprising (a) a tablet comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant (e.g. silica gel) is provided.

[0031] Methods of producing solid oral dosage forms such as tablets are also provided, as discussed in more detail below.

[0032] In addition, methods for treating patients are provided, which are also discussed in more detail below.

BRIEF DESCRIPTION OF DRAWINGS

[0033]

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Figure 1 shows the results of studies carried out on Formulations F1, F2, and F3 to assess the dissolution of 78 mg of the Compound of Formula II as a single agent compared to a bi-layer using fasted simulated intestinal fluid as a dissolution medium.

Figure 2 shows the results of studies carried out on Formulations F1 and F2 to assess the dissolution of 78 mg of the Compound of Formula II as a single agent compared to a bi-layer using fed simulated intestinal fluid as a dissolution medium.

Figure 3 shows the results of studies carried out on Formulations F1, F2, F4, F5, and F6 to assess the dissolution of 78 mg of the Compound of Formula II in tablets containing various excipients.

Figure 4 shows the results of studies carried out on Formulations F7 and F8 to assess the dissolution of 52 mg of the Compound of Formula II as a single agent compared to a bi-layer using fasted simulated intestinal fluid as a dissolution medium

Figure 5 is a flow diagram illustrating the preparation of a tablet formulation containing the compound of Formula II.

Figure 6 is a flow diagram illustrating the preparation of a tablet formulation containing the compound of Formula II, emtricitabine, and tenofovir alafenamide hemifumarate.

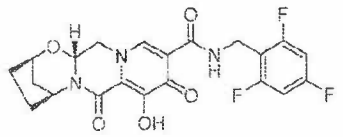
DETAILED DESCRIPTION

[0034] Typically, the oral dosage forms disclosed herein comprise three active pharmaceutical ingredients: the compound of Formula I (or a pharmaceutically acceptable salt thereof), tenofovir alafenamide (or a pharmaceutically acceptable salt thereof), and emtricitabine (or a pharmaceutically acceptable salt thereof).

(2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide

[0035] (2R,5S,13aR)-8-Hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide (Formula I), is a potent HIV integrase inhibitor with *in vitro* activity against wild type HIV-1. It has the following formula (see WO2014/100323):

(I)

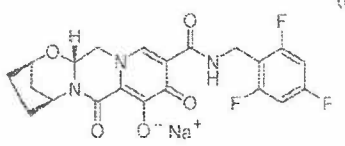


[0036] Its IUPAC name is (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide. Its CAS name is 2,5-Methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, 2,3,4,5,7,9,13,13a-octahydro-8-hydroxy-7,9-dioxo-N-[(2,4,6-trifluorophenyl)methyl]-, (2R,5S,13aR). The compound of Formula I is a weak acid with pKa of 8.6. The aqueous solubility of the compound of Formula I free acid is pH-dependent, with solubility increasing with increasing pH, with a maximum at pH 10.5. The chemical stability of the compound of Formula I is also pH dependent, with maximum stability at pH 4. The compound of Formula I is considered a BCS Class 2 compound, with low solubility and high permeability.

[0037] Solid oral dosage forms disclosed herein include the compound of Formula I, usually in the form of a pharmaceutically acceptable salt. The compound of Formula I can be present within an oral dosage form in solvated or unsolvated form, and references to "Formula I" include both of these forms. Typically, the compound of Formula I is in the form of the compound of Formula II, having the formula below:

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(II)

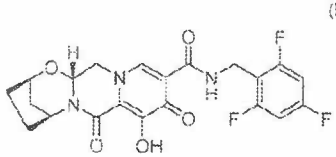


[0038] In certain specific embodiments, solid oral dosage forms containing 50 mg of the compound of Formula I, *e.g.* as about 52 mg of the compound of Formula II, are provided.

[0039] In certain specific embodiments, solid oral dosage forms containing 75 mg of the compound of Formula I, *e.g.* as about 78 mg of the compound of Formula II, are provided.

[0040] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of the compound of Formula I (e.g. Formula II), any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of the compound of Formula I free acid, *i.e.* the amount of:

(I)

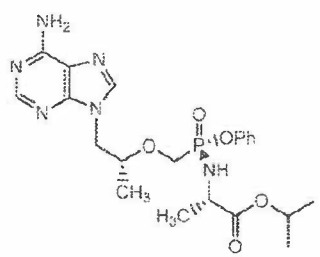


[0041] For example, therefore, a reference to "50 mg of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of the compound of Formula I as 50 mg of the compound of Formula I free acid.

[0042] For example, therefore, a reference to "75 mg of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of the compound of Formula I or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of the compound of Formula I as 75 mg of the compound of Formula I free acid.

Tenofovir alafenamide

[0043] Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor having the formula below (see WO02/08241 A2).

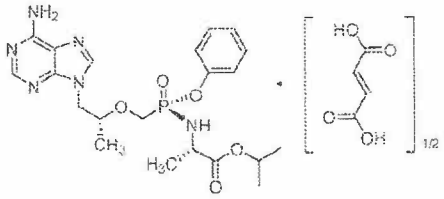


[0044] Its IUPAC name is (*S*)-isopropyl-2-[((*S*)-((((*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl)oxy)methyl)(phenoxy)phosphoryl)amino]propanoate. It is also referred to as (9-[(R)-2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]-methoxy]propyl]adenine). Tenofovir alafenamide is a weak base, with a pKa of 3.9. Its solubility increases with decreasing pH, with a maximum solubility at about pH 3. Tenofovir alafenamide is considered a BCS Class 3 compound, with high equilibrium solubility and lower apparent permeability.

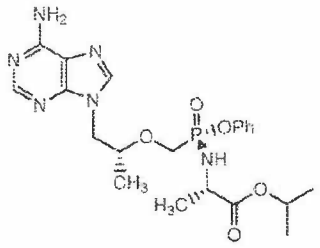
[0045] Solid oral dosage forms disclosed herein include tenofovir alafenamide, usually in the form of a pharmaceutically acceptable salt. Tenofovir alafenamide can be present within an oral dosage form in solvated or unsolvated form, and references to "tenofovir alafenamide" include both of these forms. In particular, tenofovir alafenamide may be associated

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with fumarate, such as monofumarate or hemifumarate. Typically, tenofovir alafenamide is in the form of tenofovir alafenamide hemifumarate having the formula below (see WO 2013/025788 A1):



[0046] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of tenofovir alafenamide, any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of tenofovir alafenamide, i.e. the amount of:

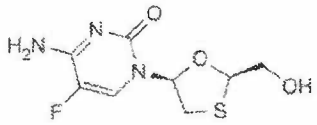


[0047] For example, therefore, a reference to "25 mg tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof' means an amount of tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of tenofovir alafenamide as 25 mg of tenofovir alafenamide free base.

[0048] The amount of tenofovir alafenamide in a solid oral dosage form provided herein is generally between 10 mg and 30 mg, for instance within the range of 20 mg to 30 mg, and more typically between 24 mg and 28 mg. In certain specific embodiments, solid oral dosage forms containing 25 mg of tenofovir alafenamide e.g. as about 28 mg of tenofovir alafenamide hemifumarate, are provided.

Emtricitabine

[0049] Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor having the formula below:



[0050] Its IUPAC name is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one. It is also referred to as 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. It is currently authorised as part of EMTRIVA® (emtricitabine 200 mg), TRUVADA® (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg), ATRIPLA® (emtricitabine 200 mg, efavirenz 600 mg, tenofovir disoproxil fumarate 300 mg) and STRIBILD® (emtricitabine 200 mg, cobicistat 150 mg, tenofovir disoproxil fumarate 300 mg, elvitegravir 150 mg) and COMPLERA®/EVIPLERA® (rilpivirine 25 mg, emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg).

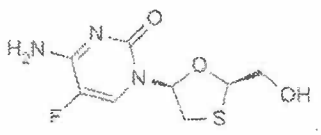
[0051] Emtricitabine is a free base, exhibiting a pKa of 2.65. Solubility is enhanced under acidic conditions. It is considered a BCS Class 1 compound, with high solubility and high permeability.

[0052] Solid oral dosage forms disclosed herein include emtricitabine, optionally as a pharmaceutically acceptable salt. Emtricitabine can be present within an oral dosage form in solvated or unsolvated form, and references to "emtric-

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itabine" include both of these forms. Typically, emtricitabine is present as a free base.

[0053] As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of emtricitabine, any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of emtricitabine, *i.e.* the amount of:



[0054] For example, therefore, a reference to "200 mg emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof' means an amount of emtricitabine or a pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of emtricitabine as 200 mg of emtricitabine free base.

[0055] The amount of emtricitabine in a solid oral dosage form provided herein is generally between 180 mg and 220 mg, for instance between 190 mg and 210 mg, and more typically between 195 mg and 205 mg. In certain specific embodiments, solid oral dosage forms containing 200 mg of emtricitabine are provided.

Solid oral dosage forms

[0056] The inventors have successfully formulated the compound of Formula I, emtricitabine and tenofovir alafenamide in a single, stable dosage form that is pharmacologically efficacious and physically acceptable. The solid oral dosage forms disclosed herein are intended for pharmaceutical use in human subjects. Accordingly, they must be of an appropriate size and weight for oral human administration (e.g. they should have a total weight of less than about 1.5 g, e.g., less than about 1.0 g), in addition to being therapeutically efficacious.

[0057] In certain embodiments, formulations of the three active ingredients into a solid oral dosage form which has a total weight of less than about 1.0 g are provided, for instance less than about 800 mg, or even less than about 750 mg, or even less than 700 mg. This is advantageous given that TRIUMEQ® (abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine) has a total weight of more than about 1000 mg, based on the weight of the active ingredients in each tablet (due to the amount of excipients that are required to produce a pharmaceutically acceptable tablet). The provision of a relatively small dosage form (in particular a tablet) represents a clinical advantage because it may be expected to increase patient convenience and thus compliance as compared to larger dosage forms which are more burdensome for patients to swallow. In specific embodiments, the solid oral dosage form disclosed herein has a total weight of between 700 and 750 mg. In certain embodiments, the solid oral dosage form disclosed herein has a total weight of between 700 and 725 mg, or about 700 mg. In specific embodiments, the solid oral dosage form disclosed herein has a total weight of between about 50 and about 750 mg, between about 100 and about 750 mg, between about 200 and about 750 mg, or between about 250 and about 750 mg. The presently disclosed dosage forms may comprise less than 600 mg of excipients, such as less than 500 mg of excipients, or less than 450 mg of excipients. For example, solid oral dosage forms disclosed herein may comprise between 300 and 600 mg of excipients, or between 350 mg and 500 mg of excipients, or between 400 mg and 500 mg of excipients. Most typically, solid oral dosage forms disclosed herein comprise between 425 mg and 450 mg of excipients. In such embodiments, the dosage forms comprise as active ingredients (a) 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms comprise as active ingredients (a) 52 mg of the compound of Formula II, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine. In some embodiments, the dosage forms comprise as active ingredients (a) 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms comprise as active ingredients (a) 78 mg of the compound of Formula II, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine.

[0058] The solid oral dosage forms disclosed herein will typically be in the form of a fixed dose combination tablet. This is because the inventors have found that the use of fixed dose combination tablets may assist in optimizing the pharmacokinetic properties of the active ingredients, particularly the total exposure of the compound of Formula I or a pharmaceutically acceptable salt thereof, as measured by area under the curve (AUC) and C_{max}. In particular embodiments, the solid oral dosage forms disclosed herein are in the form of a multilayer tablet. In certain embodiments, the use of a fixed dose combinations, e.g., multilayer tablets, may affect the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore likely to have an impact on the *in vivo* pharmacokinetics of the

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dosage form. In particular, it has been observed that the dissolution of the compound of Formula I (e.g., as Formula II) varies depending on whether the tablet is in a fixed dose combination formulation with tenofovir alafenamide and emtricitabine and/or whether the tablet is a monolayer or multilayer tablet. It has also been observed that the presence of certain excipients in the multilayer tablet formulation (or absence of others) affects the dissolution profile of one or more of the active ingredients within the dosage form. The provision of a tablet with particular pharmacokinetic parameters, e.g. pharmacokinetic parameters is a particular advantage afforded by the present disclosure.

[0059] In one embodiment, a multilayer tablet comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided. Typically, each layer contains at least one of (a), (b), and (c). For instance, in certain embodiments, the tablet comprises a first layer comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof, and a second layer comprising (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and further comprises (c) emtricitabine or a pharmaceutically acceptable salt thereof. In such embodiments, typically the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g. the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof).

[0060] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., Formula II) and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein the first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0061] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., Formula II) and is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 52 mg of the compound of Formula II and is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing emtricitabine or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0062] A particular embodiment provides a tablet, wherein the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., Formula II) and is substantially free of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight each of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof

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and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof). In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide and emtricitabine or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch. In one embodiment, the layer containing the compound of Formula I or a pharmaceutically acceptable salt thereof does not contain lactose, crospovidone and/or sodium stearyl fumarate.

[0063] In a particular embodiment, a tablet is provided, wherein (a) the first layer comprises 78 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g. the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 355 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. In one embodiment, the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch.

[0064] Unless otherwise specified, the terms "first layer", "second layer", "third layer" and so forth do not specify a particular order or orientation of the multilayer tablet formulations disclosed herein. Rather, these terms are used to distinguish the sections of the composition from each other and to specify the characteristics or components of each section or compartment. By way of example, in an embodiment, a tablet is provided wherein a first layer comprises 52 mg of the compound of Formula II and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g., the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g., the second layer contains less than 1% by weight of the compound of Formula I or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 325 mg, and the second layer has a total weight of less than about 450 mg, such as about 380 mg. The first layer may be synthesized first or may be synthesized second. The first layer may be on the bottom or may be on the top or may be on a side. The term "first layer" is not limiting as to order and orientation.

[0065] The tablets disclosed herein are typically immediate release tablets. In one embodiment, a tablet is provided which releases at least 50% of the compound of Formula I or a pharmaceutically acceptable salt thereof in about 20 minutes, measured using USP apparatus II, in 333 mL of fasted state simulated intestinal fluid, pH 6.5, at 37 °C and paddle speed of 100 rpm. In certain embodiments, the tablets disclosed herein release at least 60% of the compound of Formula I or a pharmaceutically acceptable salt thereof in 20 minutes, measured using USP apparatus II, in 333 mL of 50 mM fasted state simulated intestinal fluid, at 37 °C and paddle speed of 100 rpm. In some embodiments, a tablet that releases at least 70% of the compound of Formula I in 60 minutes is provided, measured using USP Apparatus II, in 333 mL of fasted state simulated intestinal fluid at 37 °C and paddle speed of 100 rpm.

[0066] Tablets disclosed herein will generally have a hardness within the range 14-20 kP, and, in certain specific embodiments, have a hardness of 17 kP. Hardness can conveniently be assessed by driving an anvil to compress a tablet at a constant loading rate until it fractures, operating in accordance with USP <1217> (using e.g. a TBH 220, ERWEKA GmbH, Heusenstamm Germany hardness tester).

[0067] Tablets disclosed herein will generally have a friability of <1% by weight. Friability can be assessed according to USP <1216>.

[0068] The core of a tablet provided herein may have a hardness of between 14-20 kP, and a friability of <1% by weight.

[0069] Tablets will typically include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of tablet formulation and may be found e.g. in Handbook of Pharmaceutical Excipients (eds. Rowe, Sheskey & Quinn), 6th edition 2009. As used herein the term "excipients" is intended to refer to *inter alia* basifying agents, solubilisers, glidants, fillers, binders, lubricant, diluents, preservatives, surface active agents, and/or dispersing agents. The term also includes agents such as sweetening agents, flavoring agents, coloring agents, preserving agents, and coating agents. Such components will generally be present in admixture within the tablet.

[0070] Examples of solubilisers include, but are not limited to, ionic surfactants (including both ionic and non-ionic

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surfactants) such as sodium lauryl sulphate, cetyltrimethylammonium bromide, polysorbates (such as polysorbate 20 or 80), poloxamers (such as poloxamer 188 or 207), and macrogols. In a particular embodiment, a tablet that comprises the compound of Formula I or a pharmaceutically acceptable salt thereof, includes a polysorbate, in particular polysorbate 20. In certain specific embodiments, the amount of polysorbate 20 in a tablet disclosed herein is less than about 5 mg, such as less than about 1 mg, or about 0.5 mg.

[0071] Examples of lubricants, glidants and flow aids include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl behenate, sodium stearyl fumarate, colloidal silicon dioxide, and talc. The amount of lubricant in a tablet is generally between about 0.5-5% by weight. In certain embodiments, the amount of lubricant in a tablet is about 1.5% by weight. In certain specific embodiments, tablets disclosed herein include magnesium stearate. In certain other embodiments, the tablets disclosed herein do not include sodium stearyl fumarate. In certain embodiments, the tablet includes less than about 10 mg magnesium stearate, or less than about 7.5 mg magnesium stearate. In certain embodiments, the tablet includes less than about 9 mg magnesium stearate, or less than about 8.75 mg magnesium stearate. In certain embodiments, the tablet includes about 5 mg to about 10 mg magnesium stearate, or about 6 mg to about 9 mg magnesium stearate, or about 7 mg to about 9 mg magnesium stearate, or about 8 mg to about 9 mg magnesium stearate, or about 8.1 mg, about 8.2 mg, about 8.3 mg, about 8.4 mg, about 8.5 mg, about 8.6 mg, about 8.7 mg, about 8.8 mg or about 8.9 mg magnesium stearate.

[0072] Examples of disintegrants include, but are not limited to, starches, celluloses, cross-linked PVP (crospovidone), sodium starch glycolate, croscarmellose sodium, *etc.* In certain embodiments, the tablets disclosed herein include croscarmellose sodium. In certain other embodiments, the tablets disclosed herein do not include crospovidone. In certain embodiments, the tablet includes less than about 50 mg croscarmellose sodium, or less than about 25 mg croscarmellose sodium. In certain embodiments, the tablet includes about 30 mg to about 60 mg croscarmellose sodium, or about 40 mg to about 60 mg croscarmellose sodium, or about 45 mg to about 55 mg croscarmellose sodium, or about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg or about 53 mg, or about 54 mg, or about 55 mg croscarmellose sodium.

[0073] Examples of fillers (also known as bulking agents or diluents) include, but are not limited to, starches, maltodextrins, polyols (such as lactose), and celluloses. In certain embodiments, tablets provided herein may microcrystalline cellulose. In certain other embodiments, tablets provided herein do not contain lactose. In certain embodiments, tablets provided herein include less than about 300 mg microcrystalline cellulose, in particular less than about 250 mg microcrystalline cellulose, and/or less than about 225 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include less than about 500 mg microcrystalline cellulose, or less than about 450 mg microcrystalline cellulose, or less than about 400 mg microcrystalline cellulose, or less than about 375 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include about 250 mg to about 500 mg microcrystalline cellulose, or about 300 mg to about 450 mg microcrystalline cellulose, or about 300 mg to about 400 mg microcrystalline cellulose, or about 325 mg to about 375 mg microcrystalline cellulose, or about 350 mg to about 370 mg microcrystalline cellulose. In certain embodiments, tablets provided herein include about 300 mg, or about 310 mg, or about 320 mg, or about 330 mg, or about 340 mg, or about 350 mg, or about 360 mg, or about 370 mg, or about 380 mg, or about 390 mg, or about 400 mg microcrystalline cellulose.

[0074] Examples of binders include, but are not limited to, cross-linked PVP, HPMC, sucrose, starches, *etc.*

[0075] In certain embodiments, tablets provided herein are uncoated. In certain other embodiments, tablets provided herein are coated (in which case they include a coating). Although uncoated tablets may be used, it is more usual in the clinical setting to provide a coated tablet, in which case a conventional non-enteric coating may be used. Film coatings are known in the art and can be composed of hydrophilic polymer materials, but are not limited to, polysaccharide materials, such as hydroxypropylmethyl cellulose (HPMC), methylcellulose, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), poly(vinylalcohol-*co*-ethylene glycol) and other water soluble polymers. Though in certain embodiments the water soluble material included in the film coating of the embodiments disclosed herein includes a single polymer material, in certain other embodiments it is formed using a mixture of more than one polymer. In certain embodiments, the coating is yellow or brown. Suitable coatings include, but are not limited to, polymeric film coatings such as those comprising polyvinyl alcohol e.g. 'Opadry® II' (which includes part-hydrolysed PVA, titanium dioxide, macrogol 3350 (PEG) and talc, with optional colouring such as iron oxide (e.g., iron oxide red or iron oxide black) or indigo carmine or iron oxide yellow or FD&C yellow #6). The amount of coating is generally between about 2-4% of the core's weight, and in certain specific embodiments, about 3%. Unless specifically stated otherwise, where the dosage form is coated, it is to be understood that a reference to % weight of the tablet means that of the total tablet, *i.e.* including the coating.

Pharmacokinetics

[0076] In certain embodiments, the pharmaceutical compositions disclosed herein result in increased systemic exposure (AUC_{Inf}, C_{max}) for the compound of Formula I or a pharmaceutically acceptable salt thereof. In particular embodiments, the multilayer tablet formulations disclosed herein result in increased systemic exposure for the compound of

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Formula I or a pharmaceutically acceptable salt thereof compared to a single agent tablet formulation of the compound of Formula I or a pharmaceutically acceptable salt thereof. In certain embodiments, the multilayer tablet formulation results in an increase of at least about 20% in the systemic exposure of the compound of Formula I or a pharmaceutically acceptable salt thereof compared to a single agent tablet formulation of the compound of Formula I or a pharmaceutically acceptable salt thereof. In some embodiments, the increase in systemic exposure is at least about 25% or at least about 30%. In some embodiments, the increase in systemic exposure is about 30%.

C_{max}

[0077] C_{max} is the maximum observed plasma/serum concentration of drug.

[0078] In particular embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fasted patients of from about 5300 to about 8900 ng/mL, e.g. about 7100 ng/mL.

[0079] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fasted patients of from about 1700 to about 2800 ng/mL, e.g. about 2300 ng/mL.

[0080] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fasted patients of from about 190 to about 320 ng/mL, e.g. about 250 ng/mL.

[0081] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the Compound of Formula I of from about from about 4200 ng/mL to about 8000 ng/mL, regardless of whether the subject was fed or fasted.

[0082] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fasted patients of from about 4200 ng/mL to about 6600 ng/mL, or from about 4700 ng/mL to about 5300 ng/mL, or from about 4700 ng/mL to about 5800 ng/mL, or from about 5000 ng/mL to about 5500 ng/mL.

[0083] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of the compound of Formula I in fed patients of from about 4500 ng/mL to about 8000 ng/mL, or from about 4800 ng/mL to about 7900 ng/mL, or from about 5300 ng/mL to about 6900 ng/mL, or from about 5600 ng/mL to about 6800 ng/mL.

[0084] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine of from about from about 1770 ng/mL to about 2800 ng/mL, regardless of whether the subject was fed or fasted.

[0085] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fasted patients of from about 1770 ng/mL to about 2800 ng/mL, or from about 2000 ng/mL to about 2600 ng/mL, or from about 2000 ng/mL to about 2500 ng/mL, or from about 2100 ng/mL to about 2400 ng/mL.

[0086] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of emtricitabine in fed patients of from about 1000 ng/mL to about 3000 ng/mL, or from about 1500 ng/mL to about 2000 ng/m from about 1700 ng/mL to about 2200 ng/mL L, or from about 1800 ng/mL to about 2100 ng/mL.

[0087] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide of from about from about 185 ng/mL to about 315 ng/mL, regardless of whether the subject was fed or fasted.

[0088] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the

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compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fasted patients of from about 185 ng/mL to about 315 ng/mL, or from about 200 ng/mL to about 300 ng/mL, or from about 210 ng/mL to about 290 ng/mL, or from about 220 ng/mL to about 275 ng/mL, or from about 230 ng/mL to about 265 ng/mL, or from about 240 ng/mL to about 260 ng/mL.

[0089] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma C_{max} of tenofovir alafenamide in fed patients of from about 150 ng/mL to about 350 ng/mL, or from about 185 ng/mL to about 300 ng/mL from about 210 ng/mL to about 280 ng/mL, or from about 250 ng/mL to about 265 ng/mL.

AUC_{inf}

[0090] AUC_{inf} is the area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$.

[0091] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fed patients of from about 117000 to about 196000 h•ng/mL, *e.g.* about 157000 h•ng/mL.

[0092] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 8700 to about 14500h•ng/mL, *e.g.* about 2300h•ng/mL.

[0093] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 150 and 260 h•ng/mL, *e.g.* about 210 h•ng/mL.

[0094] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the Compound of Formula I of from about from about 84450 h•ng/mL to about 141000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0095] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fasted patients of from about 84450 h•ng/mL to about 141000 h•ng/mL, or from about 90000 h•ng/mL to about 135000 h•ng/mL, or from about 95000 h•ng/mL to about 130000 h•ng/mL, or from about 100000 h•ng/mL to about 125000 h•ng/mL, or from about 110000 h•ng/mL to about 120000 h•ng/mL.

[0096] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of the compound of Formula I in fed patients of from about 100000 h•ng/mL to about 200000 ng/mL, or from about 112000 h•ng/mL to about 175000 ng/mL, or from about 126000 h•ng/mL to about 155000 ng/mL, or from about 133000 h•ng/mL to about 147000 ng/mL.

[0097] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine of from about from about 8100 h•ng/mL to about 13600 h•ng/mL, regardless of whether the subject was fed or fasted.

[0098] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fasted patients of from about 8100 h•ng/mL to about 13600 h•ng/mL, or from about 8700 h•ng/mL to about 13000 h•ng/mL, or from about 92000 h•ng/mL to about 12500 h•ng/mL, or from about 9700 h•ng/mL to about 12000 h•ng/mL, or from about 10000 h•ng/mL to about 11400 h•ng/mL.

[0099] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt

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thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 7500 h•ng/mL to about 15000 ng/mL, or from about 8300 h•ng/mL to about 14000 ng/mL, or from about 9500 h•ng/mL to about 12000 ng/mL, or from about 9900 h•ng/mL to about 11600 ng/mL.

[0100] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide of from about from about 200 h•ng/mL to about 500 h•ng/mL, regardless of whether the subject was fed or fasted.

[0101] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fasted patients of from about 200 h•ng/mL to about 265 h•ng/mL, or from about 200 h•ng/mL to about 300 h•ng/mL, or from about 210 h•ng/mL to about 290 h•ng/mL, or from about 220 h•ng/mL to about 270 h•ng/mL, or from about 230 h•ng/mL to about 265 h•ng/mL.

[0102] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 200 h•ng/mL to about 500 ng/mL, or from about 230 h•ng/mL to about 400 ng/mL, or from about 260 h•ng/mL to about 350 ng/mL, or from about 275 h•ng/mL to about 370 ng/mL.

AUC_{last}

[0103] AUC_{last} is the area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration.

[0104] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fed patients of from about 114000 to about 190000 h•ng/mL., e.g. about 152000 h•ng/mL.

[0105] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine in fed patients of from about 8600 to about 14000 h•ng/mL, e.g. about 11000 h•ng/mL.

[0106] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 75 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 150 and 260 h•ng/mL., e.g. about 210 h•ng/mL.

[0107] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I of from about from about 81700 h•ng/mL to about 140000 h•ng/mL, regardless of whether the subject was fed or fasted.

[0108] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fasted patients of from about 81700 h•ng/mL to about 140000 h•ng/mL, from about 87000 h•ng/mL to about 131000 h•ng/mL, from about 92000 h•ng/mL to about 130000 h•ng/mL, from about 98100 h•ng/mL to about 120000 h•ng/mL, from about 104000 h•ng/mL to about 115000 h•ng/mL.

[0109] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the compound of Formula I in fed patients of from about 100000 h•ng/mL to about 200000 ng/mL., or from about 108000 h•ng/mL to about 170000 ng/mL., or from about 122000 h•ng/mL to about 150000 ng/mL., or from about 128000 h•ng/mL to about 142000 ng/mL.

[0110] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine of from about from about 7500 h•ng/mL to about 15000 h•ng/mL, regardless of whether the

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subject was fed or fasted.

[0111] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the emtricitabine in fasted patients of from about 8000 h•ng/mL to about 13400 h•ng/mL, from about 8500 h•ng/mL to about 12600 h•ng/mL, from about 9000 h•ng/mL to about 12300 h•ng/mL, from about 9500 h•ng/mL to about 11000 h•ng/mL, from about 10000 h•ng/mL to about 11200 h•ng/mL.

[0112] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of emtricitabine in fed patients of from about 7500 h•ng/mL to about 15000 ng/mL, or from about 8000 h•ng/mL to about 14000 ng/mL, or from about 9000 h•ng/mL to about 12000 ng/mL, or from about 9700 h•ng/mL to about 11300 ng/mL.

[0113] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide of from about from about 165 h•ng/mL to about 400 h•ng/mL, regardless of whether the subject was fed or fasted.

[0114] In certain specific embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of the tenofovir alafenamide in fasted patients of from about 165 h•ng/mL to about 390 h•ng/mL, from about 186 h•ng/mL to about 227 h•ng/mL, from about 196 h•ng/mL to about 217 h•ng/mL.

[0115] In particular embodiments, a pharmaceutical composition comprising a tablet containing 50 mg of the compound of Formula I or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 200 h•ng/mL to about 400 ng/mL, or from about 230 h•ng/mL to about 390 ng/mL, or from about 260 h•ng/mL to about 345 ng/mL, or from about 275 h•ng/mL to about 330 ng/mL.

C_{last}

[0116] C_{last} is the last observed quantifiable plasma/serum concentration of the drug.

[0117] C_{max}, C_{last}, AUC_{inf}, and AUC_{last} are standard pharmacokinetic parameters that can be estimated manually or by using modelling software well known in the art, such as the Pharsight WinNonlin package using a non-compartmental model. The general basis for calculation of these quantities is well-known (e.g. see Rowland & Tozer (2010) Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications ISBN 978-0781750097, or Jambhekar & Breen (2012) Basic Pharmacokinetics ISBN 978-0853699804). Typically the parameters will be assessed as the average (e.g. geometric or arithmetic mean) from within a group of at least 12 (and normally between 24 and 36) healthy human adults. Parameters should be measured in accordance with standards and practices which would be acceptable to a pharmaceutical regulatory agency such as FDA, EMA, MHLW, or WHO. The values may be based on measurements taken at appropriate intervals following the time of tablet ingestion, such as every hour, or at increasingly sparse sampling intervals, such as 1, 3, 5, 7, 9, 11, 13, 15, 20, and 24 hours after ingestion. They can be assessed either following a single-dose of drug or at steady state, but will typically be assessed following a single-dose.

[0118] It is well known in the bioavailability and bioequivalence arts how to determine whether any particular tablet meets regulatory requirements for equivalent bioavailability and pharmacokinetic bioequivalence e.g. see: Niazi (2014) Handbook of Bioequivalence Testing, 2nd Edition, ISBN 978-1482226379; Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations FDA March 2003; and Guideline On The Investigation Of Bioequivalence. EMEA 2010 CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. To ensure statistical power a study to measure the C_{max}, AUC_{last} and AUC_{inf} values will be performed in multiple subjects e.g. in a group of at least 12 (and normally between 24 and 36) healthy human adults.

[0119] Because determining the C_{max}, AUC_{last} and AUC_{inf} values is necessarily destructive these parameters will not be determined directly for the dosage form (in particular the tablet) in question, but rather for a dosage form made by the same manufacturing process with the same components. Thus a batch of a dosage form (e.g. tablets) can be made by a particular process, and the 90% confidence interval of C_{max}, AUC_{last} and AUC_{inf} will be assessed on a sample of those tablets. If these values meet the 80-125% requirement noted above then tablets made by the manufacturing process in question are tablets of the present invention.

[0120] A fixed dose combination tablet is provided comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. Formula II), (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

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[0121] In an embodiment, a multilayer tablet is provided, comprising (a) the compound of Formula I or a pharmaceutically acceptable salt thereof (e.g. Formula II), (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

[0122] In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

[0123] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0124] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0125] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof and tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0126] In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising the compound of Formula I or a pharmaceutically acceptable salt thereof, (b) a second layer containing emtricitabine or a pharmaceutically acceptable salt thereof, and (c) further comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof.

[0127] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer is substantially free of emtricitabine or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0128] In an embodiment of the multilayer tablet disclosed herein, (a) the first layer comprises the compound of Formula I or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0129] In an embodiment of the multilayer tablet disclosed herein, the first layer is substantially free of emtricitabine.

[0130] In one embodiment, the multilayer tablet disclosed herein comprises 50 ± 6 mg of the compound of Formula I. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 25 ± 3 mg of tenofovir alafenamide.

[0131] In one embodiment, the multilayer tablet disclosed herein comprises 75 ± 6 mg of the compound of Formula I. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 25 ± 3 mg of tenofovir alafenamide.

[0132] In one embodiment, the multilayer tablet disclosed herein comprises 52 ± 6 mg of the compound of Formula II. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

[0133] In one embodiment, the multilayer tablet disclosed herein comprises 78 ± 6 mg of the compound of Formula II. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

[0134] In one embodiment, a first layer of the multilayer tablet disclosed herein comprises one or more excipients, for example one or more diluents, disintegrants, binders, or lubricants.

[0135] In one embodiment, a first layer of the multilayer tablet comprises croscarmellose sodium. In one embodiment, a first layer of the multilayer tablet comprises croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

[0136] In one embodiment a tablet is provided wherein less than about 25 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 20 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein less than about 16 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 5 to about 20 weight percent, or about 10 to about 18 weight percent, or about 14 to about 18 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof. In one embodiment a tablet is provided wherein about 16 weight percent of a first layer is the compound of Formula I or a pharmaceutically acceptable salt thereof.

[0137] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 290 mg.

[0136] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 300 mg.

[0139] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of

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Formula II and wherein the total weight of the first layer is at least about 310 mg.

[0140] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 320 mg.

[0141] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 330 mg.

[0142] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 340 mg.

[0143] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 350 mg.

[0144] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 360 mg.

[0145] In one embodiment a tablet is provided wherein the first layer comprises 52± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 290 mg and is less than about 360 mg.

[0146] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 300 mg and is less than about 350 mg.

[0147] In one embodiment a tablet is provided wherein the first layer comprises 52 ± 2.8 mg of the compound of Formula II and wherein the total weight of the first layer is at least about 310 mg and is less than about 330 mg.

[0148] In one embodiment, the first layer of the multilayer tablet has a total weight of 323 ± 75 mg, or 323 ± 25 mg, or 323 ± 10 mg, or 323 mg.

[0149] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
The compound of Formula I or a salt thereof	40-60
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	1-10

[0150] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
the compound of Formula II	30-60
Microcrystalline cellulose	200-400
Croscarmellose sodium	1-40
Magnesium stearate	2-8

[0151] In one embodiment, the first layer of the multilayer tablet comprises:

Ingredient	Mass (mg)
the compound of Formula II	50 ± 6
Microcrystalline cellulose	250 ± 20
Croscarmellose sodium	20 ± 5
Magnesium stearate	5 ± 1.5

[0152] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52 ± 5.6
Microcrystalline cellulose	246 ± 10

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(continued)

Ingredient	Mass (mg)
Croscarmellose sodium	19 ± 2.5
Magnesium stearate	5 ± 0.75

[0153] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52 ± 2.6
Microcrystalline cellulose	246 ± 5
Croscarmellose sodium	19 ± 1.75
Magnesium stearate	5 ± 0.5

[0154] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
the compound of Formula II	52.5
Microcrystalline cellulose	246.3
Croscarmellose sodium	19.4
Magnesium stearate	4.9

[0155] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula I or a pharmaceutically acceptable salt thereof	52.5 ± 1.6
Microcrystalline cellulose	214 ± 7.3
Croscarmellose sodium	19 ± 0.6
Magnesium stearate	2.4 ± 0.5
Extragranular	
Microcrystalline cellulose	32 ± 1
Magnesium stearate	2.4 ± 0.5
Total layer weight	323

[0156] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 7.3
Croscarmellose sodium	19 ± 0.6
Magnesium stearate	2.4 ± 0.5

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(continued)

Extragranular	
Microcrystalline cellulose	32 ± 1
Magnesium stearate	2.4 ± 0.5
Total layer weight	323

[0157] In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.45 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.45 ± 0.5
Total layer weight	323

[0158] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula I, or a pharmaceutically acceptable salt therof	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.43 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1
Magnesium stearate	2.43 ± 0.5
Total layer weight	323

[0159] In one embodiment, the first layer of the multilayer tablet includes:

Ingredient	Mass (mg)
Intergranular	
the compound of Formula II	52.5 ± 1.6
Microcrystalline cellulose	214 ± 6.4
Croscarmellose sodium	19.4 ± 0.6
Magnesium stearate	2.43 ± 0.5
Extragranular	
Microcrystalline cellulose	32.3 ± 1