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 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

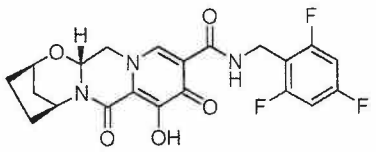
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will 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.

AMENDMENTS TO THE CLAIMS

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

1. (Previously Presented) A multilayer 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 wherein the tablet has a total weight of less than about 1000 mg.

2. (Previously Presented) The tablet of claim 1, 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.

3. (Previously Presented) The tablet of claim 1 or 2, wherein the tablet comprises 52 mg of the sodium salt of the compound of Formula I and 28 mg tenofovir alafenamide hemifumarate.

4. (Previously Presented) The tablet of claim 3, wherein the tablet has a total weight of less than about 800 mg.

5. (Previously Presented) The tablet of claim 3, wherein the tablet has a total weight of less than about 730 mg.

6-25 (Canceled)

26. (Previously Presented) The tablet of claim 1 or 2, wherein the tablet contains less than about 15% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

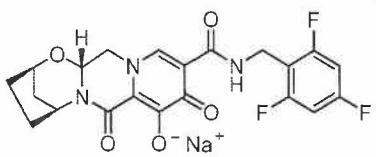
27. (Previously Presented) The tablet of claim 1 or 2, wherein the tablet contains less than about 11% of the compound of Formula I or a pharmaceutically acceptable salt thereof.

28-51 (Canceled)

52. (Previously Presented) The tablet of claim 1 or 2, wherein the tablet is a coated tablet.

53. (Currently Amended) ~~The~~ A tablet ~~of claim 3~~, comprising:

(II)



(i) a first layer including: 52.5 mg of the compound of Formula II, 246.3 mg microcrystalline cellulose, 19.4 mg croscarmellose sodium, and 4.9 mg magnesium stearate; and

~~Ingredient~~	~~Mass (mg/tablet)~~
~~Compound of Formula II~~	~~52.5 (*equivalent to 50 mg of the Compound of Formula I*)~~
~~Microcrystalline cellulose~~	~~246.3~~
~~Croscarmellose sodium~~	~~19.4~~
~~Magnesium Stearate~~	~~4.9~~

(ii) a second layer including: 200 mg emtricitabine, 28 mg tenofovir alafenamine hemifumarate, 113.2 mg microcrystalline cellulose, 30.2 mg croscarmellose sodium, and 5.7 mg magnesium stearate;

~~Ingredient~~	~~Mass (mg/tablet)~~
~~Emtricitabine~~	~~200~~
~~Tenofovir alafenamide hemifumarate~~	~~28 (*equivalent to 25 mg tenofovir alafenamide*)~~

~~Microcrystalline cellulose~~	~~113.2~~
~~Croscarmellose sodium~~	~~30.2~~
~~Magnesium Stearate~~	~~5.7~~

and (iii) a film coating.

54. (Canceled)

55. (Previously Presented) The tablet of claim 3, wherein the first layer comprises 52 mg of the compound of Formula II:

(II)



and is substantially free of 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.

REMARKS

Claims 1-5, 26, 27, 52, 53, and 55 are pending. Claim 53 is currently amended. The amendments add no new matter to the claims. Accordingly, upon entry, claims 1-5, 26, 27, 52, 53, and 55 are pending examination.

Claim 53 has been amended to recite the components of the first and second layers of the tablet in text format rather than tabular format.

Applicant respectfully requests reconsideration of the application in view of the amendments and remarks made herein.

Applicant gratefully acknowledges withdrawal of the claim objections and the rejection under 35 U.S.C. § 102(a)(2).

Claim Rejections under 35 U.S.C. § 112(b)

Claim 53 has been rejected as being allegedly indefinite. The Office Action notes that claim 53 recites the first and second layer in table form, which it asserts is permitted only in limited instances. The Office Action also notes that claim 53 recites the compound of Formula II, while the claim from which it depends (claim 3) recites the compound of Formula I. Solely in an effort to advance prosecution and without conceding to the merits of the rejections, claim 53 has been revised to be an independent claim and amended to recite the components of the first and second layers in text format. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 55 has been rejected as being allegedly indefinite. The Office Action alleges that the term "substantially free" is indefinite. Applicant respectfully disagrees and submits that one of ordinary skill in the art would be reasonably apprised of the scope of the invention in view of the teachings of the specification. For example, paragraph [0289] of the specification as-filed provides:

> "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.

Accordingly, the specification provides a standard for ascertaining the requisite metes and bounds of the term "substantially free". Reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 103

Claims 1-5, 26-27, 52-53, and 55 have been rejected as being allegedly being obvious over Carra *et al.* (WO2015/196116, hereinafter "Carra 1") in view of Dahl *et al.* (U.S. Patent Application Publication No. 2007/0099902). Claims 1-5, 26-27, 52-53, and 55 have also been rejected as being allegedly being obvious over Carra *et al.* (US Patent Application Publication No. 2016/0016973, hereinafter "Carra 2") in view of Dahl *et al.* (U.S. Patent Application Publication No. 2007/0099902). In particular, the Examiner alleges it would have been obvious to one of ordinary skill in the art to formulate the dosage form in a bilayer tablet to separate tenofovir from the compound of Carra *et al.* in order to prevent destabilizing contact of tenofovir with the surfactant.

Applicant notes the publication dates of Carra 1 and Carra 2 are December 23, 2015 and January 21, 2016, respectively, and the effective filing date of the instantly claimed invention is November 9, 2015. Because both Carra 1 and Carra 2 were published after November 9, 2015, they 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, noting Carra 1 and Carra 2 do not teach a multilayer tablet (see page 5, first paragraph and page 7, first paragraph of the Office Action). 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.

Response to Arguments

Notwithstanding the Examiner's indication that the anticipation rejections have been withdrawn (see page 2, item 2 of the Office Action), the following remarks address the Response to Arguments, in which the rejections are maintained.

In response to Applicant's arguments regarding the unexpected results obtained using the instantly claimed formulation of a compound of Formula I, tenofovir alafenamide, and emtricitabine—namely, increased exposure of the compound of Formula I (*i.e.*, bictegravir) in the fixed dose combination of bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) relative to its exposure when co-administered as a single agent with a fixed dose combination of emtricitabine and tenofovir alafenamide (B + F/TAF)—the Examiner alleges the data provided is not commensurate in scope with the claims, therefore a side by side analysis cannot be conducted.

Applicant submits the Examiner has mischaracterized the claimed invention. While the instantly claimed formulation comprises specific amounts of bictegravir, tenofovir alafenamide, and emtricitabine, the unexpected results are associated with the *combination* of bictegravir, tenofovir alafenamide, and emtricitabine, not the specific amounts. The data provided in paragraph [0317] demonstrate this unexpected result. Specifically, the data demonstrate the approximately 30% higher exposure of bictegravir in a fixed dose combination of bictegravir, emtricitabine, tenofovir alafenamide (Formulation F2 = B/F/TAF) relative to its exposure when co-administered as a single agent (Formulation F1 = B) with a fixed dose combination of emtricitabine and tenofovir alafenamide (Formulation F3 = F/TAF).

Because of the increased exposure observed for bictegravir in fixed dose combination with tenofovir alafenamide and emtricitabine, efforts to develop a fixed dose combination incorporating a lower dose of bictegravir commenced. Paragraph [0345] of the specification provides such a combination, comprising 50 mg bictegravir, as Formulation F7. The data

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1556 of 1915

provided in paragraph [0345] demonstrate that the exposure of bictegravir in Formulation F7 relative to its exposure in a formulation containing 75 mg bictegravir as a single agent (Formulation F1 + Formulation F3) is (predictably) lower, yet still provides anti HIV antiviral efficacy. The data also demonstrate that the exposures of tenofovir alafenamide and emtricitabine in Formulation F7 are consistent with those observed when bictegravir was co-administered as a single agent with a fixed dose combination of tenofovir alafenamide and emtricitabine (Formulation F1 + F3). Thus, reducing the dose of bictegravir reduced the exposure of bictegravir, but did not reduce the exposure of tenofovir alafenamide and emtricitabine. It follows that reducing the amount of bictegravir in the fixed dose combination from 75 to 50 mg can result in a lower weight (or smaller) tablet—an advantage of the instantly claimed formulation that is recited in claim 1.

In view of the foregoing, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant requests reconsideration of this application in view of the present amendments. If the Office finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Director is hereby authorized to charge our Deposit Account No. 07-1250, under Order No. 1147.P2C from which the undersigned is authorized to draw for any fees due in this transaction.

Dated: March 20, 2019

Respectfully submitted,

By: /Donna Johnson Gressler/
Donna Johnson Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 522-1816
Attorney For Applicant

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1558 of 1915

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/346,335	Filing Date 11/08/2016	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $420 =	
☐ 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).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	03/20/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** 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 number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. 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 12 minutes to complete, including gathering, preparing, and submitting the completed application 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-10,035,809	07-31-2018	Bacon et al.	
	AB	US-2018/0022757-A1	01-25-2018	Chiu et al.	
	AC	US-2018/0065986-A1	03-08-2018	Carra et al.	
	AD	US-2019/0015420-A1	01-17-2019	Carra et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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: April 12, 2019 Signature: /Donna Johnson Gressler/ (Donna Gressler)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Examination Report dated 2018-08-15 for New Zealand Appl. No. 741957, 5 pages.	
	CB	Examination Report dated 2019-11-05 for Australian Appl. No. 2016354007, 4 pages.	
	CC	Office Action dated 2018-09-18 for Bolivian Appl. No. SP260-2016, 8 pages.	√
	CD	Office Action dated 2018-10-03 for Panamanian Appl. No. 92163, 8 pages.	√
	CE	Office Action dated 2018-11-13 for Pakistani Appl. No. 696/2016, 3 pages.	
	CF	Office Action dated 2019-01-21 for European Appl. No. 16798063.0, 5 pages.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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15 August 2018

DAVIES COLLISON CAVE PTY LTD
DCC NZ Limited
Private Bag 3140
Waikato Mail Centre
Hamilton 3240
New Zealand

Your reference: 35283363/MJC

IP Number: 741957
Patent: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS
Applicant: Gilead Sciences, Inc.

First Examination Report

Section 67 – Deadline for substantive response to report

The deadline by which the applicant must make a substantive response to this report is **15 February 2019**. The time to respond is extendable by one month to **15 March 2019** if requested within the extended period.

Section 71 – Time for putting application in order for acceptance

The application is void if it is not placed in order for acceptance by **15 August 2019**.

Examination

Examination has been performed on the most recent specification and in consideration of the documents listed below

- International Preliminary Report on Patentability

Notice under the GPPH Pilot Programme

Unless an objection has been made in this report that the invention so far as claimed in a claim is not patentable, then the Commissioner is satisfied, on the balance of probabilities and at the date of this

report, that the invention claimed in that claim is patentable in accordance with section 14 of the New Zealand Patents Act 2013.

1. **Section 61 – Basic application not first application for protection**

   The present application claims priority from the basic application 62/253,042 dated 09 November 2015 and 62/399,999 dated 26 September2016. However, it appears that the claimed subject matter of the present application was first disclosed by the Applicant in the basic application number 62/015,245 dated 20 June2014, corresponding to WO 2015/196116 (D1).

   62/015,245 discloses combinations of the compound of Formula I with tenofovir alafenamide and emtricitabine. 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 [0058]). Tenofovir alafenamide is present in amounts of 5-30 mg and emtricitabine is present at 200 mg (see [0096]).

   The present application is considered to be filed after the expiration of 12 months from the day on which a basic application was first made in the convention country in respect of the invention. Either the claims should be amended such that they no longer encompass the subject matter disclosed in the first basic application, or else the application can be converted to a nonconvention application with the accompanied loss of the right of priority.

   For the purposes of this examination, the application is considered to take the priority date of the international filing date, 08 November 2016. Should priority be restored, D1 will form part of prior art base under section 8(2).

2. **Section 14(b)(i) – Invention claimed forms part of prior art base, section 8(1)**

   In view of the loss of priority as discussed in item 1 the subject matter of the claims 1-3, 6-8, 11-15, 34-35 and 38-39 is not novel having regard to the following material from the prior art base:

   - WO 2015/196116 (D1)

   The term "obtainable" in claims 34-35 is non-limiting on the scope of the claims. The first and second layers of claims 34-35 are therefore not defined and cannot be acknowledged to be novel.

   D1 discloses combinations of the compound of Formula I with tenofovir alafenamide and emtricitabine. 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 [0058]). Tenofovir alafenamide is present at 5-30 mg and emtricitabine is present at 200 mg (see [0096]). The combination may be administered as a tablet.

   In view of D1, claims 1-3, 6-8, 11-15, 34-35 and 38-39 lack novelty.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1563 of 1915

3. **Section 14(b)(ii) – Invention claimed is obvious having regard to the prior art base, section 8(1)**

The invention claimed in claims 1-51 does not involve an inventive step, being obvious to a person skilled in the art having regard to the following material of the prior art base:

- WO 2015/196116 (D1)
- WO 2014/100323 (D2)
- WO 2014/100323 (D3)

3.1 Claims 1-3, 6-8, 11-15, 34-35 and 38-39 lack novelty over D1, so cannot be acknowledged to involve an inventive step. Furthermore, the remaining claims do not appear to relate to a surprising technical effect, and are therefore attainable to a skilled person by routine trial and error and non-inventive workshop modification. Consequently, all claims are considered obvious.

3.2 Should the priority of the claims be restored, WO 2014/100323 (D2) will be considered the closest prior art. D2 discloses a tablet as a single dosage form comprising a compound of formula (I). The compound of formula (I) is shown to be therapeutically effective in the treatment of HIV. Its combination with another anti-HIV agent including tenofovir alafenamide and emtricitabine is also suggested in D2.

D3 teaches that tenofovir alafenamide and emtricitabine are also known to be effective in the treatment of HIV when used alone or in combination with other anti-HIV agents in a single dosage form.

It is not considered inventive to combine two or more active ingredients for treating a particular disease in the case where said two or more active agents are each known to be therapeutically effective alone in treating said particular disease. An inventive step may be acknowledged should such a combination display a surprising technical effect, such as synergy. However, the specification provides no such evidence of synergy. Consequently, all claims are considered obvious.

4. **Section 39(2)(a) – Claims do not relate to one invention only**

Claims 40-41 are not unified with the rest of the claims. Claims are unified where they share common novel subject matter or share special technical features. The only feature that claims 40-41 share with the rest of the claims is the presence of the compound of Formula I. However, this feature was known at the time of filing, having being disclosed by WO 2014/100323 (D3).

The claims may be restricted to claim only one invention, and further divisional applications in which the other inventions are claimed may be filed and accorded the date and priorities of this application.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1564 of 1915

5. **Section 39(2)(b) – Claims not clear**

5.1 Claims 4-5, 40, 42-44, 46-48 and 50 are not clear. The term "about" renders the scope of the claims ambiguous and unclear.

5.2 Claims 34-35 are not clear. The term "obtainable" is non-limiting on the scope of the claims. The first and second layers of claims 34-35 are therefore not defined.

5.3 Claims 28-30 and 46-51 are not clear. These claims are defined by a result to be achieved, and appear to lack the technical features necessary for achieving said result. A person skilled in the art, reading the specification should not have to perform undue experiments in order to determine the scope of the claim.

6. **Section 39(2)(b) – Claims not concise**

6.1 Claims 7-9, 11-12, 16 and 43-44 are not concise as they fall wholly within the scope of independent claim 1.

6.2 Claims 49-51 are not concise as they fall wholly within the scope of independent claim 46.

A claim that falls wholly within the scope of another claim should not be presented as an independent claim, but instead should be made dependent on a broader claim.

7. **Section 16(2) – Method of treatment of human beings by surgery or therapy**

Claim 39 that is directed to methods of treatment of human beings by therapy is not eligible for grant of a patent.

8. **Regulation 33 – Abstract not suitable**

The abstract does not indicate the principal use or uses of the invention.

Further, the abstract drawing should be replaced with an image of a compound of Formula I to supplement the abstract.

9. **Section 73 – Notice of entitlement not filed**

A notice of entitlement has not been filed. If the notice is not filed before the expiry of the period prescribed under section 71 the application will be void.

If you wish to file a notice of entitlement, please follow the steps below:

- Log on to the IPONZ case management facility.
- Select Maintain a Patent from the left hand menu of your Inbox. The Request Patent Change page will display. Select Amendment/Correction of Error.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1565 of 1915

- The Search Patent Cases screen displays. Search for the patent case that you wish to amend. Once you have identified the correct case, check the radio button to the left of that case number to select it. (Do not click on the case number itself.) Then click the Select button.
- In the Type of Amendment field, select Voluntary Amendment.
- Upload your Notice of Entitlement in the Additional Documents field at the bottom of the page.
- Select Submit.

If you are filing the notice of entitlement as part of a task without making a substantive response to the objections in this report, you may select Respond to Examination Issues Later after submitting your file(s). This will allow you to provide a substantive response to the examination report at a later date.

Yours faithfully

Matthew Allan
Patent Examiner
DDI: +64 4 8965382
For the Commissioner of Patents

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1566 of 1915

Australian Government
IP Australia

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5 November 2018

Examination report No. 1 for standard patent application

Davies Collison Cave Pty Ltd
Level 15
1 Nicholson Street
MELBOURNE VIC 3000
Australia

Your reference	35283360/MJC
Application number	2016354007
Applicant name	Gilead Sciences, Inc.
Earliest priority date	09 November 2015

Final date for acceptance:	**5 November 2019**
Date of this report:	5 November 2018
Examination request date:	26 April 2018

Dear Davies Collison Cave Pty Ltd,

Your application has been examined under *section 45 of the Patents Act 1990*. I consider that this application does not meet the requirements of the Act because there are issues with the application that are explained in the report details.

You have **12 months** from the date of this report to overcome all my objection(s) otherwise this application will lapse.

You will also need to pay any annual continuation fees that apply. Your next continuation fee is due on **8 November 2020**.

NOTE: There is a current postponement of acceptance in place. If you overcome all other objections before the expiration of that postponement, the Commissioner will only accept the application at that time if you have filed a clear and unambiguous statement requesting the withdrawal of that postponement. Otherwise, a further adverse report will be issued.

Details of this patent application can be viewed on AusPat, our Australian patent search database.

Yours sincerely,

Thomas Case
Section: CHEM 5 - PHARMACEUTICALS
Phone: (612) 6283 2656

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1567 of 1915

Your reference	35283360/MJC
Application number	2016354007

Report details

Basis of the report

In examining this application I have considered:

- the PCT pamphlet as originally filed

Summary of novelty, inventive step and patentable subject matter

	Satisfy requirements?	*Claim numbers*
Novelty/inventive step	**Yes**	NONE
	No	1-51
Patentable subject matter	**Yes**	1-51
	No	NONE

Detailed objections on issues that have been identified

Documents cited or considered relevant

D1 : WO 2015/196116 A1 (GILEAD SCIENCES, INC) 23 December 2015 [1]
Category: **P,X** Claims: 1-6, 8, 11-15, 38-42, 44, 46-51

D2 : WO 2015/196137 A1 (GILEAD SCIENCES, INC) 23 December 2015 [1]
Category: **P,X** Claims: 1-6, 8, 11-15, 38-42, 44, 46-51

D3 : WO 2014/100323 A1 (GILEAD SCIENCES, INC) 26 June 2014 [1]
Category: **X** Claims: 34
Category: **Y** Claims: 1-51

D4 : WO 2013/116720 A1 (GILEAD SCIENCES, INC) 08 August 2013 [1]
Category: **X** Claims: 35
Category: **Y** Claims: 1-51

D5 : WO 2015/022351 A1 (RATIOPHARM GMBH) 19 February 2015 [1]
Category: **Y** Claims: 1-51

D6 : "Gilead and Tibotec finalize agreement on single-tablet HIV regimen", Thomson Reuters Drug News, (2011-11-17), URL: https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_ficha_ref?p_ref_id=1729357, (2013-02-01) [1]
Category: **Y** Claims: 1-51

[1] Cited in WO 2017083304

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1568 of 1915

Note that this report has cited non-patent literature document/s. Copies of non-patent literature document/s can be requested for a fee (see *Patent Regulations, schedule 7, fee item 233 and 234*) through online services.

Please provide the citation details and associated patent application number with your request. Note that because of copyright restrictions we can only provide copies of hard copy books, journals and newspapers (see the Australian Patent Office Manual of Practice and Procedure at part 2.13.14 Copying of Material and Copyright Implications). However copies of any remaining documents should be readily obtainable from known electronic database sources.

Special categories of cited documents:

X: The claimed invention cannot be considered novel under *subsection 7(1)* in light of the document and/or cannot be considered to involve an inventive step under *subsection 7(2)* of the Act in light of the common general knowledge considered together with the document.
Y: The claimed invention cannot be considered to involve an inventive step under *subsection 7(2)* of the Act in light of the common general knowledge when considered together with a combination of the document and one or more other such documents.
P: Document published prior to the filing date but on or after the priority date claimed

Novelty and inventive step

1 Claims 1-6, 8, 11-15, 38-42, 44, 46-51 are not novel when compared D1. Although D1 was published later than the priority date of the present claims its information has an earlier priority date than the present claims.

D1 discloses compositions comprising compounds of Formula I and II (the sodium salt) ([0002]) for the treatment of HIV ([0008-0014)]. D1 discloses compositions comprising 25-100 mg Formula II, 5-30 mg tenofovir alafenamide and 200 mg emtricitabine ([0058, 0096]; claims 12-18). D1 discloses pharmaceutical compositions that are solid oral dosage forms such as tablets and capsules ([0065]). D1 discloses compositions comprising microcrystalline cellulose and croscarmellose sodium as excipients ([0145]).

A similar objection also applies in light of D2.

2 Claim 34 is not novel or inventive in light of D3 and claim 35 is not novel or inventive in light of D4.

Note that these claims are directed to the specific layer and do not comprise the other layer of the tablet. A single dosage form is within the scope of these claims.

D3 discloses single dosage forms comprising compounds of Formula I (see page 40; example 42). D4 discloses a monolayer and bilayer tablet comprising in one single layer tenofovir alafenamide and emtricitabine compressed together.

3 Claims 1-51 are not inventive in light of D3 when combined with anyone of D4 or D5.

D3 discloses compounds of Formula I and II in the treatment of HIV (see abstract, example 42) and suggests combination therapy with other anti-HIV agents such as emtricitabine and

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1569 of 1915

tenofovir alafenamide (page 38).

D3 does not directly disclose the solid dosage form as defined in the present claims comprising compounds of Formula I, emtricitabine and tenofovir alafenamide. D4 and D5 both disclose compositions comprising combinations of emtricitabine and tenofovir alafenamide.

It is noted that the application has not described any unexpected or surprising effect such as synergy resulting from the specific combination of Formula I, emtricitabine and tenofovir alafenamide. It does not involve an inventive step to combine multiple agents known for treating the same condition into one composition. Therefore, it would be obvious to the person skilled in the art to combine the known anti-HIV drugs of Formulas I/II (D3) with other known anti-HIV drugs emtricitabine and tenofovir alafenamide (D4, D5) into one formulation.

Claim features relating to specific formulation options such: as coated tablets; multilayered tablets; specific excipients including croscarmellose sodium, magnesium stearate, microcrystalline cellulose; and particular concentrations of active ingredients are not considered to provide an inventive step over the prior art. Such features are obvious to the person skilled in the art as they relate to routine or standard pharmaceutical formulation options known in the art.

Please note that IP Australia was unable to obtain D6. It appears that D6 provides a disclosure similar to that of D4 and D5 and it is therefore likely a similar objection would be taken in light of D3 when combined with D6. The applicant would assist the examination process by providing a copy of D6 with their response.

END OF REPORT

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1570 of 1915

TECHNICAL REPORT
INF/SNP/DGE/DPI/ADP N° 0433/2018
SNP/2018-06970

Dear Sirs
GILEAD SCIENCES, INC.
SP260-2016
Publication 12193

Reference: **Technical Report N°337/2018**

"PHARMACEUTICAL FORMULATIONS"

As a result of the substantive examination, carried out based on Article 45 of Decision 486 of the Commission of the Andean Community, the following is communicated:

- **Documents studied**

  - Patent Application SP260-2016 dated 09/11/2016.
  - WO 2014/100323 A1 "Polycyclic-carbamoylpyridone compounds and their pharmaceutical use".
  - Set of claims dated May 29, 2018.

- **Patentability requirements**
(Clarity, Sufficiency, Concision, Unity of invention and Patentability)

Art. 30 Decision 486

- Claims 1 and 2 lack conciseness when mentioning "salt", a general term that does not allow determining the scope of protection of the claim and that gives many possibilities that are not supported by the examples of the description.
  Regarding the salt, this is formed by cations (positively charged ions) linked to anions (negatively charged ions), the claim does not indicate what is the cationic and anionic part of the claimed compounds.
- Claim 4 lacks conciseness when mentioning "less than about", a general expression that does not allow determining the scope of protection of the claim and that gives many possibilities that are not supported by the examples of the description. It lacks clarity because it characterizes the tablet by a parameter. In addition, it gives many possibilities of weight which causes that the matter to be protected is not clear.
- Claim 5 would be convenient to place endpoint.
- Claims 6 and 7 lack of conciseness when mentioning "less than approximately", "salt" general expressions that do not allow determining the scope of protection of the claim and that give many possibilities that are not supported in the examples of the description.

- **Determination of the State of the Art**
(Novelty, Inventive Step and Industrial Application)
Art 14, Art 16 y Art 18 Decision 486

- The following are the RELEVANT DOCUMENTS that affect the inventive step of the application.

No.	DOCUMENT	TITLE	PUBLICATION DATE
D1	WO 2014/100323 A1	"Polycyclic-carbamoylpyridone compounds and their pharmaceutical use"	22/06/2000

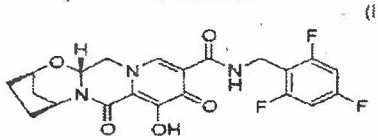
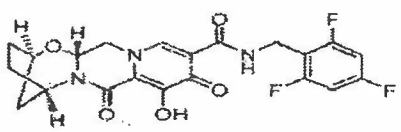
No.	DOCUMENT	AFFECTED CLAIMS	DOCUMENT CATEGORY	AFFECTED REQUIREMENT
D1	WO 2014/100323 A1	1 to 8	X/D	INVENTIVE STEP

X: means the importance of the document alone for the possibility of revoking the patent application by the concept of novelty or inventive level.
Y: means the importance of the document that combined with another document, can affect the feature of inventive step of the patent application.
A: means that not being important for the novelty and inventive step examination is referred as a document related with the patent application.
O: referred to non-written disclosure.
D: are the document cited in the specification of the invention.
P: are the documents published between the filing date of the application and the recognized priority date
E: prior document, but published after the filing date of the application
F: designates the document published abroad, application or patent, corresponding to the application under examination
G: designates patent family members

- D1 discloses compounds for use in the treatment of human immunodeficiency virus (HIV) infection (abstract). D1 teaches pharmaceutical compositions comprising the compound of formula I of the present application, or a pharmaceutically acceptable salt thereof (page 37). The additional therapeutic agent is selected from one or more of: emtricitabine and tenofovir alafenamide fumarate (page 38). D1 teaches that the pharmaceutical composition can be in the form of a tablet and that the compound of formula I is in an amount of 50 mg (pages 35-36).

  In the following table the similarities between the compounds of D1 and claim 1 of the application are shown:

TABLE No. 1

Application	D1
1. A tablet comprising 50 mg of the compound of formula I (I) 	Tablet comprising 50 mg of the compound:  Compound 42
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.	emtricitabine, tenofovir alafenamide fumarate

As can be seen in table N° 1, D1 and the application disclose tablets comprising 50 mg of the compound of formula I, emtricitabine and tenofovir alafenamide fumarate. The difference between D1 and the application is that D1 does not disclose the amounts of emtricitabine and tenofovir alafenamide, however, this difference does not demonstrate an unexpected technical effect with respect to the disclosure of D1. Likewise, it is necessary to indicate that it is common practice to combine two or more active ingredients that are useful in the treatment of the same disease and it is also known that

said combination will have a better therapeutic effect than a single drug. The compound of formula I is known to be therapeutically effective in the treatment of HIV and the combination of this compound with other agents useful for the treatment of HIV such as teneofovir alafenamide and emtricitabine is suggested in D1.
Furthermore, the present application does not demonstrate that the combination of the compound of formula I, tenofovir alafenamide and emtricitabine has a synergistic therapeutic effect, therefore, the combination of the three drugs useful in treating HIV is considered obvious.
So in light of D1 and in the absence of an unexpected technical effect attributed to the technical features of claim 1, the matter claimed by claims 1 to 8 is considered obvious and without inventive step.

- **Conclusions**

  - Patent Application N° 260-2016 does not comply with Articles 14, 18 and 30 of CAN Decision 486 as to clarity, conciseness, support and inventive step.

In compliance with Article 45 of Decision 486 of the Andean Community Commission, it is indicated that this action must be responded within the term of sixty (60) days counted from the date of notification of this communication. In the event of failure to respond to this request, or if in spite of the answer the impediments to the concession continue, the patent will be denied.

La Paz, September 17, 2018
Illegible signature

Pharmaceutical Chemist Deisy Jimenez Gomez
Patent Examiner
SENAPI
Appointments (Fridays 9 am – 11 am)

PUBLICATION N. 12193

To, September 18, 2018

In accordance with Technical Report No. 337/2018, notify the applicant in order to correct the observations made by the examiner of the area, or with the formalities of Law.

Pablo G. Arocena Cortes
RESPONSABLE DEL AREA DE PATENTES
DIRECCION DE PROTECCION INDUSTRIAL
SENADI

SERVICIO [illegible] PROPIEDAD INTELECTUAL
Copia de [illegible] Marcos Morado D.
Expediente [illegible] 11991
Fecha: 29 [illegible] 17:50

INFORME TÉCNICO
INF/SNP/DGE/DPI/ADP N° 0433/2018
SNP/2018-06970

Señores:
GILEAD SCIENCES, INC.
SP260-2016
Publicación 12193

Ref. **Informe técnico N°337/2018**

"FORMULACIONES FARMACEUTICAS"

Como resultado del examen de fondo, realizado con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

- **Documentos estudiados**

  - Solicitud de Patente SP260-2016 de fecha 09/11/2016.
  - WO 2014/100323 A1 "Polycyclic-carbamoylpyridone compounds and their pharmaceutical use".
  - Pliego reivindicatorio de fecha 29 de mayo de 2018.

- **Requisitos de Patentabilidad**

  (Claridad, Suficiencia, Concisión, Unidad de invención y Patentabilidad)

  Art. 30 Decisión 486

  - Reivindicaciones 1 y 2 carecen de concisión al mencionar "sal", término general que no permite determinar el alcance de protección de la reivindicación y que da muchas posibilidades que no están sustentadas en los ejemplos de la descripción.
    En cuanto a la sal ésta está formada por cationes (iones con carga positiva) enlazados a aniones (iones con carga negativa), la reivindicación no indica cual es la parte catiónica y aniónica de los compuestos reclamados.
  - Reivindicación 4 carece de concisión al mencionar "menos que aproximadamente", expresión general que no permite determinar el alcance de protección de la reivindicación y que da muchas posibilidades que no están sustentadas en los ejemplos de la descripción. Carece de claridad porque caracteriza al comprimido por un parámetro. Además, da muchas posibilidades de peso lo cual provoca que no quede clara la materia que se pretende proteger.
  - Reivindicación 5 sería conveniente colocar punto final.
  - Reivindicaciones 6 y 7 carecen de concisión al mencionar "menos de aproximadamente", "sal" expresiones generales que no permiten determinar el alcance de protección de la reivindicación y que dan muchas posibilidades que no están sustentadas en los ejemplos de la descripción.

- **Determinación del Estado de la Técnica**
  (Novedad, Nivel Inventivo y Aplicación Industrial)

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1575 of 1915

Art. 14, Art.16 y Art. 18 Decisión 486

- A continuación se detallan los DOCUMENTOS RELEVANTES que afectan el nivel inventivo de la solicitud.

No.	DOCUMENTO	TITULO	FECHA DE PUBLICACIÓN
D1	WO 2014/100323 A1	"Polycyclic-carbamoylpyridone compounds and their pharmaceutical use"	22/06/2000

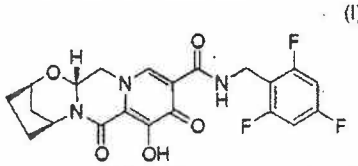
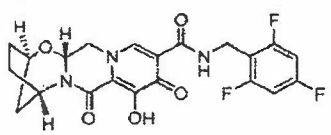
No.	DOCUMENTO	REIVINDICACIONES AFECTADAS	CATEGORÍA DEL DOCUMENTO	REQUISITO QUE AFECTA
D1	WO 2014/100323 A1	1 a 8	X/D	Nivel Inventivo

X: significa la importancia del documento por si solo para la posibilidad de revocar la solicitud de patente por el concepto de novedad o nivel inventivo.
Y: significa la importancia del documento que, combinado con otro, puede afectar la característica del nivel inventivo de la solicitud de patente.
A: significa que no siendo importante para la evaluación de la novedad y para la del nivel inventivo está referida como documento relacionado a la solicitud de patente.
O: referido a divulgación no escrita
D: son los documentos que se citan en la descripción de la invención
P: son los documentos publicados entre la fecha de presentación de la solicitud y la fecha de prioridad reconocida
E: documento anterior, pero publicado después de la fecha de la presentación de la solicitud
F: designa el documento publicado en el extranjero, solicitud o patente, que corresponde a la solicitud que se está examinando
G: designa a patentes miembros de la familia

- D1 divulga compuestos para el uso en el tratamiento de la infección del virus de inmunodeficiencia humana (HIV) (resumen). D1 enseña composiciones farmacéuticas que comprenden el compuesto de fórmula I de la presente solicitud, o una de sus sales farmacéuticamente aceptables, en combinación con uno o más agentes terapéuticos adicionales, y un portador, diluyente o excipiente farmacéuticamente aceptable (página 37). El agente terapéutico adicional se selecciona de uno o más de: emtricitabina y tenofovir alafenamida fumarato (página 38). D1 enseña que la composición farmacéutica puede estar en forma de un comprimido y que el compuesto de fórmula I está en una cantidad de 50 mg (páginas 35 y 36).

En la tabla N°1 se muestran las similitudes entre D1 y la reivindicación 1 de la presente solicitud:

TABLA N°1

Solicitud	D1
1. Un comprimido que comprende 50 mg del compuesto de Fórmula I: (I) 	Comprimido que comprende 50 mg del compuesto:  Compound 42
una sal farmacéuticamente aceptable del mismo, 25 mg de tenofovir alafenamida o una sal farmacéuticamente aceptable de la misma, y 200 mg de emtricitabina o una sal farmacéuticamente aceptable de la misma.	emtricitabina, tenofovir alafenamida fumarato.

AREA DE PATENTES V°B° SENAPI

Como se puede observar en la tabla N°1, D1 y la solicitud divulgan comprimidos que comprenden 50 mg del compuesto de Fórmula I, emtricitabina y tenofovir alafenamida fumarato. La diferencia entre D1 y la solicitud es que D1 no divulga las cantidades de emtricitabina y tenofovir alafenamida, sin embargo, esta diferencia no demuestra un efecto técnico inesperado respecto a la divulgación de D1. Asimismo, es necesario indicar que es práctica común la combinación de dos o más principios activos que son útiles en el tratamiento de una misma enfermedad y también es conocido que dicha combinación tendrá un mejor efecto terapéutico que un solo fármaco. El compuesto de fórmula I es conocido porque es terapéuticamente efectivo en el tratamiento de VIH y la combinación de este compuesto con otros agentes útiles para el tratamiento de VIH tal como tenofovir alafenamida y emtricitabina es sugerido en D1.
Además, la presente solicitud no demuestra que la combinación del compuesto de fórmula I, tenofovir alafenamida y emtricitabina presente un efecto terapéutico sinérgico, por lo tanto, la combinación de los tres fármacos útiles para tratar VIH se considera obvia.
Por lo que a la luz de D1 y en ausencia de un efecto técnico inesperado atribuido a las características técnicas de la reivindicación 1, la materia reclama por las reivindicaciones 1 a 8 se considera obvia y sin nivel inventivo.

- **Conclusiones**

  - La Solicitud de Patente N°260-2016 no cumple con los Artículos 14, 18 y 30 de la Decisión 486 de la CAN en cuanto a claridad, concisión, sustento y nivel inventivo.

En cumplimiento del Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

La Paz, 17 de septiembre del 2018

Lic. Q.F. Deisy Jiménez Gomez
EXAMINADORA DE PATENTES
"SENAPI"

Entrevistas (viernes 9 am – 11 am)

PUBLICACIÓN Nro. 12193

A, 18 de septiembre de 2018

En atención al Informe Técnico Nro. 337/2018, notifíquese al solicitante a efectos de subsanar las observaciones realizadas por el examinador del área, sea con las formalidades de Ley.

DVG

Pablo G. Aracena Vargas
RESPONSABLE DEL AREA DE PATENTES
DIRECCIÓN DE PROPIEDAD INDUSTRIAL
SENAPI

SERVICIO NACIONAL DE PROPIEDAD INTELECTUAL
Copia de leyenda Marcos Mercado
Expediente No. 12193
Fecha: 12/10/18 11:00

EDICT N° 506

In the present application of registry N° 92163-01 dated May 3, 2018 of the INVENTION PATENT named THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN INMUNIODEFICENCY VIRUS, property of GILEAD SCIENCES, INC. presented by its legal representative BENEDETTI STUDIO, the following has been issued:

MINISTRY OF COMMERCE AND INDUSTRIES

The General Direction of the Industrial Property Registry

PANAMA, July 17, 2018

Once issued the REPORT ON THE STATE OF THE ART of the application of INVENTION PATENT N° 92163-01, named THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN INMUNIODEFICENCY VIRUS, the transfer is processed and is ordered to be published in the BORPI, prior payment of the corresponding fees for which the term of six (6) months extendible to additional (6) months is granted, at the request of the applicant, from the date of notification.

DECLARATION OF FUNDING: Articles 45 and 49 of Law No. 35 of May 10, 1996, article 35 of Executive Decree No. 7 of February 17, 1998.

NOTIFY AND COMPLY.... (FDO) DESIDERIO DE LEON, **head of the Invention Patent Department ... (FDO) secretary ad-hoc**

Therefore, the present notification edict is fixed, at a public and visible place of the General Direction of the Industrial Property Registry of the Ministry of Commerce and Industries, for the term of five working days counted from October 3, 2018.

Illegible signature

DESIDERIO DE LEON

Chief of the invention Patents Department

MINISTRY OF COMMERCE AND INDUSTRIES

PANAMA, October 3, 2018

Once issued the REPORT ON THE STATE OF THE ART of the application of INVENTION PATENT N° 92163-01, named THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN INMUNODEFICENCY VIRUS, the transfer is processed and ordered to be published in the BORPI, prior payment of the corresponding fees for which the term of six (6) months extendible to additional (6) months is granted, at the request of the applicant, from the date of notification.

DECLARATION OF FUNDING: Articles 45 and 49 of Law No. 35 of May 10, 1996, article 35 of Executive Decree No. 7 of February 17, 1998.

NOTIFY AND COMPLY

Illegible signature

DESIDERIO DE LEON

Chief of the invention Patents Department

Ministry of Commerce and Industries General Direction of Industrial Property Registry Patents Department	PATENT OF INVENTION
State of Art Report	Application No.: 92163-01

Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN INMUNODEFICIENCY VIRUS
Application date: May 3, 2018
Applicant: GILEAD SCIENCIES, INC.
Attorney: BENEDETTI STUDIO
Examiner: VIELKA YASMINA JIMENEZ RODRIGUEZ
Priorities from: United States of America Application No.62/253,042 of November 9, 2015
United States of America Application No.62/399,999 of September 26, 2016

Category of the cited documents

A	Document that describes the general state of art, considered as not particularly relevant
D	Document cited in the application
E	Prior document published on the date of international filing or at a later date.
L	Document that may raise doubts about a priority claim or that is cited to determine the date
O	Oral disclosure, to a use, to an exhibition or any other means
P	Document issued before the international filing date but after the claimed priority date
T	Document cited to understand the theory or principle on which the invention is based
X	Particularly relevant document, the claimed invention cannot be considered novel or that implements an inventive step by reference to the document considered in isolation.
Y	Particularly relevant document; the claimed invention cannot be considered to imply an inventive step when the document is associated with one or more of the same nature, a combination is apparent to one skilled in the art.
&	Document of the same patent family

Data base	Observation
ESPACENET.COM	INTERNET DATA BASE

Consulted Documents.

Categories	Documents	Type Claims
X,P	WO 2015/191116 A1 (GILEAD SCIENCES INC [US] DECEMBER 23, (2015 2015-13-23) ABSTRACT; CLAIMS 1, 12, 18-21	**1-10**
X, P	WO 2015/196137 (GILEAD SCIENCES INC [US] DECEMBER 23, 2015 (2015-13-23) ABSTRACT; CLAIMS 1, 38, 44-48	**1-10**
Y	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) JUNE 26, 2014 (2014-06-26) CITED IN THE APPLICATION ABSTRACT; CLAIMS 1, 32, 33-46; EXAMPLES 104-107; COMPOUNDS 42, 45 PAGE 36, PARAGRAPH 12-13 PAGE 37, PARAGRAPH 8-12 PAGE 38, LINE 14, 20	**1-10**
Y	WO 2013/116720 A1(GILEAND SCIENCES INC [US]) AUGUST 8 2013 (2013-08-08) ABSTRACT; CLAIMS 21-32 PAGE 82, LINES 13-15 PARAGRAPHS [0337], [0338], [0342], [0344] – [0345], [0349], [0355] PARAGRAPHS [0340], [0347]	**1-10**

Ministry of Commerce and Industries General Direction of Industrial Property Registry Patents Department	PATENT OF INVENTION
State of Art Report	Application No.: 92163-01

Title: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN INMUNODEFICIENCY VIRUS
Application date: May 3, 2018
Applicant: GILEAD SCIENCIES, INC.
Attorney: ESTUDIO BENEDETTI
Examiner: VIELKA YASMINA JIMENEZ RODRIGUEZ
Priorities from: United States of America Application No.62/253,042 of November 9, 2015
United States of America Application No.62/399,999 of September 26, 2016

Categories	Documents	Claims
Y	WO 2015/022351 A1 (RATIOPHARM GMBH [DE]) FEBRUARY 19 2015 (2015-02-19) ABSTRACT; CLAIMS 1-6, 8-10, 12-15 PAGE 18, LINES 7-22 PAGE 19, LINES 3-12 PAGE 19, LINE 30 – PAGE 20, LINE 12 PAGE 22, LINE 31 – PAGE 15, LINE 17	**1-10**
Y	"GILEAD AND TIBOTEC FINALIZE AGREEMENT ON SINGLE-TABLET HIV REGIMEN", THOMSON REUTERS DRUG NEWA, NOVEMBER 17, 2011 (2011-11-17), XP055052007 RETRIVED FROM THE INTERNET; URL: HTTPS://INTEGRITY.THOMPSON-PHARMA.COM/INTEGRITY/XMLXSL/PK_REF_LIST.XML_SHOW_FICHA_REF?P_REF_ID=1729357 [RETRIEVED ON 2013-02-01] ABSTRACT	**1-10**

Claims Observations:

SIX (6) DOCUMENTS OF PARTICULAR RELEVANCE WERE FOUND WITHIN THE STATE OF THE ART WHEREIN THE CLAIMED INVENTION CANNOT BE CONSIDERATED TO IMPLY INVENTIVE STEP. THE APPLICANT HAS THE RIGHT TO MODIFY THE CLAIMS THAT ARE AFFECTED BY THIS REPORT. THESE MODIFICATIONS, FOR NO REASON, SHALL CONTAIN ADDITIONAL OR MORE EXTENSIVE CLAIMS THAN THE CLAIMS CLAIMED IN THE ORIGINAL APPLICATION.

General observation:

THIS REPORT WAS BASED IN THE PCT INTERNATIONAL SEARCH REPORT OF THE EUROPEAN PATENT OFFICE UNDER THE N° WO 2017/083304

SIGNATURE ILLEGIBLE

Examiner's signature

SIGNATURE ILLEGIBLE

DESIDERIO DE LEON
Head of the Invention Patent Department

Performed on October 3, 2018

EDICTO N° 506

En la presente solicitud de registro N° 92163-01 de fecha 2 de mayo de 2018 de la PATENTE DE INVENCION denominada COMPOSICIONES TERAPÉUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA, propiedad de GILEAD SCIENCES, INC. presentada por su apoderado legal ESTUDIO BENEDETTI se ha dictado la siguiente providencia:

MINISTERIO DE COMERCIO E INDUSTRIAS

Dirección General del Registro de la Propiedad Industrial

PANAMA, 3 de octubre de 2018.

Realizado el INFORME SOBRE EL ESTADO DE LA TÉCNICA de la solicitud de PATENTE DE INVENCION N° 92163-01 denominada COMPOSICIONES TERAPÉUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA, se corre el traslado y se ordena su publicación en el BORPI, previo pago de las tasas correspondientes para lo cual se le concede el término de seis (6) meses prorrogables por seis (6) meses adicionales a petición del solicitante, contados a partir de la notificación.

FUNDAMENTO DE DERECHO: Artículos 45 y 49 de la Ley N° 35 de 10 de mayo de 1996, articulo 35 del Decreto Ejecutivo N° 7 del 17 de febrero de 1998.

NOTIFIQUESE Y CUMPLASE,... (FDO) DESIDERIO DE LEON, Jefe del Departamento de Patentes de Invención,... (FDO) , secretario ad-hoc

Por lo tanto se fija el presente edicto de notificación a las partes, en lugar público y visible de la Dirección General del Registro de la Propiedad Industrial del Ministerio de Comercio e Industrias,por el término de cinco días hábiles contados a partir de 3 de octubre de 2018.

DESIDERIO DE LEON

Jefe del Departamento de Patentes de Invención

MINISTERIO DE COMERCIO E INDUSTRIAS

PANAMA, 3 de octubre de 2018.

Realizado el INFORME SOBRE EL ESTADO DE LA TÉCNICA de la solicitud de PATENTE DE INVENCION N° 92163-01 denominada COMPOSICIONES TERAPÉUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA, se corre el traslado y se ordena su publicación en el BORPI, previo pago de las tasas correspondientes para lo cual se le concede el término de seis (6) meses porrogables por seis (6) meses adicionales a petición del solicitante, contados a partir de la notificación.

FUNDAMENTO DE DERECHO: Artículos 45 y 49 de la Ley N° 35 de 10 de mayo de 1996, artículo 35 del Decreto Ejecutivo N° 7 del 17 de febrero de 1998.

NOTIFIQUESE Y CUMPLASE

DESIDERIO DE LEON

Jefe del Departamento de Patentes de Invención

Ministerio de Comercio e Industrias
La Dirección General del Registro de la Propiedad
IndustDepartamento de Patentes
Informe Del Estado De La Técnica

PATENTE DE INVENCION

Solicitud No: 92163-01

Título: COMPOSICIONES TERAPÉUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA

Fecha Solicitud: 3 de mayo de 2018

Solicitante: GILEAD SCIENCES, INC.

Abogado: ESTUDIO BENEDETTI

Examinador: VIELKA YASMINA JIMENEZ RODRIGUEZ

Prioridades de: Estados Unidos de América SOLICITUD No.62/253,042 DEL 9 de noviembre de 2015
Estados Unidos de América SOLICITUD No.62/399,999 DEL 26 de septiembre de 2016

Categoria de los Documentos Citados

A	Documento que define el estado general de la técnica no considerado como particularmente relevante.
D	Documento citado en la aplicación.
E	Documento anterior; pero publicado en la fecha de presentación internacional o en fecha posterior.
L	Documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de la publicación de otra cita o por una razón especial (como la indicada).
O	Docs que se refiere a una divulgación oral, a una utilización, a una exposición o cualquier otro medio.
P	Documento publicado antes de la fecha de presentación internacional; pero con posterioridad a la fecha de prioridad reivindicada.
T	Documento citado para entender el principio o teoría bajo la cual se desarrolla la invención.
X	Documento de particularmente relevante, la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.
Y	Documento de particular relevante: la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.
&	Documento de la misma familia de patentes.

Base de Datos	Observación
ESPACENET. COM	BASE DE DATOS DE INTERNET

Documentos Consultados.

Categorias	Documentos	Tipo Reivindicaciones
X,P	WO 2016/196116 A1 (GILEAD SCIENCES INC [US] 23 DECEMBER 2016 (2016-12-23) ABSTRACT; CLAIMS 1, 12, 18-21	1-10
X,P	WO 2016/196137 A1 (GILEAD SCIENCES INC [US] 23 DECEMBER 2016 (2016-12-23) ABSTRACT; CLAIMS 1, 38, 44-48	1-10
X	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 JUNE 2014 (2014-06-26) CITED IN THE APPLICATION ABSTRACT; CLAIMS 1, 32, 33-46; EXAMPLES 104-107; COMPOUNDS 42, 45 PAGE 36, PARAGRAPH 12-13 PAGE 37, PARAGRAPH 8-12 PAGE 38, LINE 14, 20	1-10
Y	WO 2013/116720 A1 (GILEAND SCIENCES INC [US]) 8 AUGUST 2013 (2013-08-08) ABSTRACT; CLAIMS 21-32 PAGE 82, LINES 13-15 PARAGRAPHS [0337], [0338], [0342], [0344] - [0345], [0349], [0355] PARAGRAPHS [0340], [0347]	1-10

Ministerio de Comercio e Industrias
La Dirección General del Registro de la Propiedad
IndustDepartamento de Patentes
Informe Del Estado De La Técnica

PATENTE DE INVENCION

Solicitud No: 92163-01

Titulo: COMPOSICIONES TERAPÉUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA

Fecha Solicitud: 3 de mayo de 2018

Solicitante: GILEAD SCIENCES, INC.

Abogado: ESTUDIO BENEDETTI

Examinador: VIELKA YASMINA JIMENEZ RODRIGUEZ

Categorias	Documentos	Reivindicaciones
Y	WO 2015/022351 A1 (RATIOPHARM GMBH [DE]) 19 FEBRUARY 2015 (2015-02-19) ABSTRACT; CLAIMS 1-6, 8-10, 12-15 PAGE 18, LINES 7-22 PAGE 19, LINES 3-13 PAGE 19, LINE 30 - PAGE 20, LINE 12 PAGE 22, LINE 31 - PAGE 16, LINE 17	1-10
Y	"GILEAD AND TIBOTEC FINALIZE AGREEMENT ON SINGLE-TABLET HIV REGIMEN", THOMSON REUTERS DRUG NEWS, 17 NOVEMBER 2011 (2011-11-17), XP055052007 RETRIEVED FROM THE INTERNET: URL: HTTPS://INTEGRITY.THOMSON-PHARMA.COM/ INTEGRITY/XMLXSL/PK_REF_LIST.XML_SHOW_FICHA_REFFP_REF_ID=1729357 [RETRIEVED ON 2013-02-01] ABSTRACT	1-10

Observacion de Reivindicaciones:
SE ENCONTRARON SEIS (6) DOCUMENTOS DE PARTICULAR RELEVANCIA DENTRO DEL ESTADO DE LA TÉCNICA EN DONDE LA INVENCIÓN REIVINDICADA NO PUEDE CONSIDERARSE QUE IMPLIQUE UNA ACTIVIDAD INVENTIVA. EL TITULAR TIENE EL DERECHO DE MODIFICAR LAS REIVINDICACIONES QUE SE VEAN AFECTADAS POR ESTE INFORME. ESTAS MODIFICACIONES POR NINGÚN MOTIVO CONTENDRÁN REIVINDICACIONES ADICIONALES O CON MAYOR ALCANCE QUE LAS REIVINDICACIONES RECLAMADAS EN LA SOLICITUD ORIGINAL.

Observacion general:
ESTE INFORME FUE BASADO EN EL REPORTE DE BÚSQUEDA INTERNACIONAL PCT DE LA OFICINA EUROPEA DE PATENTE CON EL N° WO 2017/083304

Firma Examinador
Realizado el 3 de octubre de 2018

DESIDERIO DE LEON
Jefe del Departamento de Patentes de Invención

PAKISTANI & FOREIGN PATENTS DESIGNS & TRADE MARKS

TELEPHONES : (21) 3517 1442
(21) 3517 1443

Please update your record with our new Address, Telephone & Fax number

Remfry & Son
(FOUNDED 1827)
PATENT AND TRADE MARK ATTORNEYS
CMJ House
110-A, POPULAR AVENUE
Phase VI, D.H.A.
KARACHI - 75500
(PAKISTAN)

FAX : 92 (21) 3517 1443
WEB : www.remfrypakistan.com
E-MAIL : remfry@ptcl.net
remfry@cyber.net.pk

YOUR REF : **1147.P2PK**

OUR REF : **CMJ/ IC/ 18/ P-1770**

By E-Mail
of pages 3

13th November, 2018

GILEAD SCIENCES, INC.
333 Lakeside Drive
Foster City, CA 94404
U.S.A.

Attn: **Abigail Edesan**
Paralegal, IP

Dear Sirs,

Re: Gilead Ref. No. **1147.PK**
Prosecution : Examination Report
Pakistan Patent Application No.**696/2016**
filed on **9th November, 2016**
in the name of **Gilead Sciences, Inc.**
claiming priorities of **9th November, 2015** &
26th September, 2016 based on US Patent Application
Nos. **62/253,042** & **62/399,999** respectively
Our Ref: **CMJ/IC/18/P-1770**

We have to report that this application has been examined and we have now received first official action from the Patent Office. Objections raised by the Examiner are reproduced below for your consideration and instructions:

1. The invention defined in claims 1-51 does not involve an inventive step in the light of the following documents and open to objection under Section 9 of 'Patent Ordinance, 2000':

   a) WO2013116720

   b) WO2015022351

   c) WO2014100323

   d) "Gilead and Tibotec finalize agreement on single-tablet HIV regimen". Thomson Reuters Drug News, (2011-11-17), URL:https://integrity.thomsonpharma.com/integrity/xmlxsl/pk_ref_list.xml_show_ficha_ref_id=1729357.

C:\Users\ibrar.iqbal\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\QGV824QI\696-2016 (Gilead Sciences, Inc) - 0021.docx

YOUR REF : **1147.PK**
GILEAD SCIENCES, INC.
U.S.A.

2. Kit and package are not an allowable subject matter. The matter underlined in claims 36-37 may be amended to remove the objection.

3. Claim 39 is not for an invention within the meaning of Section 7(4)(c) of The 'Patent Ordinance, 2000' in that it amount to a method for treatment of human beings or animals which is not patentable. The claim should therefore be cancelled to meet the objection.

4. While resubmitting the amended documents in response to the examination report, you are requested to do so along with Form P-17 under Rule 28(8) of the 'Patents Rules, 2003'.

Our parawise comments and suggestions to the objection raised are as follows:

Re Para 1:

The Examiner has raised objection against novelty, and inventive step of this invention in view of its being anticipated by **above mentioned document,** we leave it to the applicant/inventors to rebut this objection or make necessary amendments to overcome the objection. We would appreciate receiving your remarks comments and instructions concerning the opposability of the documents cited.

Re Para 2:

Since kit and package claims are not allowable in Pakistan. We suggest claims **36** and **37** may be deleted without prejudice to overcome the objection.

Re Para 3:

- Claim 39 relates to a method of treatment of human-beings and as such is not allowable under Section 7(4)(c) of Patent Ordinance 2000. *"A Patent*

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YOUR REF : **1147.PK**
GILEAD SCIENCES, INC.
U.S.A.

shall not be granted for diagnostic, therapeutic and surgical methods for the treatment of human and animals".

- We suggest claim 39 may be deleted without prejudice to overcome the objection.

Re Para 4:

We will take care of these official requirements at our end.

Please note although as per 'Patent (amendment) Ordinance 2006' there is no deadline associated with the filing of response to the above official action. However, in order to place the above application in a condition for acceptance at an early date, we would request you to let us have your instructions for responding to the outstanding official action as early as possible.

As per the requirement of Section 20(2)(ii) and 20(3) of 'Patent Ordinance, 2000', please provide us copy of corresponding granted Patent relating to the same or essentially the same invention with claims substantially the same as in the present Pakistan Application as soon as available.

We would appreciate your acknowledging receipt of this email by return email.

Best Regards, we remain at disposal.

Yours faithfully,

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY
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Fax: +49 89 2399 4465

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Substantive Examiner
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Tel: +49 89 2399 - 8625

Application No.	Ref.	Date
16 798 063.0 - 1114	P072824EP	21.01.2019

Applicant
Gilead Sciences, Inc.

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 2 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter
EPO Form 2001 11.16TRI

Madalinska, K
Primary Examiner
For the Examining Division

Enclosure(s): 3 page/s reasons (Form 2906)

Registered letter
EPO Form 2001 11.16TRI

The examination is being carried out on the **following application documents**

Description, Pages

1-101 as published

Claims, Numbers

1-11 filed with entry into the regional phase before the EPO

Drawings, Sheets

1/6-6/6 as published

1 Reference is made to the following documents:

D1 WO 2015/196116 A1

D2 WO 2015/196137 A1

D3 WO 2014/100323 A1

D4 WO 2013/116720 A1

D5 WO 2015/022351 A1

D6 Thomson Reuters Drug News, 2011, XP055052007

2 Upon entering the European phase, the applicant filed amended set of claims 1-11.

Claim 1 finds the basis in the combination of claims 1, 2 and 6 as originally filed.

Claim 2 is based on the combination of claims 2 and 6 as originally filed..

Claims 3 is based on the combination of claims 2, 3 and 6 as originally filed.

Claim 4 is based on original claims 4 and on [0053] of the application as originally filed.

Claim 5 is based on claim 7 and [0012] as originally filed.

Claim 6 finds the basis in original claim 16 in combination with [0117], [0126] and [0209]-[0211] as originally filed.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1592 of 1915

Claims 7, 8, 9 are based on original claims 17, 26 and 27, respectively

Therefore, claims 1-9 meet the requirements of Article 123(2) EPC.

3 The examining division cannot, however, agree with the applicant that example 6 on page 90 provides the basis for the subject-matter of claim 10.

Whereas in example 6, the specific coating OPADRY II Brown 85F165072 was used a very specific amount, claim 10 claims a tablet comprising any coating at any amount.

Since there is no general teaching in the application as filed to support the generalisation of this example 6, the requirements of Article 123(2) EPC for claims 10-11 are not met.

4 The approximate term "about" used in claims 4 and 8-9 leaves the reader in doubt as to the exact meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 84 EPC).

5 According e.g. to [0343] and table of page 95 Example 9 focuses on the comparison of pharmacokinetics of bilayered tablet F7 and monolayer tablet F1 coadministered with emtricitabine+tenofovir alafenamide (F/TAF).

It is noted that [0038] of example 9 disclosed the administration of a bilayered formulation F2, and not a bilayered formulation F7.

Furthermore, according to [0337] of example 9 the formulation F7 is that of example 7. Example 7, however, relates to a single agent tablet F8.

There thus some inconsistencies in the descriptive part of example 9.

6 None of the documents in the prior art discloses a tablet comprising 50 mg of the compound of formula I, 25 mg of tenofovir alafenamide and 200 mg of emtricitabine.

7 The intermediate documents D1 and D2 disclose a pharmaceutical formulation , such as tablet, comprising a combination of a compound of formula I with tenofovir alafenamide and emtricitabine. The specific amounts of the active agents are however not disclosed in D1-D2.

Hence, claims 1-9 are considered as novelty within the sense of Article 54 EPC.

8 The presently claimed priority right appear to be valid. Thus, D1-D2 cannot be used in the assessment of inventive step of the presently claimed subject-matter.

9 The subject-matter of independent claim 1 is found inventive in view of the available priori art and the data provided and thus, meets the requirements of Article 56 EPC.

10 Were the above-mentioned objections under Article 123(2) and 84 EPC overcome by the suitable amendments, the subject-matter claimed would be considered as patentable.

11 The description should be adapted to the claims.

12 The examples 1 and 7 relating to a single agent tablet and example 2A relating to a tablet comprising emtricitabine and tenofovir alafenamide should be marked as reference examples.

13 If not yet done, D1-D6 should be identified in the description and the relevant background art disclosed therein should be briefly discussed (Rule 42(1)(b) EPC).

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1594 of 1915

Electronic Acknowledgement Receipt	
EFS ID:	35716915
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
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.P2C
Receipt Date:	12-APR-2019
Filing Date:	08-NOV-2016
Time Stamp:	17:34:44
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	Transmittal Letter	1147P2C_2019-04-12_Supplemental_IDS.PDF	94339 5150d4c55a5653714f3d765d998c4a83bc0 49c9e	no	2
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	1147P2C_2019-04-12_Supplemental_SB08.PDF	112374 add2eb6161011d62aa239d7096607afd0bcb729	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Non Patent Literature	NZ_ExaminationReport_for_741957.PDF	88459 5a005ad88d7a8d5465a0522aa2c95c8a3591e1414	no	5
Warnings:					
Information:					
4	Non Patent Literature	AU_ExamReport_2016354007_2019-11-05.PDF	274506 1da7a6788217c2c7df7c21a7bad01794f6ed05c5	no	4
Warnings:					
Information:					
5	Non Patent Literature	BO_Office_Action_SP260-2016.PDF	481644 038a1a4095646989e351c8f44e66813fc2793794	no	8
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
6	Non Patent Literature	PA_Office_Action_92163.PDF	1448628 12cd52d613c1066f118338afae87aa587427e9ea	no	8
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
7	Non Patent Literature	PK_Office_Action_6962016.PDF	234817 9ccc56a34409aa93a440d6c9eb74a43e19619543	no	3
Warnings:					
Information:					

8	Non Patent Literature	EP_Office_Action_167980630.PDF	191685 7cb5b8d202c94da1abf8478079244949105 08b53	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	2926452		

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 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.

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: April 12, 2019
Electronic Signature for Trent Bastian: /TRENT BASTIAN/

Docket No.: 1147.P2C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/346,335

Confirmation No.: 1307

Filed: November 8, 2016

Art Unit: 1615

For: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

Examiner: J. N. Worsham

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114 (37 C.F.R. § 1.97(b)(4)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance

with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to the patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

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.P2C from which the undersigned is authorized to draw.

Dated: April 12, 2019

Respectfully submitted,

Electronic signature: /Donna Johnson Gressler/
Donna Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 574-3000
Attorney For Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

25000 7590 05/02/2019

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

EXAMINER	
WORSHAM, JESSICA N	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 05/02/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	08/02/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1600 of 1915

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25000 7590 05/02/2019
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	08/02/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
WORSHAM, JESSICA N	1615	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively.
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1601 of 1915

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 05/02/2019

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

EXAMINER	
WORSHAM, JESSICA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 05/02/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1602 of 1915

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 30 minutes to complete, including gathering, preparing, and submitting the completed application 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
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.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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 inspection 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.

Notice of Allowability	Application No. 15/346,335	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--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE filed 20 March 2019.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 4/12/19.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1604 of 1915

Continuation of 3. The allowed claim(s) is/are: 1-5,26-27,52-53 and 55

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

Reasons for Allowance

1. The following is an examiner's statement of reasons for allowance: The closest prior art of Carra et al. (WO2015/196116 and U.S. Patent Application Publication No. 2016/0016973) were published after the effective filing date of the instant application and have a common assignee. The next closest prior art of WO2014/100323 comprises administering the compound of Formula 1 at a different time than additional drugs such as tenofovir or emtricitabine. The prior art does not teach all three drugs within the same tablet. Applicants have shown a 30% higher exposure of bictegravir in a fixed dose combination of bictegravir, emtricitabine, and tenofovir alafenamide relative to its exposure when co-administered as a single agent of bictegravir with a fixed dose combination of emtricitabine and tenofovir alafenamide.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

2. 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 on 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 an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner
No classified search performed.		

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
No classified search performed.		

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No classified search performed.		

* 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: EAST, PALM	05/03/2018	JW
EAST: See attached	05/03/2018	JW
SciFinder: See attached	05/03/2018	JW

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(tenofovir adj alafenamide and emtricitabine and bictegravir).clm.	04/23/2019	JW

/JESSICA N WORSHAM/ Primary Examiner, Art Unit 1615	

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1608 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC Symbol					Type	Version
A61K	/	9	/	209	F	2013-01-01
A61K	/	9	/	2054	I	2013-01-01
A61K	/	31	/	513	I	2013-01-01
A61K	/	31	/	553	I	2013-01-01
A61K	/	31	/	675	I	2013-01-01
A61K	/	9	/	0053	I	2013-01-01
A61K	/	9	/	2013	I	2013-01-01
A61K	/	9	/	2095	I	2013-01-01
A61K	/	9	/	28	I	2013-01-01
A61K	/	31	/	5365	I	2013-01-01
A61K	/	9	/	2086	I	2013-01-01

CPC Combination Sets Symbol					Type	Set	Ranking	Version
A61K	/	31	/	513	I	1	1	2013-01-01
A61K	/	2300	/	00	A	1	2	2013-01-01
A61K	/	31	/	553	I	2	1	2013-01-01
A61K	/	2300	/	00	A	2	2	2013-01-01
A61K	/	31	/	675	I	3	1	2013-01-01
A61K	/	2300	/	00	A	3	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	23 April 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20190423

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1609 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	5365
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	23 April 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20190423

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1610 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		10		19		28		37		46	10	55		
2	2		11		20		29		38		47				
3	3		12		21		30		39		48				
4	4		13		22		31		40		49				
5	5		14		23		32		41		50				
	6		15		24		33		42		51				
	7		16		25		34		43	8	52				
	8		17	6	26		35		44	9	53				
	9		18	7	27		36		45		54				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	23 April 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20190423

PTO/SB/08a (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-10,035,809	07-31-2018	Bacon et al.	
	AB	US-2018/0022757-A1	01-25-2018	Chiu et al.	
	AC	US-2018/0065986-A1	03-08-2018	Carra et al.	
	AD	US-2019/0015420-A1	01-17-2019	Carra et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/JESSICA WORSHAM/	Date Considered	04/23/2019

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Dated: April 12, 2019 Signature: /Donna Johnson Gressler/ (Donna Gressler)

1050807.1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Examination Report dated 2018-08-15 for New Zealand Appl. No. 741957, 5 pages.	
	CB	Examination Report dated 2019-11-05 for Australian Appl. No. 2016354007, 4 pages.	
	CC	Office Action dated 2018-09-18 for Bolivian Appl. No. SP260-2016, 8 pages.	√
	CD	Office Action dated 2018-10-03 for Panamanian Appl. No. 92163, 8 pages.	√
	CE	Office Action dated 2018-11-13 for Pakistani Appl. No. 696/2016, 3 pages.	
	CF	Office Action dated 2019-01-21 for European Appl. No. 16798063.0, 5 pages.	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	04/23/2019

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Request for Continued Examination (RCE) Transmittal

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Alexandria, VA 22313-1450

Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. [ ] Other _____
   - b. [X] Enclosed
     - i. [ ] Amendment/Reply
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     - iii. [X] Information Disclosure Statement (IDS)
     - iv. [X] Other SB08
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. [ ] Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 07-1250.
     - i. [X] RCE fee required under 37 CFR 1.17(e)
     - ii. [ ] Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
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Signature	/Donna Johnson Gressler/	Date	July 31, 2019
Name (Print/Type)	Donna Johnson Gressler	Registration No.	45,544

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Docket No.: 1147.P2C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/346,335 | Confirmation No.: 1307

Filed: November 8, 2016 | Art Unit: 1615

For: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus | Examiner: J. N. Worsham

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
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Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

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It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

The Director is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 07-1250, under Order No. 1147.P2C.

Dated: July 31, 2019

Respectfully submitted,

Electronic signature: /Donna Johnson Gressler/
Donna Johnson Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
Correspondence Customer Number: 25000
(650) 574-3000
Attorney For Applicant

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Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

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	BA	WO-2008/043829-A2	04-17-2008	Boehringer Ingelheim Int		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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	Complete if Known
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Exam Report dated 2019-07-26 for Indian Appl. No. 201817013772	
	CB	Office Action dated 2019-03-25 for Bolivian Appl. No. SP260-2016	x
	CC	Office Action received 2019-05-27 for Salvadoran Appl. No. 2018005682	x
	CD	Office Action received 2019-07-01 for Eurasian Appl. No. 201890654	x
	CE	Opposition dated 2017-06-20 for Colombian Appl. No. 15-265.717	x
	CF	TIVICAY Product Label (Revised September 2018) GlaxoSmithKline, 44 Pages.	
	CG	TRIUMEQ Product Label (Revised November 2017) GlaxoSmithKline, 48 Pages.	

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(19) World Intellectual Property Organization
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60/829,529 14 October 2006 (14.10.2006) US

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Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/043829 A2

(54) Title: METHOD FOR TREATING HIV-1 INFECTION BY THE COMBINED ADMINISTRATION OF NEVIRAPINE, TENOFOVIR AND EMTRICITABINE

(57) Abstract: The invention provides a method for treating HIV wherein emtricitabine, tenofovir and nevirapine are administered once per day.

Method for Treating HIV-1 Infection by the Combined Administration of Nevirapine, Tenofovir and Emtricitabine

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The present invention relates to a method for treating HIV-1 infection by the combined administration of nevirapine, tenofovir and emtricitabine.

2. BACKGROUND INFORMATION

Nevirapine, the systematic chemical name for which is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which is used to treat infection by HIV-1 (human immunodeficiency virus, type 1). Its synthesis and use are described in various publications including, *inter alia*, U.S. Patent No. 5,366,972; European Patent Application No. 0 429 987, U.S. Patent 5,571,912 and U.S Patent No. 5,569,760. Viramune ® tablets, a pharmaceutical comprising nevirapine in tablet form, was approved by the U.S. FDA in 1996 for the treatment HIV-1 infection. It has since been approved for use in numerous other countries.

Tenofovir, the systematic chemical name for which is 1-(6-aminopurin-9-yl) propan-2-yloxymethylphosphonic acid, is a nucleoside reverse transcriptase inhibitor (NRTI) which is also used to treat infection by HIV-1. Its synthesis and use are described in various publications including, inter alia, U.S. Patent Nos. 5,922,695; 5,935,946 and 5,977,089. Tenofovir disoproxil fumarate (TDF) is marketed by Gilead Sciences under the trade name Viread®.

Emtricitabine, the systematic chemical name for which is 4-amino-5-fluoro-1- [2-(hydroxymethyl)- 1,3-oxathiolan-5-yl]- pyrimidin-2-one, is another nucleoside reverse transcriptase inhibitor (NRTI) which is used to treat infection by HIV-1. Its synthesis and use are described in various publications including, inter alia, U.S. Patent No. 6,703,396. Emtricitabine (FTC) is marketed by Gilead Sciences under the trade name Emtriva®.

Tenofovir is also available in a fixed-dose combination with emtricitabine in a product with the brand name Truvada®, which has been approved for once-a-day dosing.

Efavirenz, the systematic chemical name for which is 8-chloro-5-(2-cyclopropylethynyl)-5-(trifluoromethyl)- 4-oxa-2-azabicyclo [4.4.0]deca- 7,9,11-trien-3-one, is another NNRTI which is used for the treatment of HIV-1 infection. Its synthesis and use are described in various publications including, inter alia, U.S. Patent Nos. 5,519,021; 5,811,423; 6,639,071 and 6,939,964. Efavirenz is marketed by Bristol Myers Squibb under the brand name Sustiva®.

Atripla® is the brand name for a fixed-dose triple combination of tenofovir, emtricitabine and efavirenz. It has been approved by the US FDA for the treatment of HIV, with once per day dosing.

ClinicalTrials.gov Identifier NCT00344461, published at http://www.clinicaltrials.gov/, describes an open label, two year study of the clinical efficacy of the combination of Emtricitabine (200mg po qd.), Tenofovir (300 mg qd), and Nevirapine (200 mg b.i.d.).

The treatment of HIV by means of once daily dosing of Emtricitabine/Tenofovir with a third agent which can be, inter alia, nevirapine has been generically proposed at http://www.aids-ed.org/aidsetc?page=et-03-00-01. However, this specific combination is not described.

It is important to note that nevirapine is not approved for once daily dosing and that a high rate of early virologic failure has been seen when HIV-1 is treated by the coadministration of didanosine, tenofovir and nevirapine. Thus, the efficacy of once daily dosing of emtricitabine, tenofovir and nevirapine cannot be assumed.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1622 of 1915

BRIEF SUMMARY OF THE INVENTION

The invention provides a method for treating HIV wherein emtricitabine, tenofovir and nevirapine are administered once per day.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the invention, emtricitabine, tenofovir and nevirapine are administered once per day to a host infected by HIV-1. While dosages of these three agents may be adjusted to take into consideration the size, weight and condition of the patient to be treated, typical dosages for an adult human will be 200 mg of emtricitabine, 300 mg of tenofovir, and 400 mg of nevirapine. It is preferred that patients receive 200 mg of nevirapine once per day for the first two weeks of treatment, because it has been demonstrated that this lead-in dosing regimen reduces the frequency of nevirapine-induced rash. At the beginning of the third week of treatment, the nevirapine dose may be increased to 400 mg once per day.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1623 of 1915

CLAIMS:

1. A method for treating HIV wherein emtricitabine, tenofovir and nevirapine are administered once per day.

2. The method of claim 1, wherein 200 mg of emtricitabine, 300 mg of tenofovir, and 400 mg of nevirapine are administered.

3. The method of claim 2, wherein a patient so treated receives 200 mg of nevirapine once per day for the first two weeks of treatment, and thereafter the nevirapine dose is increased to 400 mg once per day.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1624 of 1915

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सं.संख्या/Ref.No /आवेदन संख्या/Application No/ 201817013772 दिनांक/Date of Dispatch/Email: 26/07/2019

सेवा मे,/To
AMRISH TIWARI,
K&S PARTNERS Intellectual Property Attorneys 515-B, Platinum Tower, 5th Floor, Sohna Road, Sector 47, Gurgaon 122002, National Capital Region, India
Email : ipo@knspartners.com

विषय: एकस्व अधिनियम, 1970 की धारा 12 व 13 तथा एकस्व नियम, 2003 के अधीन परीक्षण रिपोर्ट
Subject: Examination report under sections 12 & 13 of the Patents Act, 1970 and the Patents Rules, 2003.

1. उपर्युक्त आवेदन के संदर्भ मे परीक्षण रिपोर्ट (अर्थात, एकस्व नियम, 2003 (यथा संशोधित) के नियम 24-ख(3) में विनिर्दिष्ट आपत्तियों का प्रथम कथन) इसके साथ संलग्न है। यह रिपोर्ट परीक्षण हेतु अनुरोध दिनांक 11/04/2018 के उत्तर मे जारी की गयी है। परीक्षण रिपोर्ट का उत्तर दाखिल करने की अंतिम तिथि (अर्थात, इस रिपोर्ट में लगाई गयी सभी आवश्यकताओं के अनुपालन की अवधि) आवेदक को आपत्तियों का प्रथम कथन जारी होने की तिथि से छः माह है।
Please find enclosed herewith an Examination Report (i.e. a first statement of objections as specified in Rule 24-B(3) of The Patents Rules, 2003 (as amended)) in respect of above-mentioned application. This report is issued with reference to a request for examination dated 11/04/2018.The last date for filing a response to the Examination Report (i.e. a period to comply with all the requirements raised in this examination report) is six months from the date on which the first statement of objections is issued to the Applicant.

2. यदि रिपोर्ट के अंतर्गत लगाई गयी आवश्यकताओं का अनुपालन एकस्व नियम, 2003 (यथा संशोधित) के नियम 24 ख(5) में विनिर्दिष्ट अवधि के भीतर अंतर अनुपालन नहीं किया गया तो एकस्व अधिनियम 1970 की धारा 21(1) के अधीन वर्तमान आवेदन को परित्यक्त माना जाएगा।
The instant application shall be deemed to have been abandoned under Section 21(1) of The Patents Act, 1970, unless all the requirements raised in this report are complied with in the period as specified in Rule 24-B (5) of The Patents Rules, 2003 (as amended).

3. आपका ध्यान एकस्व नियम, 2003 के नियम 24 ख(6) के प्रावधानों की ओर भी आमंत्रित किया जाता है।
Your attention is also invited to the provisions of Rule 24-B (6) of the Patents Rules 2003.

4. आपको सलाह दी जाती है कि शीघ्र निपटान हेतु अपना उत्तर शीघ्र प्रस्तुत करें।
You are advised to file the reply at the earliest for early disposal.

Dr. Rajesh Patel
नियंत्रक पेटेंट/ Controller of Patents

संलग्न/**Enclosed:** उपरोक्त अनुसार/As above

टिप्पणी: यह इलेक्ट्रोनिक रूप से उत्पन्न रिपोर्ट है।
NOTE: This is an electronically generated report.

सभी पत्राचार नियंत्रक एकस्व को उपरोल्लिखित पते पर भेजा जाये।
All communications should be sent to the Controller of Patents at the above mentioned address.

THE PATENT OFFICE

परीक्षण रिपोर्ट /Examination Report

आवेदन संख्या /Application Number	201817013772
दाखिल करने की तिथि /Date of Filing	11/04/2018
पूर्विका दिनांक /Date of Priority	09/11/2015
पीसीटी अंतर्राष्ट्रीय आवेदन की संख्या व दिनांक / PCT International Application No. & Date	US2016060989 -- 08/11/2016
आवेदक /Applicant	GILEAD SCIENCES INC.
परीक्षण हेतु अनुरोध की संख्या व दिनांक /Request for Examination No. & Date	R20181010959 11/04/2018
प्रकाशन की तिथि /Date of Publication	10/08/2018

इस परीक्षण रिपोर्ट के चार भाग हैं, अर्थात रिपोर्ट का सारांश, विस्तृत तकनीकी रिपोर्ट, औपचारिक आवश्यकताएँ तथा रिकॉर्ड में दस्तावेज़ /
This examination report consists of four parts, namely summary of the report, detailed technical report, formal requirements and documents on record.

भाग -1: रिपोर्ट का सारांश
PART-I: SUMMARY OF THE REPORT

क्र. सं. /Sl. No.	अधिनियम के तहत आवश्यकताओं पर विस्तृत टिप्पणियां /Requirements under the Act		दावों की संख्या /Claim Numbers	टिप्पणी /Remarks
1.	धारा 2(1)(ज) के तहत आविष्कार /Invention u/s 2(1)(j)	नवीनता /Novelty	दावे /Claims:	हाँ /Yes
			दावे /Claims: 1-51	नहीं /No
		आविष्कारी कदम / Inventive step	दावे /Claims:	हाँ /Yes
			दावे /Claims: 1-51	नहीं /No
		औद्योगिक उपयोगिता /Industrial Applicability	दावे /Claims: 1-51	हाँ /Yes
			दावे /Claims:	नहीं /No
2.	धारा 3 के अधीन पेटेंट-अयोग्यता (यदि हाँ, खंड 3(क-त) /Non-patentability u/s 3 (if yes, specify section3(a-p))		दावे /Claims: 1-51	हाँ /Yes 3(d), 3(e), 3(i)
			दावे /Claims:	नहीं /No
3.	[धारा 10(5) व 10(4) (ज)] के अधीन दावे /Claims [u/s 10(5) & 10(4) (c)]	स्पष्टता/ संक्षिप्तता /Clarity / Conciseness	दावे /Claims:	हाँ /Yes
			दावे /Claims: 28-30, 34-35, 46-51	नहीं /No

भाग –II विस्तृत तकनीकी रिपोर्ट
PART-II: DETAILED TECHNICAL REPORT

क. उद्धृत दस्तावेजों की सूची /A.List of documents cited:

(क) पेटेंट साहित्य / (a). Patent Literature :

क्र. सं. / Sl.no	दस्तावेज़ों का विवरण /Details of documents	प्रकाशन तिथि(दिन/माह/वर्ष) / Publication date	उद्धरित दस्तावेज़ का प्रासंगिक विवरण (पृष्ठ व अनुच्छेद संख्या) / Relevant description (page and paragraph no.) of cited document	उद्धरित दस्तावेज़ के प्रासंगिक दावे / Relevant claims of cited document	अभिकथित आविष्कार के दावे /Claims of alleged invention
1	D1: WO2014100323A1	26/04/2014	Whole Document	1-108	1-51

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1626 of 1915

2	D2: WO2013116720A1	08/08/2013	Whole Document	1-32	1-51
3	D3: WO2015022351A1	19/02/2015	Whole Document	1-15	1-51
4	D4: WO2008043829A2	17/04/2008	Whole Document	1-3	1-51

(ख) गैर-पेटेंट साहित्य /(b).Non-patent literature

कोई दस्तावेज़ नहीं है /No Document Cited

ख. अधिनियम के तहत आवश्यकताओं पर विस्तृत टिप्पणियां /B. Detailed observations on the requirements under the Act:

(1).नवीनता / NOVELTY:

(I) ऊपर उद्धरित दस्तावेज़ के संदर्भ (1-51) में दिये गए प्रकटन के पूर्वानुमान को ध्यान में रखते हुए, निम्नलिखित कारणों से दावा(वों) (1-51) में नवीनता की कमी है /
Claim(s) (1-51) lack(s) novelty, being anticipated in view of disclosure in the document cited above under reference D1 for the following reasons:

Document D1 discloses the pharmaceutical composition comprising compound of formula I, HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, tenofovir alafenamide, etc and HIV nucleoside inhibitors of reverse transcriptase selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, etc. This composition is 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 (Page 36 lines 12-15; Page 40 lines 18-20). This composition is used in the treatment of HIV. Further the physical state of the composition cannot be used as a criterion for patentability. Thus the subject matter of claims 1-51 lacks novelty u/s 2(1)(j) of the Patents Act, 1970.

(2).आविष्कारी कदम / INVENTIVE STEP:

(I) ऊपर उद्धरित दस्तावेज़(जों) के संदर्भ D1-D4 में स्पष्ट अध्यापन(नों) को ध्यान में रखते हुए, निम्नलिखित कारणों से दावा(वों) (1-51) में आविष्कारी कदम की कमी है
Claim(s) (1-51) lack(s) inventive step, being obvious in view of teaching (s) of cited document(s) above under reference D1-D4 for the following reasons:

It is not considered inventive to combine two or more active ingredients for treating a particular disease in the case where said two or more active agents are each known to be therapeutically effective alone in treating said particular disease. In this regard, it would normally be expected that such a composition of active agents would be more effective than either active agent alone. Exceptions to this general principle may be made if the new combination has a surprising property, e.g. synergistic therapeutic effect, which could not have been fairly predicted on the basis of the prior art.

The compound of formula I is known to be therapeutically effective in the treatment of HIV (see documents D1). Its combination with another anti-HIV agent including tenofovir alafenamide and emtricitabine is also suggested in D1.

Tenofovir alafenamide and emtricitabine are also known to be effective in the treatment of HIV when used alone (D2) or in combination with other anti-HIV agents in a single dosage form (see D2-D4).

The present application provides no example of the putative synergistic effect between compound of formula (I), tenofovir alafenamide and emtricitabine. It should be noted that the unexpected or surprising effect that is alleged in support for such a demonstration must be made plausible over the whole scope of the claimed subject-matter. Thus, a surprising effect must be demonstrated for each and every embodiment of the claims. As a result, the subject matter of claims 1-51 cannot be considered as inventive u/s 2(1)(ja) of the Patents Act, 1970.

A marked-up copy of claims clearly indicating the amendments in claims must be submitted along with the examination report reply u/r 14(2) of the Patent Rule 2003 (as amended in 2016).

(3).पेटेंट अयोग्यता /NON PATENTABILITY:

(I) निम्नलिखित कारणों से धारा 3 के खंड (3(d), 3(e), 3(i))के प्रावधान के तहत दावा(वे) (1-51) सांविधिक रूप से पेटेंट योग्य नहीं हैं / Claim(s) (1-51) are statutorily non-patentable under the provision of clause (3(d), 3(e), 3(i)) of Section 3 for the following reasons:

[1]. The subject-matter of claims 1-7, 26-30, and 38 relates to the oral dosage form comprising compound of formula I, tenofovir alafenamide, and emtricitabine. The subject-matter of claims 8-25, 43-44 relates to the tablet composition. Further the composition defined in different claims is used for human treatment. Oral dosage form and tablet are covered within the scope of method of treatment. Therefore subject matter of claims 1-51 are not patentable u/s 3(i) of the Patents Act, 1970.

[2]. Subject matter of claims 40-42 and 45-51 describes the compositions comprising compound of formula I, tenofovir alafenamide, and emtricitabine. The combined therapeutic effect of the composition is not shown over the separate therapeutic effect of other constituents. Thus the overall effect is considered as the properties of the constituents only. Applicant had failed to establish the synergistic effect of the said composition over the separate effect of other constituent. In the absence of experimental data, it is considered as the aggregation of properties of constituent only. Further the dosage form and tablet comprises the said compositions. Therefore subject matters of claims 1-51 are not patentable u/s 3(e) of the Patents Act, 1970.

[3]. The subject-matter of claim 1-51 describes the composition in different forms comprising the compound of formula I, tenofovir alafenamide, and emtricitabine for use in the treatment of HIV. Document D1 discloses the said composition as dosage form and in tablet form. Section 3(d) of the Patents Act, 1970 explains that the mere discovery of new form of a known substance which does not result in the enhancement of the known efficacy of that substance, are not patentable. The new form may be salts and derivatives of the known substance. Therefore subject matter of claims 1-51 is not patentable u/s 3(d) of the Patents Act, 1970.

(4).प्रकटन की दक्षता /SUFFICIENCY OF DISCLOSURE:

(I) सार /Abstract:

Abstract of the alleged invention is not filed in prescribed format u/r 13(7)(a) of Patents Rules, 2003 as it does not commence with the title of the invention. Further abstract should be amended to incorporate the essential features of current invention.

(5).स्पष्टता एवं संक्षिप्तता /CLARITY AND CONCISENESS:

(I) दावा(वे) 28-30, 34-35, 46-51 के संबंध में स्पष्ट रूप से परीभाषित नहीं हैं.
Claim(s) 28-30, 34-35, 46-51 are not clearly worded in respect of:

[1]. The subject-matter of claims 28-30 and 46-51 do not meet the requirements of section 10(5) of the Patents Act, 1970 because the matter for which protection is sought is not clearly defined. The claims attempt to define

the subject-matter in terms of the result to be achieved, namely in the form of release/dissolution profile/rate, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

[2]. The subject-matter of claims 34-35 is not clear u/s 10(5) of the Patents Act, 1970 because the first layer and the second layers are not defined. For the purpose of the present opinion it is assumed that i) the first layer means a composition comprising a compound of formula (I) and ii) the second layer means a combination of tenofovir alafenamide and emtricitabine compressed together.

(6).अन्य आवश्यकताएँ /OTHERS REQUIREMENTS:

(I)

The subject-matter of claims 36-37 discloses a "kit" that is not considered as an invention u/s 2(1)(j) of the Patents Act, 1970 and therefore these claims are not allowed u/s 2(1)(j) of the Patents Act, 1970.

भाग – III: औपचारिक आवश्यकताएँ /PART-III: FORMAL REQUIREMENTS

आपत्तियां /Objections	टिप्पणी /Remarks
Power of Attorney (Whether GPA, SPA, Stamped, requisite fee etc.)	Power of attorney filed on 16/10/2018 cannot be taken on record u/s 127 of Patents Act, 1970 as name of the second party is not mentioned on the e-stamp page. Fresh power of attorney clearly indicating the name of both the parties on e-stamp paper duly verified by the agent should be resubmitted.
Statement & Under Taking (Form 3 Details)	Updated form 3 with correct details is required to be filed u/r 12(2) of the Patent Rule 2003 (as amended in 2016) in a prescribed manner.
Format of Drawings	Drawing referred in the specifications had not been filed in accordance with the instructions contained in the rule 15 of the Patents Rules 2003 (as amended in 2016).
Other Deficiencies	[1]. Fresh form 1 in updated format as amended in 2016 should be filed. The column in declaration part 12(iii) which is not applicable should be struck-out only and it should not to be deleted. [2]. Prescribed form 5 for declaration of inventor-ship is not filed in accordance to section 10(6) and rule 13(6) of the Patents Act, 1970. The column which is not applicable should be struck-out only and it should not to be deleted.
Format of Specification (rule 13)	[1]. Claim part of the complete specification does not commence with the phrase; "I/We claim". [2]. Dependent claims should contain the term "as claimed in claim" instead of "according to claim".

भाग-IV: रिकॉर्ड मे दस्तावेज़ /PART-IV: DOCUMENTS ON RECORD

निम्नलिखित दस्तावेज़ों के आधार पर यह परीक्षण रिपोर्ट तैयार की गयी है
The examination report has been prepared based on the following documents:

कार्यसूची तिथि / Docket Date	कार्यसूची संख्या /Docket Number	पूर्विष्टि संख्या विवरण /Entry Number Description
11 Apr 2018	31305	1-New Application For Patent With Provisional /Complete Specification
11 Apr 2018	31305	28(i)-Request For Examination After 18 months Publication - Form 18
25 May 2018	42805	Proof of Right
16 Oct 2018	82552	45-Form Of Authorisation Of Patent Agent - Form 26
22 Oct 2018	83797	OTHERS(NON CASH)
22 Oct 2018	83797	OTHERS(NON CASH)
01 Nov 2018	86991	OTHERS(NON CASH)
01 Nov 2018	86991	OTHERS(NON CASH)
02 Nov 2018	87638	3-Statement & Undertaking - Form 3
22 Apr 2019	38757	3-Statement & Undertaking - Form 3

नियंत्रक का नाम /Name of the Controller: Dr. Rajesh Patel

नियंत्रक स्थान /Controller Location: Delhi

टिप्पणी: परीक्षण रिपोर्ट का उत्तर दाखिल करने की अंतिम तिथि / Note: Last date for filing response to the Examination Report: 26/01/2020

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1630 of 1915

TECHNICAL REPORT
INF/SNP/DGE/DPI/ADP N° 0119/2019
SNP/2019-02255

Dear Sirs
GILEAD SCIENCES, INC.
SP260-2016
Publication 12193

Reference: **Technical Report N°76/2019**

"PHARMACEUTICAL FORMULATIONS"

As a result of the substantive examination, carried out based on Article 45 of Decision 486 of the Andean Community Commission, the following is communicated:

- **Documents studied**

  - Patent Application SP260-2016 dated 09/11/2016.
  - WO 2014/100323 A1 "Polycyclic-carbamoylpyridone compounds and their pharmaceutical use".
  - Set of claims dated May 29, 2018.
  - Technical Report No° 337/2018 (September 17, 2018).
  - Brief of response to Technical Report N° 337/2018 (February 22, 2019).
  - New set of claims dated February 22, 2019.

- **Patentability requirements**
(Clarity, Sufficiency, Concision, Unity of invention and Patentability)

Art. 30 Decision 486

  - Claim 1 lacks support in the specification since it describes bilayer tablets containing the compound of formula II, tenofovir alafenamide hemifumarate and emtricitabine in different layers, but not a tablet containing the 3 active principles together (see examples 2 and 6). Also, the reason for claiming a tablet comprising 50 ± 5 mg of the compound of formula I or its sodium salt, 25 mg ± 3 mg of tenofovir alafenamide or tenofovir alafenamide hemifumarate and 200 ± 20 mg of emtricitabine without mentioning the excipients accompanying said active compounds is not clear, since it is well known in the art that the release of a drug depends on the excipients accompanying it and the pharmaceutical form in which said active is presented.

    Likewise, it is reiterated that the claim lacks clarity since by mentioning the weight of the tablet it is characterizing it by a parameter.

    Finally, regarding the sustenance in the description the Andean Manual mentions "*The claims have to be supported in the specification (Article 30 D 486). This means that the object of each claim* ***must have its basis*** *in the specification and that its scope it* ***must not exceed what is justified by the content of the specification*** *and drawings*" (Page 43).

- **Determination of the State of the Art**
(Novelty, Inventive Step and Industrial Application)
Art 14, Art 16 y Art 18 Decision 486

➢ The RELEVANT DOCUMENTS that affect the inventive step of the application are reiterated below.

No.	DOCUMENT	TITLE	PUBLICATION DATE
D1	WO 2014/100323 A1	"Polycyclic-carbamoylpyridone compounds and their pharmaceutical use"	22/06/2000

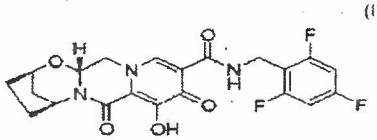
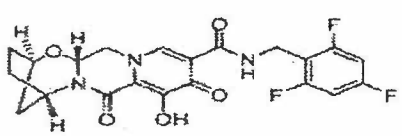
No.	DOCUMENT	AFFECTED CLAIMS	DOCUMENT CATEGORY	AFFECTED REQUIREMENT
D1	WO 2014/100323 A1	1 to 4	X/D	INVENTIVE STEP

X: means the importance of the document alone for the possibility of revoking the patent application by the concept of novelty or inventive level.
Y: means the importance of the document that combined with another document, can affect the feature of inventive step of the patent application.
A: means that not being important for the novelty and inventive step examination is referred as a document related with the patent application.
O: referred to non-written disclosure.
D: are the document cited in the specification of the invention.
P: are the documents published between the filing date of the application and the recognized priority date.
E: prior document, but published after the filing date of the application.
F: designates the document published abroad, application or parent, corresponding to the application under examination.
G: designates patent family members.

➢ D1 discloses compounds for use in the treatment of human immunodeficiency virus (HIV) infection (abstract). D1 teaches pharmaceutical compositions comprising the compound of formula I of the present application or a pharmaceutically acceptable salt thereof (page 37). The additional therapeutic agent is selected from one or more of: emtricitabine and tenofovir alafenamide fumarate (page 38). D1 teaches that the pharmaceutical composition can be in the form of a tablet and that the compound of formula I is in an amount of 50 mg (pages 35-36).

In the table N° 1 the similarities between the compounds of D1 and claim 1 of the application are shown:

TABLE No. 1

Application	D1
1. A tablet comprising 50±5 mg of the compound of formula I (I)  Or its sodium salt	Tablet comprising 50 mg of the compound:  Compound 42
25±3 mg tenofovir alafenamide or tenofovir alafenamide hemifumarate, and 200±20 mg emtricitabine.	emtricitabine, tenofovir alafenamide fumarate

As can be seen in table N° 1, D1 and the application disclose tablets comprising 50 mg of the compound of formula I, emtricitabine and tenofovir alafenamide fumarate. The difference between D1 and the application is that D1 does not disclose the amounts of emtricitabine and tenofovir alafenamide, however, this

difference does not demonstrate an unexpected technical effect with respect to the disclosure of D1. Likewise, it is necessary to indicate that it is common practice to combine two or more active ingredients that are useful in the treatment of the same disease and it is also known that said combination will have a better therapeutic effect than a single drug. The compound of formula I is known to be therapeutically effective in the treatment of HIV and the combination of this compound with other agents useful for the treatment of HIV such as tenofovir alafenamide and emtricitabine is suggested in D1.

Furthermore, the present application does not demonstrate that the combination of the compound of formula I, tenofovir alafenamide and emtricitabine has a synergistic therapeutic effect, therefore, the combination of the three drugs useful in treating HIV is considered obvious.

So, in light of D1 and in the absence of an unexpected technical effect attributed to the technical features of claim 1, the matter claimed by claims 1 to 4 is considered obvious and without inventive step.

No reference is made to the weight since it is not considered a technical characteristic of the tablet as it is only a parameter

The response to Technical Report N° 337/2018 indicates:

"*Examples 3 and 9, which demonstrate that the tablet as claimed provides improved pharmacokinetic benefits ... [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 compared to single agent tablet formulation F1 ... These results ... surprising ... would be comparable to the total exposure of compound of formula I obtained by the administration of a single unit dosage form comprising the three actives (F7)*".

From the above it can be established that the applicant justifies the unexpected technical effect of the pharmaceutical form illustrated in examples 2 and 6, that is, justifies the inventive level of the bilayer tablets defined in examples 2 and 6, however, the technical characteristics of said tablets are not included in the independent claim.

It is also necessary to point out that the release of the active principles and bioavailability of a pharmaceutical product is determined by the concentration and the excipients that accompany the active ingredient as well as the pharmaceutical form in which they are found. Consequently, the excipients and their concentrations are what determine the release of the active ingredients. However, these technical characteristics are not found in the independent claim.

It should be noted that the conclusion on that claims 1 to 4 are obvious and lack inventive step is maintained, since the technical features of claim 1 do not solve the problem raised in the application nor demonstrate an unexpected technical effect over the disclosure of D1.

It is also necessary to clarify that although the Andean Manual mentions that the lack of any technical advantage is not an absolute criterion to recognize or not the inventive step, it also points out:

"***10.4 Indications of the existence of inventive step***

In the practice of the background examination, a series of indications can be used to identify the existence of inventive step, such as:

*-**the unexpected character of the result;***

-the fact of having overcome real technical difficulties...

10.5 Indications of the lack of an Inventive step

*- **simple and direct extrapolation of known facts;***

-change of size, shape or proportion, obtained by plain test without unexpected effect ..." (page 81)

The claims must contain all the essential technical features of the invention which define the invention and make it or could make it distinctive from the state of the art. These **essential technical characteristics define the solution to the technical problem** that the invention tries to solve (Page 35).

The claims are the most important part of the application, because they define the invention to be protected and delimit the scope of that protection (Article 51). It is essential that they are clear and concise (Article 30) so that:
- They can be compared and differentiated from the state of the art in order to verify the patentability requirements; y
-they can unambiguously determine the extent of the rights of the patent holder (page 35).
The necessary inventive step for the approval of the patent registry is verified if the technological advances presented by the invention represent the solution to the technical problem existing in the area of its destination, that is, an invention is the solution to a problem. In this understanding the claim 1 as it is written, without mentioning all the technical characteristics that solve the technical problem raised in the application is obvious in the light of document D1, since only the amounts of the active ingredients in the compressed, but not the amounts of the excipients and active in the layers of the bilayer tablet.

- **Conclusions**

➢ Patent Application N° 260-2016 does not comply with Articles 14, 18 and 30 of CAN Decision 486 as to clarity, conciseness, support and inventive step.

In compliance with Article 45 of Decision 486 of the Andean Community Commission, it is indicated that this action must be responded within the term of sixty (60) days counted from the date of notification of this communication. In the event of failure to respond to this request, or if in spite of the answer the impediments to the concession continue, the patent will be denied.

La Paz, March 25, 2019
Illegible signature

Pharmaceutical Chemist Deisy Jimenez Gomez
Patent Examiner
SENAPI
Appointments (Fridays 9 am – 11 am)

PUBLICATION N. 12193

On, March 26, 2019

In accordance with Technical Report No. 76/2019, notify the applicant in order to correct the observations made by the examiner of the area, or with the formalities of Law.

AREA DE PATENTES V°B° SENAPI

Abg. Esteban M. Paniagua Mollea
RESPONSABLE DE PATENTES a.i.
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INFORME TÉCNICO
INF/SNP/DGE/DPI/ADP N° 0119/2019
SNP/2019-02255

Señores:
GILEAD SCIENCES, INC.
SP260-2016
Publicación 12193

Ing. Esteban M. Paniagua Mallea
RESPONSABLE DE PATENTES e.i.
SERVICIO NACIONAL DE PROPIEDAD INTELECTUAL

Ref. **Informe técnico N°76/2019**

"FORMULACIONES FARMACEUTICAS"

Como resultado del examen de fondo, realizado con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

- **Documentos estudiados**

  - Solicitud de Patente SP260-2016 de fecha 09/11/2016.
  - WO 2014/100323 A1 "Polycyclic-carbamoylpyridone compounds and their pharmaceutical use".
  - Pliego reivindicatorio de fecha 29 de mayo de 2018.
  - Informe Técnico N°337/2018 (17 de septiembre del 2018).
  - Memorial de Respuesta a Informe Técnico N°337/2018 (22 de febrero del 2019).
  - Nuevo pliego reivindicatorio de fecha 22 de febrero del 2019.

- **Requisitos de Patentabilidad**

  (Claridad, Suficiencia, Concisión, Unidad de invención y Patentabilidad)

  Art. 30 Decisión 486

  - Reivindicación 1 carece de sustento en la descripción puesto que en ésta se describen comprimidos bicapa que contienen el compuesto de fórmula II, tenofovir alafenamida hemifumarato y emtricitabina en capas diferentes no así un comprimido que contiene los 3 principios activos juntos (Ver ejemplos 2 y 6). Asimismo, no queda clara la razón de reclamar un comprimido que comprende 50 ± 5 mg del compuesto de Fórmula I o su sal sódica, 25 ± 3 mg de tenofovir alafenamida o tenofovir alafenamida hemifumarato y 200 ± 20 mg de emtricitabina sin mencionar los excipientes que acompañan a dichos compuestos activos puesto que es bien conocido en la materia que la liberación de un fármaco depende de los excipientes que lo acompañan y la forma farmacéutica en la cual se presenta dicho activo.
    Asimismo, se reitera que la reivindicación carece de claridad porque al mencionar el peso del comprimido lo caracteriza por un parámetro.

    Finalmente, respecto al sustento en la descripción el Manual Andino menciona *"Las reivindicaciones tienen que estar sustentadas en la descripción (Art. 30 D 486). Esto significa que el objeto de cada reivindicación tiene que* ***tener su fundamento*** *en la*

AREA DE PATENTES V°B° Dolly J. Jiménez SENAPI

Copia de ley para: Marcos Mercado
Expediente: 12193
Fecha y hora: 20/5/19 a 17:45

descripción y que su alcance ***no debe exceder más allá de lo justificado por el contenido de la descripción*** *y los dibujos"* (página 43).

- **Determinación del Estado de la Técnica**

(Novedad, Nivel Inventivo y Aplicación Industrial)
Art. 14, Art.16 y Art. 18 Decisión 486

➢ A continuación se reiteran los DOCUMENTOS RELEVANTES que afectan el nivel inventivo de la solicitud.

No.	DOCUMENTO	TITULO	FECHA DE PUBLICACIÓN
D1	WO 2014/100323 A1	"Polycyclic-carbamoylpyridone compounds and their pharmaceutical use"	22/06/2000

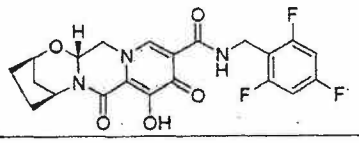
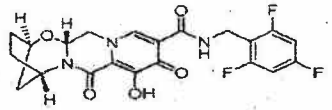
No.	DOCUMENTO	REIVINDICACIONES AFECTADAS	CATEGORÍA DEL DOCUMENTO	REQUISITO QUE AFECTA
D1	WO 2014/100323 A1	1 a 4	X/D	Nivel Inventivo

X: significa la importancia del documento por si solo para la posibilidad de revocar la solicitud de patente por el concepto de novedad o nivel inventivo.
Y: significa la importancia del documento que, combinado con otro, puede afectar la característica del nivel inventivo de la solicitud de patente.
A: significa que no siendo importante para la evaluación de la novedad y para la del nivel inventivo está referida como documento relacionado a la solicitud de patente.
O: referido a divulgación no escrita
D: son los documentos que se citan en la descripción de la invención
P: son los documentos publicados entre la fecha de presentación de la solicitud y la fecha de prioridad reconocida
E: documento anterior, pero publicado después de la fecha de la presentación de la solicitud
F: designa el documento publicado en el extranjero, solicitud o patente, que corresponde a la solicitud que se está examinando
G: designa a patentes miembros de la familia

➢ D1 divulga compuestos para el uso en el tratamiento de la infección del virus de inmunodeficiencia humana (HIV) (resumen). D1 enseña composiciones farmacéuticas que comprenden el compuesto de fórmula I de la presente solicitud, o una de sus sales farmacéuticamente aceptables, en combinación con uno o más agentes terapéuticos adicionales, y un portador, diluyente o excipiente farmacéuticamente aceptable (página 37). El agente terapéutico adicional se selecciona de uno o más de: emtricitabina y tenofovir alafenamida fumarato (página 38). D1 enseña que la composición farmacéutica puede estar en forma de un comprimido y que el compuesto de fórmula I está en una cantidad de 50 mg (páginas 35 y 36).

En la tabla N°1 se muestran las similitudes entre D1 y la reivindicación 1 de la presente solicitud:

TABLA N°1

Solicitud	D1
1. Un comprimido que comprende 50 ± 5 mg del compuesto de Fórmula I: (I) 	Comprimido que comprende 50 mg del compuesto:  Compound 42

AREA DE PATENTES V°B° Del V. Jiménez SENAPI

o su sal sódica,	
25 ±3 mg de tenofovir alafenamida o tenofovir alafenamida hemifumarato, y 200 ± 20 mg de emtricitabina.	emtricitabina, tenofovir alafenamida fumarato.

Como se puede observar en la tabla N°1, D1 y la solicitud divulgan comprimidos que comprenden 50 mg del compuesto de Fórmula I, emtricitabina y tenofovir alafenamida fumarato. La diferencia entre D1 y la solicitud es que D1 no divulga las cantidades de emtricitabina y tenofovir alafenamida, sin embargo, esta diferencia no demuestra un efecto técnico inesperado respecto a la divulgación de D1. Asimismo, es necesario indicar que es práctica común la combinación de dos o más principios activos que son útiles en el tratamiento de una misma enfermedad y también es conocido que dicha combinación tendrá un mejor efecto terapéutico que un solo fármaco. El compuesto de fórmula I es conocido porque es terapéuticamente efectivo en el tratamiento de VIH y la combinación de este compuesto con otros agentes útiles para el tratamiento de VIH tal como tenofovir alafenamida y emtricitabina es sugerido en D1.

Además, la presente solicitud no demuestra que la combinación del compuesto de fórmula I, tenofovir alafenamida y emtricitabina presente un efecto terapéutico sinérgico, por lo tanto, la combinación de los tres fármacos útiles para tratar VIH se considera obvia.

Por lo que a la luz de D1 y en ausencia de un efecto técnico inesperado atribuido a las características técnicas de la reivindicación 1, la materia reclama por las reivindicaciones 1 a 4 se considera obvia y sin nivel inventivo.

No se hace referencia al peso puesto que no se considera una característica técnica del comprimido al ser únicamente un parámetro.

El Memorial de Respuesta a Informe Técnico N°337/2018 señala:

"Ejemplos 3 y 9, que demuestran que comprimidos de acuerdo a lo reclamado proporcionan beneficios farmacocinéticos mejorados...[0317] La exposición total del compuesto de Fórmula I, bajo condiciones de ayuno, fue aproximadamente 30% mayor cuando se dosificó en la formulación F2 de comprimido bicapa...en comparación con la formulación F1 de comprimido de un solo agente...Estos resultados...sorprendentes...fuera comparable a la exposición total de compuesto de fórmula I obtenida por la administración de una forma de dosis unitaria única que comprende los tres activos (F7)". De lo anteriormente expresado puede establecerse que el solicitante justifica el efecto técnico inesperado de la forma farmacéutica ilustrada en los ejemplos 2 y 6, es decir, justifica el nivel inventivo de los comprimidos bicapa definidos en los ejemplos 2 y 6, sin embargo, no incluye las características técnicas de dichos comprimidos en la reivindicación independiente.

También es necesario señalar que la liberación de los principios activos y biodisponibilidad de un producto farmacéutico está determinado por la concentración y los excipientes que acompañan a los activos así como la forma farmacéutica en la que se encuentran. En consecuencia los excipientes y sus concentraciones son los que determinan la liberación de los principios activos. Sin embargo, dichas características técnicas no se encuentran en la reivindicación independiente.

Debe indicarse que se mantiene la conclusión de que las reivindicaciones 1 a 4 son obvias y carecen de nivel inventivo, puesto que las características técnicas de la reivindicación 1 no resuelven el problema planteado en la solicitud ni demuestran un efecto técnico inesperado sobre la divulgación de D1.

También es necesario aclarar que si bien el Manual Andino menciona que la falta de cualquier ventaja técnica no es un criterio absoluto para reconocer o no el nivel inventivo, también señala:

"10.4 Indicios de la existencia de nivel inventivo

En la práctica del examen de fondo se puede utilizar una serie de indicios para identificar la existencia de nivel inventivo, tales cómo:

A.E.I. DE PATENTES V°B° Delgy Jiménez SENAPI

- ***el carácter inesperado del resultado;***
- *el hecho de haber superado dificultades técnicas reales...*

10.5 Indicios de la falta de nivel inventivo

- ***extrapolación simple y directa de hechos conocidos;***
- *cambio de tamaño, forma,* ***o proporción,*** *obtenido por mero ensayo sin efecto inesperado..."* (página 81).

Las reivindicaciones deben contener todas las características técnicas esenciales de la invención las cuales definen a la invención y la hacen o pudieran hacerla distintiva del estado de la técnica. Estas características técnicas **esenciales definen la solución al problema técnico** que intenta resolver la invención (página 35).

Las reivindicaciones son la parte más importante de la solicitud, pues definen la invención a proteger y delimitan el alcance de esa protección (Art. 51). Es fundamental que sean claras y concisas (Art. 30) para que:

-Se puedan comparar y diferenciar del estado de la técnica con el fin de verificar los requisitos de patentabilidad; y

-puedan determinar sin ambigüedad hasta dónde llegan los derechos del titular de la patente (página 35).

La actividad inventiva necesaria para la aprobación del registro de patentes se verifica si los avances tecnológicos presentados por la invención representan la solución al problema técnico existente en el área de su destino, es decir, una invención es la solución a un problema. En ese entendido la reivindicación 1 tal y como está redactada, sin mencionar, todas las características técnicas que resuelven el problema técnico planteado en la solicitud resulta obvia a la luz del documento D1, puesto que se define únicamente las cantidades de los principios activos en el comprimido, no así las cantidades de los excipientes y activos en las capas del comprimido bicapa.

- **Conclusiones**

  - La Solicitud de Patente N°260-2016 no cumple con los Artículos 14, 18 y 30 de la Decisión 486 de la CAN en cuanto a claridad, concisión, sustento y nivel inventivo.

En cumplimiento del Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

La Paz, 25 de marzo del 2019

Lic. Q.F. Daisy Jiménez Gomez
EXAMINADORA DE PATENTES
"SENAPI"

Entrevistas (viernes 9 am – 11 am)

senapi
SERVICIO NACIONAL DE PROPIEDAD INTELECTUAL

Ministerio de Desarrollo Productivo y Economía Plural

PUBLICACIÓN Nro. 12193

A, 26 de marzo de 2019

En atención al Informe Técnico Nro. 76/2019, notifíquese al solicitante a efectos de subsanar las observaciones realizadas por el examinador del área, sea con las formalidades de Ley.

ÁREA DE PATENTES V°B° Delia J. Jiménez SENAPI

Ing. Estefani M. Paniagua Mallea
RESPONSABLE DE PATENTES a.i.
SERVICIO NACIONAL DE PROPIEDAD INTELECTUAL

Adg. Scarley Marina Valenzuela Barroso
DIRECTORA DE PROPIEDAD INDUSTRIAL
SERVICIO NACIONAL DE PROPIEDAD INTELECTUAL
SENAPI

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1640 of 1915

TECHNICAL REPORT

To: **Lic. Luis Alonso Cáceres Amaya**
Head of the Patents Department

From: **Lic. Sara Cristina Galán Mejía**
Background Examiner

Subject: **THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS**
File: 5682/2018
Priority: US201562253042P 20151109; US201662399999P 20160926
Filing date: 08/11/2016
Exam Date: 10/12/2018

ANALYZED TEXT

- Specification originally submitted.
- 10 claims originally submitted.

SUFFICIENCY AND CLARITY OF THE INVENTION

1. The phrase "a pharmaceutically acceptable salt" in claims 1, 2, 7, 8 is not clear, because it does not provide all the technical characteristics for the understanding of said claims, leaving to the option of the applicant the use of the salts that are considered necessary.

2. The term "about" in claims 4, 7, 8 is imprecise.

3. The use of the conjunction "or" in the wording of claim 3 is not clear since it is not possible to accurately determine the compound to be protected.

4. The phrase "any one of claims" in claims 4-10 is not clear, because it is not possible to accurately determine the compound to be protected.

Claims 1-10 They do not comply with the requirements of Art. 138 of the Intellectual Property Law.

PATENTABILITY

Claims 1-10 are not within the scope of Art. 107 of the Intellectual Property Law.

NOVELTY

After carrying out a bibliographic review of the state of the art both nationally and internationally, it was found that the closest publications are:

The national search is attached to the report.

D1. WO2014100323 (A1) (Published 23/12/2015)

POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE.

Compounds for use in the treatment of human immunodeficiency virus (HIV) infection are described. The compounds have the following formula (1): including the stereoisomers and the pharmaceutically acceptable salts thereof, wherein R1, X, W, Y1, Y2, Z1 and Z4. Also described are methods associated with the preparation and use of such compounds, as well as pharmaceutical compositions comprising said compounds.

Document 1 does not affect the novelty of the application examined.

D2. WO2013116720 (A1) (Published 08/08/2013)

COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

Refers to the use of the hemifumarate form of {9-[(R)2-[[(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]aminojphenoxyphosphinyl]methoxy]propyl]adenine} (tenofovir alafenamide hemifumarate) in combination with cobicistat. In addition, the combination of **tenofovir hemifumarate, alafenamide,** cobicistat, **emtricitabine** and elvitegravir and the combination of **tenofovir hemifumarate, alafenamide** cobicistat, **emtricitabine** and darunavir is described.

Document 2 does not affect the novelty of the application examined.

D3. WO2015022351 (A1) (Published 19/02/2015)

MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR

It refers to a pharmaceutical combination comprising (a) dolutegravir (b) emtricitabine and (c) tenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as drug, preferably in the treatment of a viral infection/disease such as an HIV infection. It also refers to a pharmaceutical composition comprising the pharmaceutical combination and optionally other pharmaceutical excipient (s).

Document 3 does not affect the novelty of the application examined.

No document equal to the present application was found; therefore it is determined that claims 1-10 are new according to Article 113 of the Intellectual Property Law.

INVENTIVE STEP

The purpose of the examined application is the provision of an alternative pharmaceutical formulation comprising a compound of formula (1).

Document 1 describes tablets in a single dosage form comprising a compound of formula (1) which includes compounds 42 and 45.

Document 2 describes a monolayer and bilayer tablet comprising in a single layer tenofovir alafenamide and emtricitabine compressed together.

The pharmacological effect of the compound of formula one of the present application is already known, since document 1 discloses that the compound of formula 1 is therapeutically effective in the treatment of HIV, as well as the combination with other anti-HIV agents including tenofovir alafenamide and emtricitabine; Document 2 discloses that tenofovir alafenamide and emtricitabine are effective in the treatment of HIV when used alone or in combination with other anti-HIV agents in a single dose form. In view of the foregoing, it is considered that the claimed combination is derived from the prior art and does not demonstrate the technical characteristics of an unexpected and surprising effect.

It is established that the claims 1-10 do not have an inventive step according to Article 114 of the Intellectual Property Law.

INDUSTRIAL APPLICATION

The use of a tablet in a medical treatment method cannot be used in industry, therefore claim 10 does not have industrial applicability according to Article 112 of the Intellectual Property Law.

UNITY OF INVENTION

It is established that claims 1-10 comply with the requirements of unit of invention according to Article 110 of the Intellectual Property Law.

OBSERVATIONS:

1. The phrase "a pharmaceutically acceptable salt" in claims 1, 2, 7, 8 is not clear, because it does not provide all the technical characteristics for the understanding of said claims, leaving to the option of the applicant the use of the salts that are considered necessary.

2. The term "about" in claims 4, 7, 8 is imprecise.

3. The use of the conjunction "or" in the wording of claim 3 is not clear since it is not possible to accurately determine the compound to be protected.

4. The phrase "any one of claims" in claims 4-10 is not clear, because it is not possible to accurately determine the compound to be protected.

CONCLUSIONS

Claims 1-10 are new (Art. 113), do not possess inventive step (Art. 114), claim 10 does not have Industrial applicability (Art. 112), claims 1-10 have unity of invention (Art. 110).
Based on the breach of Articles 112, 114, and 138 of the Intellectual Property Law, it is recommended not to grant the title of Patent of Invention.

Signature Illegible
Dr. Sara Cristina Galán Mejía
Examiner of Patents

NATIONAL REGISTRATION CENTER
INTELLECTUAL PROPERTY DIRECTION
Patent of Invention Department

File No.: 5682/2018	Title of the invention: **THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS**
Date of Presentation: 08/11/2019	Priority: US201562253042P 20151109; US201662399999P 20160926

APPLICATION CLASSIFICATION:

A61K31/513; A61K31/5365; A61131/553; A61K31/675: A61K9/20; A61K9/24; A61K9/28; A61P31/18

SECTORS COMPRISED IN THE SEARCH

Electronic databases consulted during the search: ESPACENET, EPOLINE	Minimum documentation sought. Epo report, state of art

CONSIDERED RELEVANT DOCUMENTS

Category	Cited documents, with indication, if proceeds from the relevant parts	Relevant to claims No.
X	**D1. WO20141010023 (A1) (Published 23/12/2015) POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE.**	1-10
X	**D2. WO2013116720 (A1) (Published 08/08/2013) COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THYE TREATMENT OF VIRAL INFECTIONS**	1-10
X	**D3. WO2015022351 (A1) (Published 19/02/2015) MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR**	1-10

Categories:
"A" document that defines the general state of the art not considered as particularly relevant.
"E" prior patent application or patent but published in the international filing date or later date.
"L" document that may raise doubts about a priority claim or that is cited or to determine the date of publication of another cite or for a special reason.
"O" document that refers to an oral disclosure, to an exposition or by any other means.
"P" document published prior to the international filing date but after the claimed priority date.
"T" a subsequent document published after the date of international filing or prior to the relevant prior art but cited as permitting an understanding of the principle or theory which forms the basis of the invention.
"X" particularly relevant document; the claimed invention cannot be considered new or that implies an inventive step by reference to the document considered in isolation.
"Y" particularly relevant document; the claimed invention cannot be considered new or that implies an inventive step when the document is associated to other or others documents of the same nature, whose combination is evident for a skilled in the art.
"&" document forming part of the same patent family.

Examiner's Name: Sara Cristina Galán Mejía	Date of preparation of the report: 10/12/2018

National Registration Center Intellectual Property Direction Fund Examination Planning and Search Strategy	**File:** **5682/2018** **Presentation Date:** 08/11/2016 **Priority:** US201562253042P 20151109; US201662399999P 20160926

1. -Invention Name: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

2. - Object of the invention:
It is the provision of an alternative pharmaceutical formulation comprising a compound of formula (1).

3. – Data bases used:

4. – Key words used in the international classification search (in Spanish and English must be written synonyms). Define search strategy

WO20141010023 (A1) (Published 23/12/2015)
LYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE.
They describe compounds for use in the treatment of human immunodeficiency virus (HIV) infection.

D2. WO2013116720 (A1) (Published 08/08/2013)
COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THYE TREATMENT OF VIRAL INFECTIONS
It refers to the use of the hemifumarate form of {9-[(R)-2-[L(S)-[[(S)-1-(isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]methoxy]propyl]adenine} (hemifumarate of tenofovir alafenamide) in combination with cobicistat.

D3. WO2015022351 (A1) (Published 19/02/2015)
MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR
Refers to a pharmaceutical combination comprising (a) dolutegravir, (b) emtricitabine and (c) tenofovir or a prodrug thereof, wherein preferably the compounds are present in a specific weight ratio and/or in specific amounts, for use as a medicament, preferably in the treatment of a viral infection/disease such as an HIV infection.

5. – Important notes:
Denied art 114, 112, 138

Date: 10/12/2018
Examiner: Sara Cristina Galán Mejia

93

INFORME TÉCNICO

A: **Lic. Luis Alonso Cáceres**
Jefe del departamento de patentes

De: **Lic. Sara Cristina Galán Mejía**
Examinador de Fondo

Asunto: COMPOSICIONES TERAPEUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA.
Expediente: 5682/2018
Prioridad: US201562253042P 20151109; US201662399999P 20160926
Fecha de Presentación: 08/11/2016
Fecha de Examen: 10/12/2018

TEXTO ANALIZADO

- Memoria descriptiva originalmente presentada
- 10 Reivindicaciones originalmente presentadas

SUFICIENCIA Y CLARIDAD DE LA INVENCION

1. La frase **"una sal farmacéuticamente aceptable"** en reivindicaciones 1, 2, 7, 8, no es clara, debido a que no proporciona todas las caracteristicas técnicas para la comprensión de dichas reivindicaciones, dejando a opción del solicitante la utilización de las sales que se consideren necesarias.

2. El término **"aproximadamente"** en reivindicaciones 4, 7, 8, es impreciso.

3. La utilización de la conjunción **"o"** en la redacción de la reivindicación 3 no es clara ya que no es posible determinar con precisión el compuesto a proteger.

4. La frase **"cualquiera de las reivindicaciones"** en reivindicaciones 4-10 no es clara, debido a que no es posible determinar con precisión el compuesto a proteger.

Las reivindicaciones 1-10 No cumplen con los requisitos del Art. 138 de la Ley de Propiedad Intelectual.

PATENTABILIDAD

Las reivindicaciones 1-10 no se encuentran dentro del alcance del Art. 107 de la Ley de Propiedad Intelectual.

NOVEDAD:

Después de realizar una revisión bibliográfica del estado de la técnica tanto en el ámbito nacional como internacional se encontró que las publicaciones más cercanas son:

La búsqueda nacional se anexa al informe.

D1. WO2014100323 (A1) (Publicado 23/12/2015)

POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE.

Se describen compuestos para uso en el tratamiento de la infección por el virus de inmunodeficiencia humana (VIH). Los compuestos tienen la siguiente fórmula (I): incluidos los estereoisómeros y las sales farmacéuticamente aceptables de los mismos, en la que R1, X, W, Y1, Y2, Z1 y Z4. También se describen métodos asociados con la preparación y el uso de tales compuestos, así como composiciones farmacéuticas que comprenden dichos compuestos.

El documento 1 no afecta la novedad de la solicitud examinada.

D2. WO2013116720 (A1) (Publicado 08/08/2013)

COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

Se refiere al uso de la forma hemifumarato de {9 - [(R) -2 - [[(S) - [[(S) -l- (isopropoxicarbonil) etil] amino} fenoxifosfinil] metoxi] propil] adenina} (hemifumarato de tenofovir alafenamida) en combinación con cobicistat. Además se describe la combinación de **hemifumarato de tenofovir, alafenamida,** cobicistat, **emtricitabina** y elvitegravir y la combinación de **hemifumarato de tenofovir, alafenamida** cobicistat, **emtricitabina** y darunavir.

El documento 2 no afecta la novedad de la solicitud examinada.

D3. WO2015022351 (A1) (Publicado 19/02/2015)

MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR

Se refiere a una combinación farmacéutica que comprende (a) dolutegravir, (b) **emtricitabina y (c) tenofovir** o un profármaco del mismo, en donde preferiblemente los compuestos están presentes en una relación en peso especifica y / o en cantidades especificas, para uso como medicamento, preferiblemente en el tratamiento de una infección / enfermedad viral como una infección por VIH. Además se refiere a una composición farmacéutica que comprende la combinación farmacéutica y opcionalmente otro (s) excipiente (s) farmacéutico (s).

El documento 3 no afecta la novedad de la solicitud examinada.

No se encontró ningún documento igual a la presente solicitud; por lo tanto se determina que las reivindicaciones 1-10 son nueva según el Artículo 113 de la Ley de Propiedad Intelectual.

NIVEL INVENTIVO.

El objetivo de la solicitud examinada es la provisión de una formulación farmacéutica alternativa que comprende un compuesto de fórmula (1).

El documento 1 describe tabletas en una forma de dosificación única que comprende un compuesto de fórmula (1) que incluye los compuestos 42 y 45.

El documento 2 describe una tableta monocapa y bicapa que comprende en una sola capa tenofovir alafenamida y emtricitabina comprimidas juntas.

El efecto farmacológico del compuesto de fórmula uno de la presente solicitud ya es conocido con anterioridad, pues documento 1 describe que el compuesto de fórmula I es terapéuticamente eficaz en el tratamiento del VIH, así como también la combinación con otros agentes anti-VIH que incluye tenofovir alafenamida y emtricitabina; documento 2 describe que tenofovir alafenamida y emtricitabina son efectivos en el tratamiento del VIH cuando se usan solos o en combinación con otros agentes anti-VIH en una forma de dosis única. En vista de lo anterior se considera que la combinación reivindicada es derivada del estado de la técnica anterior y no demuestra las características técnicas de un efecto inesperado y sorprendente.

Se establece que las reivindicaciones 1-10 No poseen nivel inventivo según el Artículo 114 de la Ley de Propiedad Intelectual.

APLICACIÓN INDUSTRIAL

El uso de un comprimido en un método de tratamiento médico no puede ser utilizado en la industria, por lo tanto la reivindicación 10 No posee aplicabilidad industrial según el Artículo 112 de la Ley de Propiedad Intelectual.

UNIDAD DE INVENCIÓN

Se establece que las reivindicaciones 1 -10 cumplen con los requisitos de unidad de invención según el Artículo 110 de la Ley de Propiedad Intelectual.

OBSERVACIONES:

1. La frase **"una sal farmacéuticamente aceptable"** en reivindicaciones 1, 2, 7, 8, no es clara debido a que no proporciona todas las características técnicas para la comprensión de dichas reivindicaciones, dejando a opción del solicitante la utilización de las sales que se consideren necesarias.

2. El término **"aproximadamente"** en reivindicaciones 4, 7, 8, es impreciso.

3. La utilización de la conjunción **"o"** en la redacción de la reivindicación 3 no es clara ya que no es posible determinar con precisión el compuesto a proteger.

4. La frase **"cualquiera de las reivindicaciones"** en reivindicaciones 4-10 no es clara, debido a que no es posible determinar con precisión el compuesto a proteger.

CONCLUSIONES

Las reivindicaciones 1-10 son nuevas (Art. 113), No poseen nivel inventivo (Art. 114), la reivindicación 10 No posee aplicabilidad Industrial (Art.112), las reivindicaciones 1-10 poseen unidad de invención (Art. 110).

En base al incumplimiento a los Artículos 112, 114, y 138 de la Ley de Propiedad Intelectual, se recomienda No otorgar el título de Patente de Invención.

Lic. Sara Cristina Galán Mejía
Examinadora de Patentes.

CENTRO NACIONAL DE REGISTROS
DIRECCION DE PROPIEDAD INTELECTUAL
Departamento de Patentes de Invención

No. Expediente 5682/2018	Título de la Invención. COMPOSICIONES TERAPEUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA
Fecha de Presentación 08/11/2016	Prioridad: US20156225S3042P 20151109; US201662399999P 20160926

CLASIFICACIÓN DE LA SOLICITUD:

A61K31/513; A61K31/5365; A61K31/553; A61K31/675; A61K9/20; A61K9/24; A61K9/28; A61P31/18

SECTORES COMPRENDIDOS EN LA BUSQUEDA

Bases de datos electrónicas consultada durante la búsqueda: ESPACENET, EPOLINE	Documentación mínima buscada. Reporte de la epo, estado de la técnica

DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría	Documentos citados, con indicación, si procede de las partes relevantes	Relevante para las reivindicaciones No.
X	**D1. WO2014100323 (A1) (Publicado 23/12/2015)** **POLYCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE.**	1-10
X	**D2. WO2013116720 (A1) (Publicado 08/08/2013)** **COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS**	1-10
X	**D3. WO2015022351 (A1) (Publicado 19/02/2015)** **MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR**	1-10

Categorías

"A" documento que define el estado general de la técnica no considerado como particularmente relevante.

"E" solicitud de patentes o patente anterior pero publicada en la fecha de presentación internacional o fecha posterior.

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita o para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada)..

"O" documento que se refiere a una divulgación oral, a una exposición o por cualquier otro medio.

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada.

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad que no pertenece al estado de la técnica pertinente pero se cita por permitir la comprensión del principio o teoría que constituye la base de la invención.

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado.

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva cuando al documento se asocia a otro u otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia.

"&" documento que forma parte de la misma familia de patentes.

Nombre del Examinador Sara Cristina Galán Mejía	Fecha de elaboración del Informe 10/12//2018

	Centro Nacional de Registros Dirección de Propiedad Intelectual Planificación del Examen De fondo y su estrategia de búsqueda	**Expediente: 5682/2018 Fecha de Presentación: 08/11/2016 Prioridad:** US201562253042P 20151109; US201662399999P 20160926

1.-Nombre de la invención: COMPOSICIONES TERAPEUTICAS PARA EL TRATAMIENTO DEL VIRUS DE INMUNODEFICIENCIA HUMANA

2.-Objeto de la Invención: Es la provisión de una formulación farmacéutica alternativa que comprende un compuesto de fórmula (1).

3.-Bases de datos utilizadas:

4.- Palabras claves utilizadas en la búsqueda (en español e inglés se debe incluir sinónimos) y clasificación internacional .Definir estrategia de búsqueda

WO2014100323 (A1) (Publicado 23/12/2015)

YCYCLIC-CARBAMOYLPYRIDONE COMPOUNDS AND THEIR PHARMACEUTICAL USE.

Describen compuestos para uso en el tratamiento de la infección por el virus de inmunodeficiencia humana (VIH).

D2. WO2013116720 (A1) (Publicado 08/08/2013)

COMBINATION THERAPY COMPRISING TENOFOVIR ALAFENAMIDE HEMIFUMARATE AND COBICISTAT FOR USE IN THE TREATMENT OF VIRAL INFECTIONS

Se refiere al uso de la forma hemifumarato de {9 - [(R) -2 - [[(S) - [(S) -l- (isopropoxicarbonil) etil] amino] fenoxifosfinil] metoxi} propil] adenina} (hemifumarato de tenofovir alafenamida) en combinación con cobicistat.

D3. WO2015022351 (A1) (Publicado 19/02/2015)

MEDICAMENT COMPRISING A PHARMACEUTICAL COMBINATION OF DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR

Se refiere a una combinación farmacéutica que comprende (a) dolutegravir, (b) emtricitabina y (c) tenofovir o un profármaco del mismo, en donde preferiblemente los compuestos están presentes en una relación en peso específica y / o en cantidades específicas, para uso como medicamento, preferiblemente en el tratamiento de una infección / enfermedad viral como una infección por VIH.

5.- anotaciones importantes: Denegada art 114, 112, 138

Fecha. 10/12/2018
Examinador: Sara Cristina Galán Mejía

100

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
1147.P2F		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/060989	8 November 2016 (08-11-2016)	9 November 2015 (09-11-2015)
Applicant		
GILEAD SCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the drawings to be published with the abstract is Figure No. 5
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/060989

1101

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/513 A61K31/5365 A61K31/675
A61P31/18 A61K9/24 A61K31/553
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)
A61K

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, WPI Data, 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.
X,P	WO 2015/196116 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) abstract; claims 1, 12, 18-21	1-51
X,P	WO 2015/196137 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) abstract; claims 1, 38, 44-48	1-51
X	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) cited in the application	34
Y	abstract; claims 1, 32, 33-46; examples 104-107; compounds 42, 45 page 36, paragraph 12-13 page 37, paragraph 8-12 page 38, lines 14, 20	1-51

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
10 January 2017	24/01/2017

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	Madalinska, K

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/060989

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/116720 A1 (GILEAD SCIENCES INC [US]) 8 August 2013 (2013-08-08)	35
Y	abstract; claims 21-32 page 82, lines 13-15 paragraphs [0337], [0338], [0342], [0344] - [0345], [0349], [0355] paragraphs [0340], [0347]	1-51
Y	WO 2015/022351 A1 (RATIOPHARM GMBH [DE]) 19 February 2015 (2015-02-19) abstract; claims 1-6, 8-10, 12-15 page 18, lines 7-22 page 19, lines 3-12 page 19, line 30 - page 20, line 12 page 22, line 31 - page 15, line 17	1-51
Y	"Gilead and Tibotec finalize agreement on single-tablet HIV regimen", Thomson Reuters Drug News, 17 November 2011 (2011-11-17), XP055052007, Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_ficha_ref?p_ref_id=1729357 [retrieved on 2013-02-01] abstract	1-51

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/060989

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015196116 A1	23-12-2015	AU 2015276860 A1	22-12-2016
		TW 201613937 A	16-04-2016
		US 2016016973 A1	21-01-2016
		UY 36177 A	08-01-2016
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		AU 2013361401 A1	27-08-2015
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		CN 104995198 A	21-10-2015
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		ES 2577283 T3	14-07-2016
		HK 1205124 A1	11-12-2015
		HK 1216643 A1	25-11-2016
		HR P20160544 T1	15-07-2016
		JP 6028105 B2	16-11-2016
		JP 2016179996 A	13-10-2016
		JP 2016508134 A	17-03-2016
		KR 20150096504 A	24-08-2015
		MD 20150064 A2	30-11-2015
		NZ 709260 A	29-07-2016
		PE 14992015 A1	29-10-2015
		PH 12015501445 A1	14-09-2015
		PL 2822954 T3	30-09-2016
		PT 2822954 E	16-06-2016
		SG 11201504857S A	30-07-2015
		SI 2822954 T1	29-07-2016
		SM T201600157 B	31-08-2016
		TW 201441224 A	01-11-2014
		US 2014221356 A1	07-08-2014
		US 2016176885 A1	23-06-2016
		UY 35213 A	30-06-2014
		WO 2014100323 A1	26-06-2014
WO 2013116720 A1	08-08-2013	AU 2013204727 A1	22-08-2013
		AU 2013204731 A1	22-08-2013
		AU 2016203666 A1	23-06-2016
		CA 2863662 A1	08-08-2013
		CN 104105484 A	15-10-2014
		EA 201491287 A1	30-04-2015
		EP 2809323 A1	10-12-2014
		HK 1202801 A1	09-10-2015
		HK 1204914 A1	11-12-2015
		JP 2015505565 A	23-02-2015
		KR 20140119177 A	08-10-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/060989

104

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		MD 20140091 A2	31-01-2015
		NZ 629896 A	31-03-2016
		US 2015105350 A1	16-04-2015
		WO 2013116720 A1	08-08-2013
		WO 2013116730 A1	08-08-2013
WO 2015022351 A1	19-02-2015	CA 2920811 A1	19-02-2015
		EA 201690146 A1	29-07-2016
		EP 3033084 A1	22-06-2016
		JP 2016528240 A	15-09-2016
		US 2016184332 A1	30-06-2016
		WO 2015022351 A1	19-02-2015

ЕВРАЗИЙСКАЯ ПАТЕНТНАЯ ОРГАНИЗАЦИЯ (ЕАПО)
The Eurasian Patent Organization

ЕВРАЗИЙСКОЕ ПАТЕНТНОЕ ВЕДОМСТВО (ЕАПВ)
The Eurasian Patent Office

Россия, 109012, Москва, М. Черкасский пер., 2
2, M. Cherkassky per., Moscow 109012, Russia
Факс (Fax) +7(495) 621-2423, Email: info@eapo.org

Application No.: **201890654/28**

CONCLUSION
on patentability of the invention

The Eurasian Patent Office invites the Applicant to analyze the information below and express an opinion regarding the Examiner's Conclusion on Patentability of the Invention.

In accordance with Rule 49(4) of the Patent Regulations under the Eurasian Patent Convention (further – the Regulations), the additional materials requested by the Examiner shall be presented by the Applicant within 4 months from the mailing date of the Conclusion.

This term may be extended according to Rule 37(2) of the Instruction on the Applicant's request which shall be submitted prior to the expiry date upon payment of the additional fee as prescribed by item 8 of the Statute on Fees of the Eurasian Patent Office.

If the prescribed time limit is not observed, or the requested materials are not filed, the Eurasian application is considered to be abandoned.

The claimed invention relates to a drug for treating HIV-infection.

The examination has been carried out with respect to the original set of claims including 18 independent claims (Claims 1, 7, 8, 9, 11, 12, 16, 31, 34, 45, 46, 38, 39, 40, 43, 44, 46, 51).

1. D1 (EA201692414A1 having a priority date of 20.06.2014 considered as a prior art based on 4th paragraph of Rule 3(1) of the Regulations) discloses a combination for treating HIV, the combination comprising a compound of formula I – (2E,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 (see [0006], [0107], [0112], [0120], [0138], [0143]), - tenofovir alafenamide and emtricitabine and a combination of sodium salt 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 (a compound of formula II) (whole text, in particular: [0008], tenofovir alafenamide and emtricitabine (see [0083], in particular TRUVADA® (tenofovir disoproxil fumarate + emtricitabine, TDF+FTC); [0089]-[0097]). Similar information is disclosed in D2: EA201591027A1 and D3: EA201890236A1 (see, in particular, p. 15, line 6; p. 21, last paragraph; p. 39, lines 31-33; p. 40, lines 3-6,

Example 1), each having a priority date of 21.12.2012 and is included into the prior art domain based on the 4th paragraph of Rule 3(1) of the Regulations.

Based on the above, the Examiner has established that the claimed group of inventions does not meet "novelty" criterion for patentability (Rule 3(1) of the Regulations).

The Applicant is invited to submit convincing arguments in favour of the patentability of the claimed invention and amend the claims also taking into account that there is no technical relationship between the inventions, which is supposed to be expressed by one or more same or corresponding special technical features, i.e. technical features defining a contribution of each of the claimed inventions over the prior art (Rule 4 of the Regulations).

2. Document D6 indicated in the International Search Report (see the **Enclosure**) is not available to the Examiner:

Y	"Gilead and Tibotec finalize agreement on single-tablet HIV regimen", Thomson Reuters Drug News, 17 November 2011 (2011-11-17), XP055052097, Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_fiche_ref?p_ref_id=1729367 [retrieved on 2013-02-01] abstract	1-51

which is however required for the examination.

The Examiner kindly asks the Applicant to submit this document and express his opinion on the information disclosed therein.

3. In order to facilitate the prosecution, the Applicant is invited to submit amended claims complying with the "unity" requirement along with the explanations regarding technical effects achieved by each of the claimed inventions. The explanations shall be accompanied by indication of particular sections of the original application materials supporting the achievement of such technical effects.

The Examiner considers its necessary to draw the Applicant's attention to the following drawbacks of the set of claims.

4. A claim shall include a generic term reflecting a purpose of the invention (Rule 24(3) of the Regulations). Inasmuch as the claimed inventions relate to a field of pharmacy, the absence of an indication that they are used for the treatment of HIV-infection results in that the claims are unjustifiably broad and not supported by the application materials (see Claims 1, 7, 8, 9, 11, 12, 16, 34, 35, 36, 40, 43, 44, 46 and 51).

5. Claims 13, 14, 15 and 31 incorrectly refer to Claims 1-6 relating to a solid oral dosage form rather than a tablet (Rule 2.6.4 of the Rules for compiling, filing and examining Eurasian applications, further – the Rules).

A similar objection applies to Claims 38, 39 and 45.

6. Claims 18-20 recite the same designations to characterize layers (a), (b), (c) as used earlier in Claims 16 and 17 to characterize the components. It makes the claims unclear (Rule 21[1](4) of the Instruction).

7. Claims 26 and 27 recite an amount of the compound I as "less than about" without indication of the lower limit of the range. The Applicant's attention is drawn to the fact that the Examiner has not found reliable data demonstrating the possibility of carrying out the claimed inventions at the very low amount of the compound I with achievement of the claimed technical effects, which raises a question whether these claims are sufficiently disclosed in the specification (Rule 21[1](3) of the Regulations; Rule 5.5 of the Rules).

8. The subject matter of Claim 38 characterizes a "use" rather than a "substance" (solid oral dosage form) (see Rules 2.5.4.8 and 2.6.9 of the Rules). In the Examiner's opinion, this claim is independent. A claim shall define an object of the invention and express its essence (Rule 21[1](4) of the Regulations).

Further, the Examiner notes that a tablet represent a specific embodiment of a solid oral dosage form and therefore it shall be made subject of a separate dependent claim (Rule 2.6.4 of the Rules).

9. In order to make the claims clear (Rule 21[1](4) of the Regulations), the Applicant is invited to specify Claims 40, 43, 44, 46 and 51 with the structure of the compound I in a similar manner as suggested in the preceding independent claims.

10. The Examiner draws the Applicant's attention to the fact that Claim 42 does not develop the features of Claims 40-41 but the features of another invention, which is a multilayer tablet. Hence Claim 42 does not comply with the requirements applicable to dependent claims (Rule 2.6.4 of the Rules).

11. The features of Claims 46-51 cannot be used to characterize a "composition" in the light of Rules 2.5.4.4 of the Rules.

The feature of Claim 46 mentioned in brackets makes the claim unclear (Rule 211(4) of the Regulation), and the feature "e.g." means that it is a particular embodiment, therefore it shall be claimed in a separate dependent claim (Rule 2.6.4 of the Rules).

The examination will be continued once the Applicant's response is received.

Any claim amendments shall not go beyond the original Eurasian application, as submitted on the filing date (Rule 49(3) of the Regulations; Rule 5.4 of the Rules).

The amended claims shall be accompanied by a letter (Rule 2.12 of the Rules) and, if necessary, an additional fee shall be paid (Rule 5.4. of the Rules).

Enclosure:

International Search Report on 5 p., 1 copy.[1]

Examiner **A.V. Golubev**

Telephone: +7(495)411-61-61 (ext.) 315

[1] See Notification in Russian.

ЕВРАЗИЙСКАЯ ПАТЕНТНАЯ ОРГАНИЗАЦИЯ (ЕАПО)
Eurasian Patent Organization

ЕВРАЗИЙСКОЕ ПАТЕНТНОЕ ВЕДОМСТВО (ЕАПВ)
Eurasian Patent Office

М. Черкасский пер., 2, Москва, 109012, Россия
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Номер заявки: **201890654/28**

ЗАКЛЮЧЕНИЕ
о патентоспособности изобретения

Евразийское патентное ведомство предлагает проанализировать нижеприведенную информацию и выразить мнение относительно заключения экспертизы о патентоспособности изобретения.

В соответствии с правилом 49(4) Патентной инструкции к Евразийской патентной конвенции (далее – Инструкция) ответ заявителя должен быть представлен в четырехмесячный срок, исчисляемый с даты направления настоящего уведомления.

Этот срок в соответствии с установленной правилом 37(2) Инструкции процедурой может быть продлен по просьбе заявителя, направленной до его истечения, при условии уплаты установленной пунктом 8 Положения о пошлинах Евразийской патентной организации дополнительной пошлины.

В случае нарушения этого срока или непредставления запрошенных в уведомлении материалов евразийская заявка считается отозванной.

Заявленное изобретение относится к средству для лечения ВИЧ-инфекции.

Рассмотрена первоначальная формула изобретения, включающая 18 независимых пунктов (пп. 1, 7, 8, 9, 11, 12, 16, 31, 34, 35, 36, 38, 39, 40, 43, 44, 46, 51).

1. Из Д1: EA201692414A1, имеющей приоритет от 20.06.2014 и содержание которой включено в предшествующий уровень техники в соответствии с абзацем четвертым правила 3(1) Инструкции, известна комбинация для лечения ВИЧ соединения формулы I - (2R,5S,13aR)-8-гидрокси-7,9-диоксо-N-(2,4,6-трифторбензил)-2,3,4,5,7,9,13,13a-октагидро-2,5-метанопиридо[1',2':4,5]пиразино[2,1-b][1,3]оксазепин-10-карбоксамида (см. [0006], [0107], [0112], [0120], [0138], [0143]), - тенофовира алафенамида и эмтрицитабина и комбинация натриевой соли (2R,5S,13aR)-8-гидрокси-7,9-диоксо-N-(2,4,6-трифторбензил)-2,3,4,5,7,9,13,13a-октагидро-2,5-метанопиридо[1',2':4,5]пиразино[2,1-b][1,3]оксазепин-10-карбоксамида (соединение формулы II) (весь текст, особенно: [0008]), тенофовира алафенамида и эмтрицитабина (см. [0083], в частности: TRUVADA® (тенофовир дизопроксил фумарат + эмтрицитабин, TDF+FTC); [0089]-[0097]). Аналогичные сведения раскрыты в Д2: EA201591027A1 и Д3: EA201890236A1 (см., в частности, с. 15 строка 6; с. 21 последний абзац; с. 39 строки 31-33; с. 40 строки 3-6; Пример 1), каждая из которых имеет приоритет от 21.12.2012 и содержание которых включено в предшествующий уровень техники в соответствии с абзацем четвертым правила 3(1) Инструкции.

В связи с вышеизложенным, экспертиза делает вывод, что заявленная группа изобретений не соответствует условию патентоспособности «новизна» (правило 3(1) Инструкции).

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1663 of 1915

Заявителю предлагается представить убедительные доводы, обосновывающие патентоспособность заявленного изобретения, и внести в формулу необходимые изменения, с учетом того, что между изобретениями также отсутствует техническая взаимосвязь, которая должна выражаться одним или несколькими одинаковыми или соответствующими особыми техническими признаками, т.е. такими техническими признаками, которые определяли бы вклад, вносимый в уровень техники каждым из заявленных изобретений (правило 4 Инструкции).

2. В доступных эксперту источниках отсутствует указанный в Отчете о международном поиске (см. **Приложение**) документ D6:

Y	"Gilead and Tibotec finalize agreement on single-tablet HIV regimen", Thomson Reuters Drug News, 17 November 2011 (2011-11-17), XP055052007, Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_ficha_ref?p_ref_id=1729357 [retrieved on 2013-02-01] abstract	1-51

с которым ему необходимо ознакомиться.

Убедительная просьба к заявителю представить указанный документ и выразить свое мнение относительно содержащейся в нем информации.

3. С целью ускорения производства по рассматриваемой заявки одновременно с представлением формулы, соответствующей требованию единства изобретения, заявителю предлагается представить свои пояснения относительно достигаемых технических результатов, связываемых им с каждым из объектов изобретения в представляемой формуле. Свои пояснения заявителю следует сопроводить ссылкой на конкретные места в первоначальных материалах заявки, где такое достижение технических результатов по отношению к конкретным объектам изобретения было раскрыто и подтверждено.

Экспертиза считает необходимым также обратить внимание заявителя на следующие недостатки формулы изобретения.

4. Пункт формулы должен включать родовое понятие, отражающее назначение изобретения (правило 24(3) Инструкции). Поскольку заявленные изобретения относится к фармацевтике, то отсутствие указания на то, что лечат ВИЧ-инфекцию, приводит к необоснованно широким притязаниям, не подтвержденным материалами заявки (см. пп. 1, 7, 8, 9, 11, 12, 16, 34, 35, 36, 40, 43, 44, 46, 51).
5. Пункты 13, 14, 15 и 31 неверно ссылаются на пп. 1-6, где заявлена твердая пероральная лекарственная форма, а не таблетка (п. 2.6.4 Правил составления, подачи и рассмотрения евразийских заявок, далее – Правила).

Аналогичное замечание относится к пп. 38, 39, 45.

6. В пп. 18-20 для характеристики слоев использованы те же самые обозначения (a), (b), (c), что были использованы ранее в пп. 16, 17, на которые они ссылаются, для характеристики

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1664 of 1915

компонентов. Указанное вносит в формулу неясность и неточность (правило 21^1(4) Инструкции).

7. В пп. 26, 27 указано содержание соединения I в формулировке «менее чем приблизительно» без указания нижней границы диапазона. Экспертиза обращает внимание заявителя на то, что в материалах заявки не найдено достоверных сведений о возможности реализации заявленного средства со сверхмалым содержанием соединения I с достижением заявленных технических результатов, что поднимает вопрос о несоответствии изобретений по указанным пунктам требованию достаточности раскрытия (правило 21^1(3) Инструкции; п. 5.5 Правил).
8. Совокупность признаков изобретения по п. 38 характеризует не объект «вещество» (твердая пероральная лекарственная форма), а объект «применение» (см. 2.5.4.8, 2.6.9 Правил); по мнению экспертизы, указанный пункт является независимым пунктом. Формула изобретения должна определять объект изобретения и выражать его сущность (правило 21^1(4) Инструкции).

   Кроме того, экспертиза отмечает, что таблетка является частным случаем твердой пероральной лекарственной формы и потому соответствующий признак должен быть вынесен в зависимый пункт (п. 2.6.4 Правил).
9. Для внесения в формулу точности (правило 21^1(4) Инструкции) заявителю следует в пп. 40, 43, 44, 46, 51 указать структуру соединения I, как это было сделано в предшествующих независимых пунктах.
10. Экспертиза обращает внимание на то, что в использованной в п. 42 формулировке развиваются не признаки изобретения по пп. 40-41, а признаки другого объекта – многослойной таблетки, что нарушает требования к зависимым пунктам (п. 2.6.4 Правил).
11. Признаки пп. 46-51 не могут быть использованы для характеристики объекта «композиция» в свете требований п. 2.5.4.4 Правил.

    Признак п. 46, указанный в скобках, в таком изложении вносит в формулу неясность и неточность (правило 21^1(4) Инструкции), а «например» указывает на частный случай выполнения, который должен быть вынесен в зависимый пункт (п. 2.6.4 Правил).

Экспертиза по существу будет продолжена после получения ответа от заявителя.

Вносимые в формулу изменения не должны выходить за рамки материалов заявки, в отношении которых была установлена дата подачи евразийской заявки (правило 49(3) Инструкции; п. 5.4 Правил).

Измененная формула должна сопровождаться письмом (п. 2.12 Правил) и уплатой в необходимых случаях дополнительной пошлины (п. 5.4 Правил).

Приложение:
Отчет о международном поиске на 5 с. в 1 экз.

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Отдела химии и медицины

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Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1665 of 1915

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
1147.P2F		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/060989	8 November 2016 (08-11-2016)	9 November 2015 (09-11-2015)
Applicant		
GILEAD SCIENCES, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. [ ] **Certain claims were found unsearchable** (See Box No. II)
3. [ ] **Unity of invention is lacking** (see Box No III)
4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority
6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 5
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/060989

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/513 A61K31/5365 A61K31/675
A61P31/18 A61K9/24 A61K31/553
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)
A61K

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, WPI Data, 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.
X,P	WO 2015/196116 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) abstract; claims 1, 12, 18-21	1-51
X,P	WO 2015/196137 A1 (GILEAD SCIENCES INC [US]) 23 December 2015 (2015-12-23) abstract; claims 1, 38, 44-48	1-51
X	WO 2014/100323 A1 (GILEAD SCIENCES INC [US]) 26 June 2014 (2014-06-26) cited in the application	34
Y	abstract; claims 1, 32, 33-46; examples 104-107; compounds 42, 45 page 36, paragraph 12-13 page 37, paragraph 8-12 page 38, lines 14, 20	1-51

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[X] Further documents are listed in the continuation of Box C. [X] 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
10 January 2017	24/01/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Madalinska, K

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/060989

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/116720 A1 (GILEAD SCIENCES INC [US]) 8 August 2013 (2013-08-08)	35
Y	abstract; claims 21-32 page 82, lines 13-15 paragraphs [0337], [0338], [0342], [0344] - [0345], [0349], [0355] paragraphs [0340], [0347] -----	1-51
Y	WO 2015/022351 A1 (RATIOPHARM GMBH [DE]) 19 February 2015 (2015-02-19) abstract; claims 1-6, 8-10, 12-15 page 18, lines 7-22 page 19, lines 3-12 page 19, line 30 - page 20, line 12 page 22, line 31 - page 15, line 17 -----	1-51
Y	"Gilead and Tibotec finalize agreement on single-tablet HIV regimen", Thomson Reuters Drug News, 17 November 2011 (2011-11-17), XP055052007, Retrieved from the Internet: URL:https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_ref_list.xml_show_ficha_ref?p_ref_id=1729357 [retrieved on 2013-02-01] abstract -----	1-51

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/060989

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015196116 A1	23-12-2015	AU 2015276860 A1	22-12-2016
		TW 201613937 A	16-04-2016
		US 2016016973 A1	21-01-2016
		UY 36177 A	08-01-2016
		WO 2015196116 A1	23-12-2015
WO 2015196137 A1	23-12-2015	AU 2015276881 A1	15-12-2016
		TW 201613936 A	16-04-2016
		US 2015366872 A1	24-12-2015
		UY 36176 A	08-01-2016
		WO 2015196137 A1	23-12-2015
WO 2014100323 A1	26-06-2014	AR 094197 A1	15-07-2015
		AU 2013361401 A1	27-08-2015
		BR 112015014714 A2	05-01-2016
		BR 122015029881 A2	22-03-2016
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Form PCT/ISA/210 (patent family annex) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/060989

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NZ 629896 A	31-03-2016
		US 2015105350 A1	16-04-2015
		WO 2013116720 A1	08-08-2013
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		JP 2016528240 A	15-09-2016
		US 2016184332 A1	30-06-2016
		WO 2015022351 A1	19-02-2015

Form PCT/ISA/210 (patent family annex) (April 2005)

Industria y Comercio
SUPERINTENDENCIA

TODOS POR UN NUEVO PAÍS

REPUBLIC OF COLOMBIA
SUPERINTENDENCE OF INDUSTRY AND TRADE

Official Letter N° 9194

File Reference N° NC2016/0005794

Mr./Ms.
GILEAD SCIENCES, INC.

Subject: PCT Patent

Based on the provisions of Article 43 of Decision 486 of the Commission of the Andean Community, it is informed that the opposition presented by Doctor José Luis Reyes Villamizar, in his capacity as attorney of TECNOQUÍMICAS S.A., meets the formal requirements required by law at the time of presentation.

In compliance with the provisions in the mentioned norm, it is granted a term of sixty (60) working days following the date of notification of this Letter, to assert its arguments and present evidence..

Notify this official letter according to the provided by Title I, Procedures before the Superintendence of Industry and Trade; Sixth Chapter, publication, communication, notification, and enforcement of the decisions of the Superintendence of Industry and Trade, informing them that no appeal may be lodged against the same.

The above letter was prepared on June 20, 2017.
Yours Sincerely,

Signature illegible
JOSE LUIS SALAZAR LÓPEZ
DIRECTOR OF NEW CREATIONS (C)

Elaborated by: CLAUDIA YANETH ALZATE RIOS.

Industria y Comercio SUPERINTENDENCIA	**File N°:** NC2016/0005794 **Folios:**0 **Dependence:** 2020 **Date:** 2016-12-26 16: **Application type:** Opposition Application **Referrer number:** 15265717

DIRECTION OF NEW CREATIONS
OPPOSITION PRESENTATION

1. **Opposition to application of:**
   - [X] Patent of invention
   - [ ] Industrial Design Registration
   - [ ] Utility Model Patent
   - [ ] Circuit Layout Scheme

File N° 15-265-717
Applicant: GILEAD SCIENCES, INC.
Agent: Alicia Lloreda Ricaurte
Title of the new creation: POLYCYCLIC CARBAMOYLPYRIDONE COMPOUNDS
Gazette: 772 of September 30, 2016.

2. Data of the Opponent

[ ] Natural person [X] Legal person

TECNOQUIMICAS S.A.

Name or designation / Full social reason

Identification document: C.C. [ ] C.E. [ ] NIT [X] Other [ ] Which_____
Number 890300466-5

Address: 23rd street No. 7-39. City: Cali
Phone: (092) 882.55.55 Fax: (092) 883.88.59 E-mail: _____

[ ] I hereby expressly authorize the Superintendence of Industry and Trade so that all communications are sent through the email address.

3. Data of the representative or agent:

REYES VILLAMIZAR JOSE LUIS	79`152.473	44655
Last name and Name	Identification document	T.P. No.

Representative address
Cra. 17 No. 88-23 Of. 205

E-mail address number	No. Fax	Phone
info@reyes-abogados.com	621.25.42	621.26.31

In case of having presented general power of attorney for matters brought before the Delegation of Industrial Property, please indicate the number of your filing.

6. Fundaments of Opposition

Causal: Non-compliance with patentability requirements (Title II, Chapter I, Decision 486 of 2000)

JUSTIFICATION: SEE ANNEX

Extension: **YES** ☒ **NO** ☐

7. Attachments

☒ Payment receipt of the fee for filing the application No._____ Date_____
☒ Power, if it was the case with which the presentation is credited
☒ Evidence of the foundations of the opposition
☐ Copies for transfers

8. Signature

JOSE LUIS REYES VILLAMIZAR	**79`152.473**	**44655**
Last name and Name	**C.C**	**T.P.**

SUPERINTENDENCE OF INDUSTRY AND TRADE

E. S.

D.

REF: FILE 15-265-717

Title: "POLYCYCLIC CARBAMOYLPYRIDONE COMPOUNDS"

PUBLICATION: Gazette No. 772 of September 30, 2016.

PRIORITY: **US 61/45,375 21/12/2012**
US 61/88,397 15/032013
US 61/845,803 12/07/2013

APPLICANT: GILEAD SCIENCES, INC.

AGENT: Alicia Lloreda Ricaurte

PROCEDURE: PRESENTATION OF OPPOSITION

JOSE LUIS REYES VILLAMIZAR, of major age, identified as appears at the foot of my signature, lawyer in office, holder of the professional card of number 44655 of the superior council of the judicature, acting as attorney of the company **TECNOQUIMICAS S.A.,** in exercise of the provisions of Article 42 of Decision 486 of 2000, very respectfully I allow myself to formulate the following

I. REQUEST

Be served to deny the patent benefit to the application contained in file 15-265-717, for do not comply with the provisions of Decision 486 of 2000, based on the grounds set out as follow.

II. LEGITIMATE INTERESTS

Attending TECNOQUIICAS S. A., legitimate interest to present this opposition, as the possible grant of the application would unreasonably restrict the use of certain substances, derivatives and processed that in our opinion lack inventive level, to the detriment of their legitimate commercial interests. Likewise, my clients are interested, due to the same condition of pharmaceutical companies, in avoiding the granting of patent privileges that include the material requirements of patentability established in the current regulations, and which pose a risk to free competition.

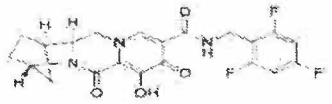
III. FUNDAMENTS OF OPPOSITION

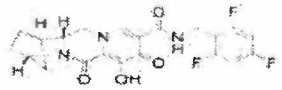
The Colombian patent application 15-265-717, referring to compounds derived from polycyclic carbamoylpyridones and their combination with additional agents against HIV, fails to comply with the material requirements for the grant of patent of invention, as may be determined by assessing the following arguments:

Lack of clarity and conciseness

First, the application lacks conciseness because it claims both the racemic mixture and the separated isomers

1. A compound having one of the following structures





or a pharmaceutically acceptable salt thereof.

In addition to the above, the application under study also does not meet the criterion of clarity in that it does not specifically define either the components nor the proportions thereof in the compositions of claims 4 to 9, as can be seen from reading the following claims.

4. A pharmaceutical composition comprising a compound of any of claims 1 to 3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

5. The pharmaceutical composition according to claim 4, wherein said pharmaceutical composition further comprises one or more additional therapeutic agents.

6. The pharmaceutical composition according to claim 4, wherein said pharmaceutical composition further comprises:

(a) an additional therapeutic agent;
(b) two additional therapeutic agents;
(c) three additional therapeutic agents; or
(d) four additional therapeutic agents

7. The pharmaceutical composition according to claim 5 or 6, wherein the additional therapeutic agent or agents are agents against HIV.

8. The pharmaceutical composition according to any of claims 5 to 7, wherein the additional therapeutic agent or agents are selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV transcriptase nucleoside inhibitors reverse, HIV nucleotides reverse transcriptase inhibitors, and combinations thereof.

According to the above, the application fails to comply with the provisions of Article 30 of D. 486 which states the following: *"Claims will define the subject matter to be protected by the patent. They should be clear and concise and fully supported by the specification"*.

The application further fails to support all and each one of the modalities teaches by the claim in the specification because the same does not disclose all the therapeutic agents, carriers or excipients claimed. Thus, claims do not find support in the specification so that this criterion is also not met in the present application.

Additionally, the only definitions of the additional active ingredients are found in claim 10, for example zidovudine, emtricitabine, didanosine, etc. Thus, the claims are not technically defined but fall within the field of speculation and cannot be considered clear without a definite structure.

Thus, the subject matter of claims and in general the application under study, cannot be object of patent since as disclosed, it fails to comply the minimum rules of presentation, such as clarity, conciseness, support, and non-patentability.

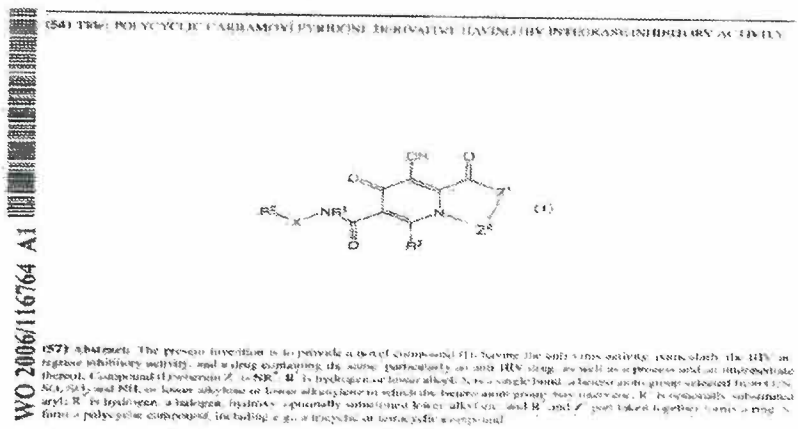
The application lacks inventive level.

Despite the objections raised in previous paragraphs, the matter claimed had already been disclosed in the state of the art, proof of this is found in the following documents published before the filing date of the application under study and which I quote below:

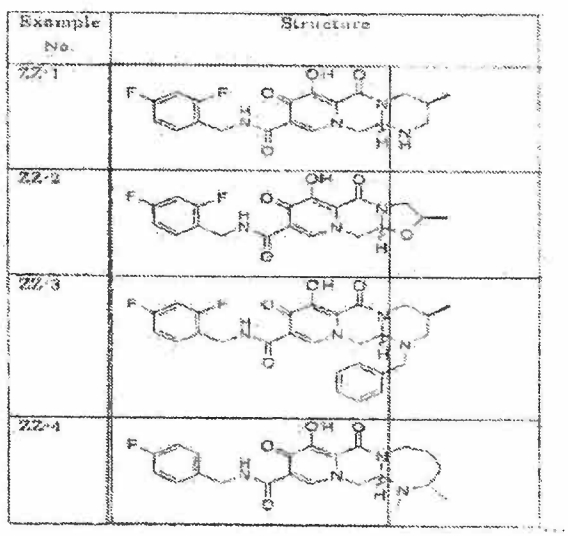
D1. WO 2006/116764 **"Polycyclic carbamoylpyridone derivates having HIV integrase inhibitory activity"** *Johns, Brian [US] Kawasuji, Takashi [JP], Taishi, Teruhiko [JP] 2006-02-11*

D2. EP 2412709 A1 **"Process for producing pyrone and pyridine derivates"** Sumino, Yukihito [JP], 2012-02-01

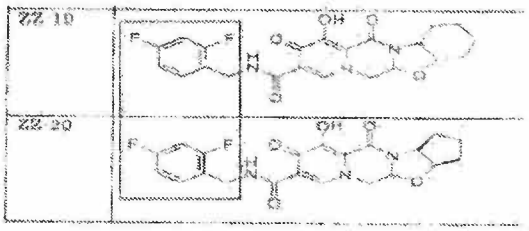
International publication WO 2016/1167764 (hereinafter Johns *et al.*) is considered to be the state of the art closest to the subject claimed by the application as it describes a compound of formula I derived from carbamoylpyridone having antiviral activity, in particular with HIV inhibitory activity and a composition thereof (see Abstract):



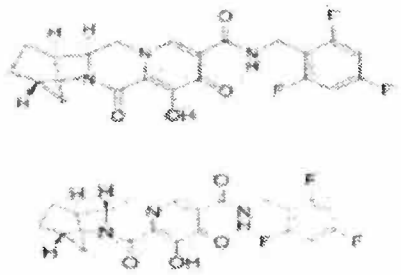
In a particular modality (examples ZZ-1 to ZZ-24), D1 refers to compounds containing the same core of the claimed compounds as shown in the following red box:



Also, R2 represents a benzyl having two fluorine atoms (see example ZZ19 and ZZ20):



and additionally the structure of the carbamoylpyridone derivative of these two compounds ZZ19 and ZZ20 suggests the enantiomer nature claimed by the application, being obvious to a person of ordinary skill in the art that the spatial configuration of the molecule is fundamental to the activity of the molecule as observed in the compound of claim 1 of the application under study as follows:



Thus, the claimed molecule differs in the presence of three fluorine atoms, instead of two, which substitution is obvious and evident to a person skilled in the art since the benzyl has a favorable position for the inclusion of a third fluorine that it is further capable of improving the liposoluble properties of the medicament, whereby the document of Jonhs *et al.*, suggests the combination of all the features defined by the claims.

Therefore, the idea of promote a carbamoylpyridone derivative compound according to the claimed formula and its enantiomeric form was suggested from the document of Johns *et al.*

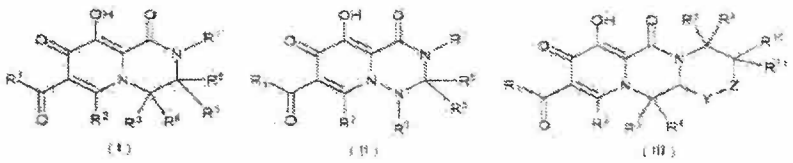
Despite this document alone is capable of misrepresenting the inventive level of the pending application, document EP 24127709 A1 (hereinafter Sumino *et al.*) also objects to the inventive level of the application being processed as it discloses pyrone and pyridone derivatives which are intermediates for the synthesis of anti-viral drugs such as anti-influenza and methods for producing them (see para. 0008) as claimed in claim 1 of the pending application:

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0008] An object of the present invention is to provide a novel pyrone derivative and a novel pyridone derivative which are novel intermediates for synthesizing an anti-influenza drug, a method of producing the same, and a method of using the same. Specifically, the object is to efficiently produce compounds and the like useful as an anti-influenza drug, which are exemplified by formula (I), formula (II) or formula (III):

[Chemical formula 1]

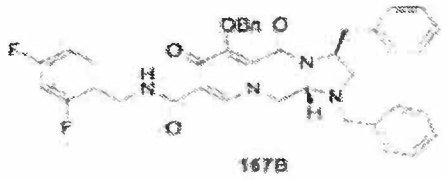


(I) (II) (III)

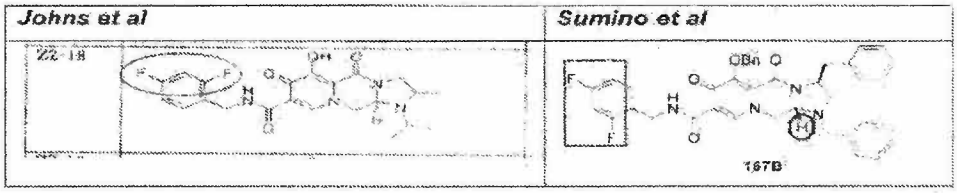
[wherein R^1 is lower alkyloxy optionally substituted by substituent E, carbocyclyl lower alkyloxy optionally substituted by substituent E, heterocyclyl lower alkyloxy optionally substituted by substituent E, carbocyclyl lower alkylamino optionally substituted by substituent E, or heterocyclyl lower alkylamino optionally substituted by substituent E.

Z is $CR^{12}R^{13}$, or a single bond,
Y is CH_2, an oxygen atom, or $N\text{-}R^{14}$,
R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently hydrogen, lower alkyl optionally substituted by substituent E, lower alkenyl optionally substituted by substituent E, lower alkynyl optionally substituted by substituent E, carbocyclyl lower alkyl optionally substituted by substituent E, or heterocyclyl lower alkyl optionally substituted by substituent E,
R^3 and R^5 may be taken together to form 4 to 8-membered carbocyclyl optionally substituted by substituent E, or 4 to 8-membered heterocyclyl optionally substituted by substituent E, or R^7 and R^9 may be taken together to form 4 to 8-membered heterocyclyl optionally substituted by substituent E,
wherein when Z is a single bond, R^{14} and R^{10} may be taken together to form 4 to 8-membered heterocyclyl optionally substituted by substituent E. Substituent E: halogen, cyano, hydroxy, carboxy, formyl, amino, oxo, nitro, lower alkyl

From the reading of the document by Sumino *et al.*, carbamoylpyridone derivative compounds can be obtained which are used as intermediates for compounds useful as therapeutic agents in reducing HIV replication and having an activity similar to that of the compounds claimed in the pending application; such is the case of compound 167B of document D2:



It is important to observed that even fluorine is in the complementary positions not cited by the Johns et al. document, so that an average technician in the field suggested by the combination of D1 and D2 teachings could have included F in all three positions under the teachings of the two documents, thus:



On the other hand, it is observed in compound 167B that the three-dimensional configuration of the H group (see blue circle) in the molecule was known and in combination with the document of Johns *et al.*, the basic structure obey the claimed by the claimed claims in the application in process.

Additionally, Johns *et al.* teaches the possibility of combining the carbamoylpyridone derivatives disclosed therein with other active agents as reverse transcriptase inhibitors and protease inhibitors:

34. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 33, or a pharmaceutically acceptable salt, or solvate thereof.

35. A pharmaceutical composition according to Claim 34, which is an anti-HIV agent.

54. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent select from reverse transcriptase inhibitors and protease inhibitors.

Therefore, the combination of the carbamoylpyridone derivatives with additional therapeutic agent such as HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV nucleoside reverse transcriptase inhibitors, and HIV nucleotide reverse transcriptase inhibitors, had already been anticipated by Johns *et al.*, so it is considered that the formulation containing said combination and its possible synergistic behavior is not new or inventive.

Finally, both the claimed compounds and compositions do not exhibit any surprising or unexpected technical property that may be considered useful to demonstrate the inventive level of the application; consequently, with the arguments given in this brief, a person skilled in the art would have easily derived the compound from the subject matter of the application, under a selection of intermediates and making use of the technical characteristics suggested by the documents of state the art and by the knowledge and own data used by the knowledge of the technical matter.

Please examine the arguments presented with the usual rigor and thoroughness and that consequently, in addition to the denial of the application in question, order the filing of the file containing it.

IV. FUNDAMENTALS OF LAW

They are the legal basis of Chapter I, (patentability requirements) and Article 42 (Opposition) of Decision 846 of 2000.

V. REQUEST FOR EXTRA TERM TO SUSTAIN THE OPPOSITION

In pursuance of the provisions of Article 42, paragraph 2 of Decree 486, I request a further period of sixty days to support the present opposition. For the above effects, I allowed myself to attach the corresponding proof of payment.

VI. PROOFS

I urge you to have as such, without prejudice to those that may arise at the expiration of the requested extension and those that the Office considers unofficially, the following:

WO 2006/116764 **"Polycyclic carbamoylpyridone derivates having HIV integrase inhibitory activity"** *Johns, Brian [US] Kawasuji, Takashi [JP], Taishi, Teruhiko [JP] 2006-02-11*

EP 2412709 A1 **"Process for producing pyrone and pyridine derivates"** Sumino, Yukihito [JP], 2012-02-01

VII. ANNEX

For the purposes of the corresponding procedure, I allowed myself to attach to this brief the following annexes:

1. Certificates of existence and legal representation of Tecnoquímicas S.A.
2. Power to act.
3. Proof of payment of opposition processing fees.
4. Proof of payment to support the request for extension referred to in Article 42, paragraph 2 of Decision 486.
5. The one mentioned in the proof paragraph.

VIII. NOTIFICATIONS

The undersigned will receive notifications in the secretariat of his Office or in my office located in Carrera 17 No. 88-23, office 205, Fax (1) 6212542 of this city. Tecnoquímicas S.A. will receive them at its offices located at Calle 23 N ° 7-39 in Cali.

Mr. Superintendent,

Siganture Illegible
JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 of Usaquén
T.P.A. 44.655 of C.S.J.

Sir
SUPERINTENDENCE OF INDUSTRY AND TRADE
E. S.
D.

REF: FILE 15-265-717

Title: "POLYCYCLIC CARBAMOYLPYRIDONE COMPOUNDS"

PUBLICATION: Gazette No. 772 of September 30, 2016.

PRIORITY: **US 61/45,375 21/12/2012**
US 61/88,397 15/032013
US 61/845,803 12/07/2013

APPLICANT: GILEAD SCIENCES, INC.

AGENT: Alicia Lloreda Ricaurte

PROCEDURE: PRESENTATION OF OPPOSITION

JOSE LUIS REYES VILLAMIZAR, known attorney of the company **TECNOQUIMICAS S.A.,** in the process of the reference, I proceed to support and complement the opposition presented on December 26, 2016, in the following terms:

I. RATIFICATION

The application 15-265-717, referring to compounds derived from polycyclic carbamoylpyridones and their combination with additional anti-HIV agents, lacks clarity and conciseness, and does not complies with the material requirements of patentability related to novelty and inventive level, according to the revelations of documents WO 2006/116764 and EP 2412709.

First, the application fails to meet the clarity requirement, as it does not specifically define the components or the proportions thereof within the compositions disclosed

in claims 4 to 9. Likewise, the application fails to provide adequate sustenance and support to the modalities claimed there.

On the other hand, there were mentioned documents which affect the inventive level of the application, firstly, the international publication WO 2006/116764, relating to a compound of formula I derived from carbamoylpyridone having antiviral activity in particular with HIV inhibitory activity and a composition thereof. In the same direction, EP 2412709 A1 discloses intermediary pyrone and pyridone derivatives for the synthesis of anti-viral drugs as anti-influenza and methods for producing them (see paragraph 0008) as claimed in claim 1 of the application in process.

II. COMPLEMENT OF INFORMATION

The application comprises compositions known in the state of the art

In connection with claims 4 to 11, the applicant maintains the possibility of claiming pharmaceutical compositions comprising the compounds of the invention without the need to exemplify their design and preparation and without the need to specify their specific ingredients, excipients and amounts/ratios. (p. 4).

In addition to noting that the claim in question conflicts with the art of writing patents of invention, I must reiterate that the claim chapter includes known compositions based on **one, two, three or four therapeutic agents** (claims 5 or 6), or containing **abacavir, tenofovir, tenofovir disoproxil fumarate, or tenofovir alaphenamide fumarate** (claims 8 to 11).

As can be seen in the following table, the modified claim chapter relates to a polycyclic compound and to a composition which may contain said polycyclic compound **or any therapeutic agent**:

Claim	Content
1-3	Polycyclic compound
4	Pharmaceutical composition of the polycyclic compound
5	Composition of the polycyclic compound with 1 or more therapeutic agents
6	Composition of the polycyclic compound with 1, 2, 3, or 4 therapeutic

	agents
7	Composition of the polycyclic compound with agents are agents against HIV.
8	A composition of the polycyclic compound wherein the additional therapeutic agent or agents are selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV nucleotide inverse transcriptase inhibitors, and combinations thereof.
9	A composition of the polycyclic compound wherein the additional therapeutic agent or agents are selected from the group consisting of HIV nucleoside reverse transcriptase inhibitors, HIV nucleotide reverse transcriptase inhibitors, and combinations thereof.
10	Composition of the polycyclic compound wherein the additional therapeutic agent or agents are selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, ±-FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxyl, apycythrin (AVX754), KP-1461, GS-9131 (Gilead Sciences), fosalvudine tidoxyl (formerly, HDP 99,0003), tenofovir, tenofovir disoproxil fumarate, alafenamida tenofovir fumarate (Gilead Sciences), GS- 7340 (Gilead Sciences), GS-9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) and CMX-157 (Chimerix).
11	A composition of the polycyclic compound wherein the additional therapeutic agent or agents are selected from the group consisting of abacavir, tenofovir, tenofovir disoproxil fumarate, and tenofovir alaphenamide fumarate.

From the foregoing, and assuming by way of example that the polycyclic compound is in a percentage between 0 and 1% w/w, the resulting compositions would contain only other therapeutic agents, such as abacavir, tenofovir, tenofovir disoproxil fumarate, and tenofovir Alafenamide fumarate.

It should be mentioned at this point that in the state of the art numerous compositions containing active substances such as Zidovudine, Emtricitabine, Didanosine, Stavudine, Abacavir, Tenofovir and Lamivudine and/or combinations thereof are known, as shown below:

- The scientific publication **"Combined Effect of Zidovudine (ZDV), Lamivudine (3TC) and Abacavir (ABC) Antiretroviral Therapy in Suppressing in Vitro FIV Replication."** by Bisset et al., 2001, presents the combined effect of zidovudine, lamivudine and abacavir as synergistic antiretroviral therapy. Let's see:

  In view of close similarities at the molecular and clinical levels, feline immunodeficiency virus (FIV) infection of the domestic cat is subject of increasing attention as an animal model for human immunodeficiency virus (HIV) infection. A range of reverse transcriptase inhibitors effective against HIV are also active against FIV, allowing successful use of the cat model to investigate drug interactions and resistance development. Nevertheless, while combined nucleoside analog and protease inhibitor usage has proven remarkably effective in treating HIV infection, combination antiretroviral therapy of FIV infection has been hampered by lack of protease inhibitors specific for FIV. In an attempt to circumvent this problem, we have examined the feasibility of applying in the FIV system combination protocols lacking a protease inhibitor. We now report that, as observed during HIV infection, the nucleoside analog abacavir (ABC or 1592U89) is able to effectively block in vitro FIV replication. Furthermore, we demonstrate that combined usage of ABC with the nucleoside analogs zidovudine (ZDV or AZT) and lamivudine (3TC) also blocks in vitro FIV replication in a synergistic manner. However, in contrast to its effect on HIV replication, the ribonucleotide reductase inhibitor hydroxyurea (HU) is unable to effectively control in vitro FIV replication.

- For its part, the scientific publication **"Synergistic Activity Profile of Griffithsin in Combination with Tenofovir, Maraviroc and Enfuvirtide against HIV-1 Clade C."** by Férir et al., 2011, mentions the use of tenofovir in combination with Carbohydrates for the treatment of HIV:}

  Tenofovir, a well-known and highly prescribed anti-HIV-1 drug for the treatment of HIV/AIDS infections, has recently also shown its effectiveness as a potential microbicide drug in the prevention of HIV transmission.
  Here, we evaluated the combination of tenofovir with various members of the class of carbohydratebinding agents (CBAs) targeting the glycans on the viral envelope gp120 for their anti-HIV efficacy. The tenofovir/CBA combinations predominantly showed synergistic antiviral activity using the median effect principle.
  These findings illustrate that combination of tenofovir with CBAs may increase the antiviral potency of the individual drugs and reducing the risk on potential side-effects.

- Third, the publication **"Synergistic in Vitro Anti-HIV Type 1 Activity of Tenofovir with Carbohydrate-Binding Agents (CBAs)"** by Férir et al., 2011 also discloses combinations of tenofovir and a novel anti-HIV agent:

  Griffithsin (GRFT) is possibly the most potent anti-HIV peptide found in natural sources. Due to its potent and broad-spectrum antiviral activity and unique safety profile it has great potential as topical microbicide component. Here, we evaluated various combinations of GRFT against HIV-1 clade B and clade C isolates in primary peripheral blood mononuclear cells (PBMCs) and in CD4+ MT-4 cells. In all combinations tested, GRFT showed synergistic activity profile with tenofovir, maraviroc and enfuvirtide based on the median effect principle with combination indices (CI) varying between 0.34 and 0.79 at the calculated EC95 level. Furthermore, the different glycosylation patterns on the viral envelope of clade B and clade C gp120 had no observable effect on the synergistic interactions.
  Overall, we can conclude that the evaluated two-drug combination increases their antiviral potency and supports further clinical investigations in pre-exposure prophylaxis for GRFT combinations in the context of HIV-1 clade C infection.

- On the other hand, the article **"Dose Proportional Inhibition of HIV-1 Replication by Mycophenolic Acid and Synergistic Inhibition in Combination with Abacavir, Didanosine, and Tenofovir"** published by Hossain et al., 2001, discloses the activity of mycophenolate mofetil in combination with Abacavir (ABC), didanosine (DDI), lamivudine (3TC) and tenofovir (TFV):

  Mycophenolate mofetil (MMF), a therapeutically used inhibitor of inosine monophosphate dehydrogenase is hydrolyzed to its active metabolite mycophenolic acid (MPA) in vivo. MPA exhibits anti-HIV activity in vitro. We tested MPA alone and in combination with abacavir (ABC), didanosine (DDI), lamivudine (3TC) and tenofovir (TFV) against wild-type human immunodeficiency virus type-1 (HIV-1) and nucleoside reverse transcriptase inhibitor (NRTI)-resistant HIV-1. MPA (62.5–500 nM), when combined with ABC or DDI, synergistically enhanced activity against wild-type HIV and the NRTI-resistant HIV clone DRSM34. MPA also enhanced the activity of TFV against both wild-type HXB2 and TFV-resistant strain HIVK65R, in a more than additive manner. No significant antiproliferative effect of MPA (S0.25 mM) alone or in the presence of ABC, DDI and TFV was observed. This indicates that the antiviral effects of MMF may be clinically achievable without fully blocking T-cell proliferation or inducing immunosuppression. These findings provide further rationale for the clinical testing of MMF in combination with ABC, DDI, and TFV.

- As a fifth reference, it should be mentioned the article **"Long-Term Successful Control of Super-Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection by Novel Combination Therapy of Raltegravir, Etravirine, and Boosted-Darunavir."** published by Nakamura et al., 2010, reveals the potential of a novel retroviral combination for the treatment of HIV infection:

  Drug-resistant virus infection has been a major hurdle in the management of human immunodeficiency virus type 1 (HIV-1) infection. Recently, three novel antiretrovirals [raltegravir (RAL), etravirine (ETR), and darunavir (DRV)] were introduced into the market almost simultaneously, and salvage regimens containing these three antiretrovirals have been reported to exhibit strong potency against drug-resistant HIV-1 infection. However, the sustainability of such regimens remains unclear, particularly for patients infected with multidrug-resistant viruses. Here we report a case of supermultidrug-resistant HIV-1 infection which has been successfully controlled by novel combination therapy including RAL, ETR, and DRV for over 2 years, indicating that the novel combination could become an ultimate weapon against drug-resistant HIV infection and could alter the landscape of HIV salvage therapy.

- Similarly, the article **"In Vivo Examination of Hydroxyurea and the Novel Ribonucleotide Reductase Inhibitors Trimidox and Didox in Combination with the Reverse Transcriptase Inhibitor Abacavir: Suppression of Retrovirus-Induced Immunodeficiency Disease"** published by Sumpter et al., reveals the potential of combined therapies for HIV treatment:

  Inhibition of ribonucleotide reductase (RR) has gained attention as a potential strategy for HIV-1 therapy through the success of hydroxyurea (HU) to potentiate the activity of the nucleoside reverse transcriptase inhibitor (NRTI) didanosine (ddI) in clinical trials. However, the use of HU has been limited by its development of hematopoietic toxicity. In this study, the novel RR inhibitors didox (DX; 3,4-dihydroxybenzohydroxamic acid), and trimidox (TX; 3,4,5-trihydroxybenzamidoxime) were evaluated along with HU for anti-retroviral efficacy in LPBM5-induced retroviral disease (MAIDS) both as monotherapeutic regimens and in combination with the guanine containing NRTI abacavir (ABC). Anti-retroviral drug efficacy was determined by measuring inhibition of splenomegaly, hypergammaglobulinemia, and splenic levels of proviral DNA. In this study, all RRIs tested showed the ability to improve the efficacy of ABC in the MAIDS model by reducing splenomegaly, hypergammaglobulinemia, and splenic proviral DNA levels.

As can be seen, combinations of antivirals for the treatment of HIV were already known in the state of the art and so would have suggested to a person skilled in the art the use of these combinations with high expectation of success, so combinations claimed by the applicant in the event that the percentage of the polycyclic compound is very low (which is possible since no preferred percentages are disclosed in the claim chapter), do not meet the requirement of novelty or inventive level.

The claims lack sustenance and support in the description

On the other hand, the applicant mentions that the specification sufficiently discloses the characteristics for developing the pharmaceutical compositions according to the invention. In view of this particular aspect, it should be noted that pages 34 to 38 of the specification relate to **general** and insufficient information as a basis of the claims, excipients and possible combination agents.

In the experimental section, it is observed that the closest to a composition is the liquid form for administering the polycycle to Beagle dogs in example 107:

Example 107

Pharmacokinetic analysis after oral or intravenous administration to Beagle dogs

Pharmacokinetic analysis was performed on various test compounds following intravenous or oral administration to Beagle dogs.

For the pharmacokinetic analysis of intravenously administered compounds, the test compounds were formulated in 5% ethanol, 55% PEG 300, and 40% water at 0.1 mg/ml for the IV infusion. For the pharmacokinetic analysis of orally administered compounds, the test compounds were formulated in an aqueous suspension in 0.1% Tween 20, 0.5% HPMC LV100 in DI water at 1 mg / kg.

However, there is no information available about a formulation containing the polycyclic in combination with an additional active ingredient, and much less, information that presents clear evidence on the advantages, unexpected and surprising technical effects achieved by the claimed combinations. Therefore, the combinations claimed specifically by the new claim chapter, i.e. the polycyclic compound + abacavir or tenofovir or tenofovir disoproxil fumarate or tenofovir alafenamide fumarate, among other combinations, cannot be considered to present evidence of such benefits.

Additionally, the mentioned references suggest the synergistic effect for combinations between antivirals as claimed in the new claim chapter, therefore, the combinations under study lack novelty and inventive level.

Finally, it is important to emphasize once again that WO 2006/116764 (Johns et al.) cited in the opposition brief teaches the possibility of combining the carbamoylpyridone derivatives disclosed therein with other active agents as reverse transcriptase inhibitors and protease inhibitors:

34. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 33, or a pharmaceutically acceptable salt, or solvate thereof.

35. A pharmaceutical composition according to Claim 34, which is an anti-HIV agent.

54. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent selected from reverse transcriptase inhibitors and protease inhibitors.

Therefore, the combination of the carbamoylpyridone derivatives with additional therapeutic agents such as HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV nucleoside reverse transcriptase inhibitors, and HIV nucleotide reverse transcriptase inhibitors, have already been anticipated by Johns et al., whereby the formulation containing said combination and its possible synergistic behavior is considered to be neither new nor inventive.

Consequently, we request the analysis of the presented arguments with the usual rigor and thoroughness, and that consequently, in addition to the denial of the application in question, oreder the filing of the file containing it.

III. PROOFS

1. Bisset, Leslie R, Hans Lutz, Jürg Böni, Regina Hofmann-Lehmann, Ruedi Lüthy, and Jörg Schüpbach. 2002 **"Combined Effect of Zidovudine (ZDV), Lamivudine (3TC) and Abacavir (ABC) Antiretroviral Therapy in Suppressing in Vitro FIV Replication."** *Antiviral Research* 53 (1): 35–45.

2. Férir, Geoffrey, Kenneth E. Palmer, and Dominique Schols. 2011. **"Synergistic Activity Profile of Griffithsin in Combination with Tenofovir, Maraviroc and Enfuvirtide against HIV-1 Clade C."** *Virology* 417 (2): 253–58.

3. Férir, Geoffrey, Kurt Vermeire, Dana Huskens, Jan Balzarini, Els J.M. Van Damme, Jan-Christoph Kehr, Elke Dittmann, Michael D. Swanson, David M. Markovitz, and Dominique Schols. 2011. **"Synergistic in Vitro Anti-HIV Type 1 Activity of Tenofovir with Carbohydrate-Binding Agents (CBAs)."** *Antiviral Research* 90 (3): 200–204.

4. Hossain, Mohammad M., Jason J. Coull, George L. Drusano, and David M. Margolis. 2002. **"Dose Proportional Inhibition of HIV-1 Replication by Mycophenolic Acid and Synergistic Inhibition in Combination with Abacavir, Didanosine, and Tenofovir."** *Antiviral Research* 55 (1): 41–52.

5. Nakamura, Hitomi, Noriaki Hosoya, Michiko Koga, Takashi Odawara, Tadashi Kikuchi, Ai Kawana-Tachikawa, Toshiyuki Miura, et al. 2011. **"Long-Term Successful Control of Super-Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection by a Novel Combination Therapy of Raltegravir, Etravirine, and Boosted-Darunavir."** *Journal of Infection and Chemotherapy* 17 (1): 105–10.

6. Sumpter, L.Ryan, Mohammed S. Inayat, Erin E. Yost, William Duvall, Espen Hagan, Christopher N. Mayhew, Howard L. Elford, and Vincent S. Gallicchio. 2004. **"In Vivo Examination of Hydroxyurea and the Novel Ribonucleotide Reductase Inhibitors Trimidox and Didox in Combination with the Reverse Transcriptase Inhibitor Abacavir: Suppression of Retrovirus-Induced Immunodeficiency Disease."** *Antiviral Research* 62 (3): 111–20.

Mr. Superintendent,

Siganture Illegible
JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 of Usaquén
T.P.A. 44.655 of C.S.J.

Industria y Comercio
SUPERINTENDENCIA

TODOS POR UN NUEVO PAÍS

REPÚBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Oficio N° 9194

Ref. Expediente N° NC2016/0005794

Señor(a)
GILEAD SCIENCES, INC.

Asunto :

Patente de Invención PCT

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por Doctor José Luis Reyes Villamizar, en su calidad de apoderado de la sociedad TECNOQUÍMICAS S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sese

Notifíquese el presente oficio conforme a lo dispuesto en el Título I, Actuaciones ante la Superintendencia de Industria y Comercio; Capítulo sexto, publicación, comunicación, notificación y ejecutoria de las decisiones de la Superintendencia de Industria y Comercio, informándoles que contra el mismo no procede el recurso de la vía gubernativa.

El anterior oficio fue elaborado el 20 de junio de 2017.

Atentamente,

JOSÉ LUIS SALAZAR LÓPEZ
DIRECTOR DE NUEVAS CREACIONES (C)

Elaboro: Claudia Yaneth Alzate Rios

Industria y Comercio
SUPERINTENDENCIA

Superintendencia de Industria y Comer

Radicado: NC2016/0005794 **Folios:** 53
Dependencia: 2020 **Fecha:** 2016-12-26 16:
Tipo aplicación: Solicitud de Oposición
Número referenciado: 15265717

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1 1

1. Oposición a solicitud de:

[X] Patente de invención
[ ] Registro de Diseño Industrial
[ ] Patente de Modelo de Utilidad
[ ] Esquema de Trazado de Circuitos Integrados

Número de expediente: 15-265-717

Solicitante: GILEAD SCIENCES, INC.

Apoderado: ALICIA LLOREDA PICAUATE

Título de la Nueva Creación: COMPUESTOS DE CARBAMOILPIRIDONA POLICICLICOS

Gaceta: 772 de 30 de septiembre de 2016

2. Datos del Opositor

[ ] Persona Natural [X] Persona Jurídica

TECNOQUIMICAS S.A.

Nombre o denominación / Razón social completa

Documento de identificación: C.C. [ ] C.E. [ ] NIT [X] Otro [ ] Cuál _____

Número 890 300 466-5

Dirección Calle 23 No. 7-39 Ciudad Cali

Teléfono (092) 882 55 55 Fax: (092) 883 88 59 E-mail _____

[ ] Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS — 79'152.473 — 44655
Apellidos y Nombre — Documento de identificación — T.P. No.

Dirección del representante
Cra 17 No. 88-23 Of 305

Dirección electrónica	No. Fax	Número telefónico
info@reyes-abogados.com	621.25.42	621.26.31

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga: SI [X] NO [ ]

7. Anexos

- [X] Comprobante de pago de la tasa para la presentación de la solicitud No. _____ Fecha: _____
- [X] Poder, si fuera el caso con el que se acredita la representación
- [X] Pruebas de los fundamentos de la oposición
- [ ] Copias para traslado

8. Firma

JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos

Firma

79.152.473 C.C.

44655 T.P.

REYES & REYES
A B O G A D O S

3

3

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF:	EXPEDIENTE 15-265-717
TÍTULO SOLICITADO:	"COMPUESTOS DE CARBAMOILPIRIDONA POLICICLICOS"
PUBLICACIÓN:	Gaceta 772 de 30 de septiembre de 2016
PRIORIDAD:	US 61/745,375 21/12/2012 US 61/788,397 15/03/2013 US 61/845,803 12/07/2013
SOLICITANTE:	GILEAD SCIENCES, INC.
APODERADO:	ALICIA LLOREDA RICAURTE
TRÁMITE:	PRESENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44855 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. **PETICIÓN**

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **15-265-717**, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

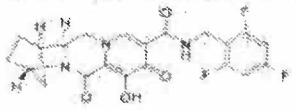
III. FUNDAMENTOS DE LA OPOSICIÓN

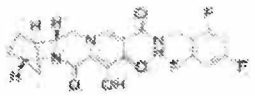
La solicitud colombiana en trámite 15-265-717, referida a compuestos derivados de carbamoilpiridonas policíclicas y su combinación con agentes adicionales contra el VIH, incumple los requisitos materiales para el otorgamiento de patente de invención, tal como puede determinarse al valorar los siguientes argumentos:

Falta de claridad y concisión

En primer lugar, la solicitud carece de concisión pues reclama tanto la mezcla racémica como los isómeros por separado:

1. Un compuesto que tiene una de las siguientes estructuras:





o una sal farmaceuticamente aceptable del mismo.

Adicional a lo anterior, la solicitud en estudio tampoco cumple con el criterio de claridad por cuanto no define específicamente ni los componentes ni las

proporciones de los mismos en las composiciones de las reivindicaciones 4 a 9, tal como se puede observar de la lectura las siguientes reivindicaciones:

4. Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1 a 3, o una sal farmacéuticamente aceptable del mismo, y un portador, diluyente o excipiente farmacéuticamente aceptable.

5. La composición farmacéutica de acuerdo con la reivindicación 4, donde dicha composición farmacéutica además comprende uno o más agentes terapéuticos adicionales.

6. La composición farmacéutica de acuerdo con la reivindicación 4, donde dicha composición farmacéutica además comprende:
   (a) un agente terapéutico adicional;
   (b) dos agentes terapéuticos adicionales;
   (c) tres agentes terapéuticos adicionales; o
   (d) cuatro agentes terapéuticos adicionales.

7. La composición farmacéutica de acuerdo con la reivindicación 5 o 6, donde el agente terapéutico adicional o los agentes son agentes contra el VIH.

8. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 5 a 7, donde el agente terapéutico adicional o los agentes son seleccionados del grupo que consiste de inhibidores de la proteasa de VIH, inhibidores no nucleósidos de la transcriptasa inversa de VIH, inhibidores nucleosidos de la transcriptasa inversa de VIH, inhibidores nucleotidos de la transcriptasa inversa de VIH, y sus combinaciones.

De acuerdo a lo anterior, la solicitud falla en cumplir con lo dispuesto por el Artículo 30 de la D. 486 que precisa lo siguiente: "- *Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción*".

La solicitud además falla en sustentar todas y cada una de las modalidades enseñadas por las reivindicaciones en la descripción debido a que en la misma no se divulgan todos los agentes terapéuticos, los portadores o excipientes reclamados. Así la cosas, las reivindicaciones no encuentran soporte en la descripción por lo que además este criterio se incumple en la presente solicitud.

Adicionalmente, las únicas definiciones de los ingredientes activos adicionales se encuentra en la reivindicación 10, como ejemplo zidovudina, emtricitabina,

didanosina, etc. De esta forma, las reivindicaciones no se definen técnicamente sino que caen dentro del campo de la especulación y no pueden ser consideradas claras y concisas mediante una definición técnica, sino mediante grupos funcionales sin una estructura definida.

Así las cosas, la materia de las reivindicaciones y en general la solicitud en estudio, no puede ser objeto de patente ya que como se expuso, incumple las normas mínimas de presentación, como es la claridad, concisión, soporte, y no patentabilidad.

La solicitud carece de nivel inventivo.

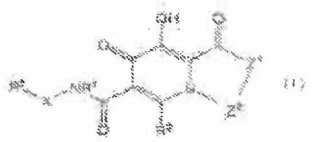
Pese a las objeciones planteadas en párrafos anteriores, la materia reclamada ya había sido divulgada en el estado de la técnica, prueba de ello se encuentra en los siguientes documentos publicados anteriormente a la fecha de presentación de la solicitud en estudio y que cito a continuación:

D1. WO 2006/116764 ***"Polycyclic carbamoylpyridone derivative having HIV integrase inhibitory activity"*** *Johns, Brian [US] Kawasuji, Takashi [JP], Taishi, Teruhiko [JP]* 2006-02-11

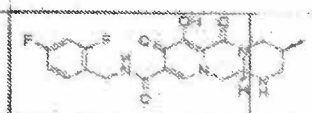
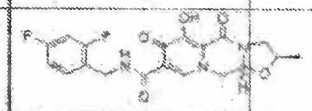
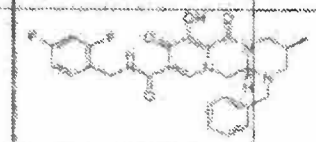
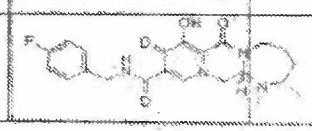
D2. EP 2412709 A1 ***"Process for producing pyrone and pyridone derivatives"*** Sumino, Yukihito [JP], 2012-02-01

La publicación internacional WO 2006/116764 (en adelante Johns *et al.*) se considera el estado de la técnica más cercano a la materia reivindicada por la solicitud en trámite ya que describe un *compuesto de fomula I derivado de carbamoilpiridona que tiene actividad antiviral*, en particular con actividad inhibitoria de HIV y una composición de la misma (ver Abstract).

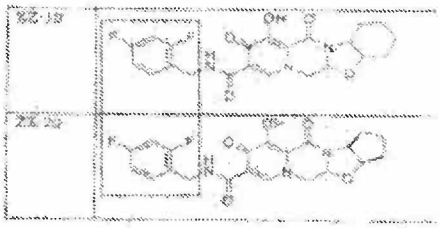
WO 2006/116764 A1



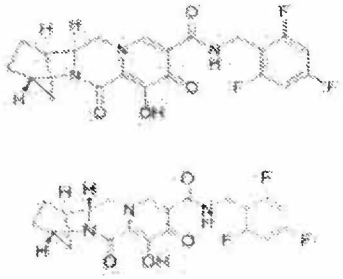
En una modalidad particular (ejemplos ZZ-1 a ZZ-24), D1 se refiere a compuestos que contienen el mismo núcleo central de los compuestos reivindicados como se presenta en el siguiente recuadro rojo:

Example No.	Structure
ZZ-1	
ZZ-2	
ZZ-3	
ZZ-4	

Así mismo, R2 representa un bencilo que cuenta con dos átomos de flúor (ver ejemplo ZZ19 y ZZ20):



y adicionalmente, la estructura del derivado de carbamoilpiridona de estos dos compuestos ZZ19 y ZZ20 sugiere la naturaleza enantiomérica reivindicada por la solicitud, siendo obvio para una persona medianamente versada en la materia que la configuración espacial de la molécula es fundamental para la actividad de la molécula tal como se observa en el compuesto de la reivindicación 1 de la solicitud en estudio así:



De esta manera, la molécula reclamada difiere en la presencia de tres átomos de flúor, en lugar de dos, sustitución que es obvia y evidente para una persona experta en la materia ya que el bencilo tiene una posición favorable para la inclusión de un tercer flúor que adicionalmente es capaz de mejorar las propiedades liposolubles del medicamento, por lo que el documento de Johns *et al.*, sugiere la combinación de todas las características definidas por las reivindicaciones.

Por lo tanto la idea de proveer un compuesto derivado de carbamoilpiridona de acuerdo con la fórmula reivindicada y su forma enantiomérica era sugerida a partir del documento de Johns *et al.*

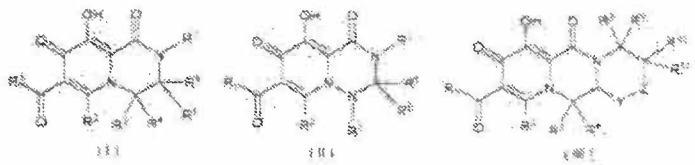
A pesar que este documento por si solo es capaz de desvirtuar el nivel inventivo de la solicitud en trámite, el documento EP 2412709 A1 (en adelante Sumino *et al.*) también objeta el nivel inventivo de la solicitud en trámite ya que describe derivados de pirona y piridona que son intermediarios para la síntesis de medicamentos anti-virales tales como anti-influenza y métodos para producirlos (ver párrafo 0008) tal como se pretende en la reivindicación 1 de la solicitud en trámite:

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0008] An object of the present invention is to provide a novel pyrone derivative and a novel pyridone derivative, which are novel intermediates for synthesizing an anti-influenza drug, a method of producing the same, and a method of using the same. Specifically, the object is to efficiently produce compounds and the like useful as an anti-influenza drug, which are exemplified by formula (II), formula (III) or formula (IIIa).

[Chemical formula 1]



(II) (III) (IIIa)

wherein R^1 is lower alkyloxy optionally substituted by substituent E, carbocyclyl lower alkyloxy optionally substituted by substituent E, heterocyclyl lower alkyloxy optionally substituted by substituent E, carbocyclyl lower alkylamino optionally substituted by substituent E, or heterocyclyl lower alkylamino optionally substituted by substituent E

Z is $CR^{11}R^{11}$, or a single bond,

Y is CH_2, an oxygen atom, or $N\text{-}R^{12}$,

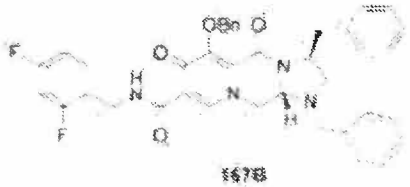
R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently hydrogen, lower alkyl optionally substituted by substituent E, lower alkenyl optionally substituted by substituent E, lower alkynyl optionally substituted by substituent E, carbocyclyl lower alkyl optionally substituted by substituent E, or heterocyclyl lower alkyl optionally substituted by substituent E,

R^2 and R^3 may be taken together to form a 4 to 8-membered carbocyclyl optionally substituted by substituent E, or a 4 to 8-membered heterocyclyl optionally substituted by substituent E, or R^7 and R^8 may be taken together to form a 4 to 8-membered heterocyclyl optionally substituted by substituent E,

wherein when Z is a single bond, R^{13} and R^{14} may be taken together to form 4 to 8-membered heterocyclyl optionally substituted by substituent E. Substituent E: halogen, cyano, hydroxy, carboxy, formyl, amino, azido, nitro, lower alkyl,

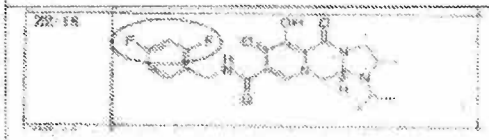
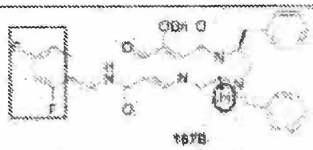
De la lectura del documento de Sumino *et al.*, se pueden obtener <u>compuestos derivados de carbamoilpiridona</u> que son usados como intermediarios para compuestos útiles como agentes terapéuticos en la reducción de la replicación de

HIV y que presentan una actividad similar a la de los compuestos reivindicados en la solicitud en trámite; tal es el caso del compuesto 167B del documento D2:



167B

Es importante observar que incluso el flúor se encuentra en las posiciones complementarias no citadas por el documento de Johns et al., por lo que un técnico medio en la materia sugerido por la combinación de enseñanzas de D1 y D2 habría podido incluir F en las tres posiciones bajo las enseñanzas de los dos documentos, así:

Johns et al	*Sumino et al*
	 167B

Por otro lado, se observa en el compuesto 167B que la configuración tridimensional del grupo H (ver círculo azul) en la molécula era conocida y en combinación con el documento de Johns et al., la estructura básica obedece a la reclamada por las reivindicaciones pretendidas en la solicitud en trámite.

Adicionalmente, Johns et al., enseña la posibilidad de combinación de los derivados de carbamoilpiridona allí revelados con otros agentes activos como inhibidores de la transcriptasa reversa e inhibidores de proteasa:

34. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 33, or a pharmaceutically acceptable salt, or solvate thereof.

35. A pharmaceutical composition according to Claim 34, which is an anti-HIV agent.

36. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent selected from reverse transcriptase inhibitors and protease inhibitors

Por lo tanto, se considera que la combinación de los derivados de carbamoilpiridona con agentes terapéuticos adicionales como inhibidores de la proteasa de VIH, inhibidores no nucleósidos de la transcriptasa inversa de VIH, inhibidores nucleósidos de la transcriptasa inversa de VIH, e inhibidores nucleótidos de la transcriptasa inversa de VIH, ya habían sido anticipadas por el Johns et al., por lo cual se considera que la formulación que contiene dicha combinación y su posible comportamiento sinérgico no es nueva ni inventiva.

Por último, tanto los compuestos como las composiciones reclamadas, no exhiben ninguna propiedad técnica sorprendente o inesperada que pueda ser considerada útil para demostrar el nivel inventivo de la solicitud; en consecuencia, con los argumentos dados en el presente escrito, un técnico medio en la materia habría fácilmente derivado el compuestos de la materia de la solicitud, bajo una selección de los intermediarios y haciendo uso solo de las características técnicas sugeridas por los documentos del estado de la técnica y por los conocimientos y datos propios empleados por el conocimiento de la materia técnica.

Rogamos se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2° de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

WO 2006/116764 ***"Polycyclic carbamoylpyridone derivative having HIV integrase inhibitory activity"*** *Johns, Brian [US] Kawasuji, Takashi [JP], Taishi, Teruhiko [JP] 2006-02-11.* Portada, páginas 1- 9, 237 - 240.

EP 2412709 A1 ***"Process for producing pyrone and pyridone derivatives"*** Sumino, Yukihito [JP], 2012-02-01. Portada, páginas 2, 67.

VII. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2° de la Decisión 486.
5. El mencionado en el acápite de pruebas.

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta

REYES & REYES
A B O G A D O S

ciudad. Tecnoquímicas S.A. las recibirá en sus oficinas localizadas en la Calle 23 N° 7-39 de Cali.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P.A. 44.655 de C.S.J.

REYES & REYES
A B O G A D O S

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF:	**EXPEDIENTE 15-265-717**
TÍTULO SOLICITADO:	**"COMPUESTO DE CARBAMOILPIRIDONA POLICICLICOS Y SU USO FARMACEUTICO"**
PUBLICACIÓN:	**Gaceta 772 de 30 de septiembre de 2016,**
PRIORIDAD:	**US 61/745,375 21/12/2012** **US 61/788,397 15/03/2013** **US 61/845,803 12/07/2013**
SOLICITANTE:	**GILEAD SCIENCES, INC.,**
APODERADO:	**ALICIA LLOREDA RICAURTE**
TRÁMITE:	**SUSTENTACIÓN DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, conocido apoderado de **TECNOQUIMICAS S.A.** en el trámite de la referencia, procedo a sustentar y complementar la oposición presentada el 26 de diciembre de 2016, en los siguientes términos:

I. RATIFICACIÓN

La solicitud 15-265-717, referida a compuestos derivados de carbamoilpiridonas policíclicas y su combinación con agentes adicionales contra el VIH, carece de claridad y concisión, e incumple los requisitos materiales de patentabilidad referidos a novedad y nivel Inventivo, de acuerdo con las revelaciones de los documentos WO 2006/116764 y EP 2412709.

En primer lugar, la solicitud incumple el requisito de claridad, pues no define específicamente los componentes ni las proporciones de estos dentro de las

composiciones que revelan las reivindicaciones 4 a 9. De igual manera, la solicitud falla en proporcionar el debido sustento y soporte a las modalidades allí reclamadas.

Por otro lado, se mencionaron documentos que afectan el nivel inventivo de la solicitud, en primer término, la publicación internacional WO 2006/116764, referida a un *compuesto de formula I derivado de carbamoilpiridona que tiene actividad antiviral* en particular con actividad inhibitoria de HIV y una composición de la misma. En la misma dirección, el documento EP 2412709 A1 describe derivados de pirona y piridona intermediarios para la síntesis de medicamentos anti-virales como anti-influenza y métodos para producirlos (ver párrafo 0008) tal como se pretende en la reivindicación 1 de la solicitud en trámite.

II. COMPLEMENTO DE INFORMACIÓN

La solicitud comprende composiciones ya conocidas en el estado de la técnica

En relación con las reivindicaciones 4 a 11, el solicitante sostiene la posibilidad de reivindicar las composiciones farmacéuticas que incluyan los compuestos de la invención sin necesidad de ejemplificar su diseño y preparación y sin necesidad de especificar sus ingredientes, excipientes y cantidades / proporciones específicas. (p. 4).

Además de anotar que la pretensión referida riñe con la técnica de redacción de patentes de invención, debo reiterar que el capítulo reivindicatorio incluye composiciones conocidas, basadas en **uno, dos, tres o cuatro agentes terapéuticos** (reivindicaciones 5 o 6), o que **contienen abacavir, tenofovir, tenofovir disoproxil fumarato, o tenofovir alafenamida fumarato** (reivindicaciones 8 a 11).

Como se puede ver en el siguiente cuadro, el capítulo reivindicatorio modificado se refiere a un compuesto policíclico y a una composición que puede contener dicho compuesto policiclico **o cualquier agente terapéutico:**

Reiv.	Contenido
1 – 3	Compuesto policiclico
4	Composición farmacéutica del compuesto policiclico
5	Composición del compuesto policíclico con 1 o más agentes terapéuticos
6	Composición del compuesto policíclico con 1, 2, 3, o 4 agentes terapéuticos
7	Composición del compuesto policíclico con agente terapéutico adicional o los agentes son agentes contra el VIH.
8	Composición del compuesto policíclico donde el agente terapéutico adicional o los agentes son seleccionados del grupo que consiste de inhibidores de la proteasa de VIH, inhibidores no nucleósidos de la transcriptasa inversa de VIH, inhibidores nucleósidos de la transcriptasa inversa de VIH, inhibidores nucleótidos de la transcriptasa inversa de VIH, y sus combinaciones.
9	Composición del compuesto policíclico donde el agente terapéutico adicional o los agentes son seleccionados del grupo que consiste de inhibidores nucleósidos de la transcriptasa inversa de VIH, inhibidores nucleótidos de la transcriptasa inversa de VIH, y sus combinaciones.
10	Composición del compuesto policíclico donde el agente terapéutico adicional o los agentes son seleccionados del grupo que consiste de zidovudina, emtricitabina, didanosina, estavudina, zalcitabina, lamivudina, abacavir, amdoxovir, elvucitabina, alovudina, MIV–210, ±– FTC, D–d4FC, emtricitabina, fosfazida, fozivudina tidoxil, apricitibina (AVX754), KP–1461, GS–9131 (Gilead Sciences), fosalvudina tidoxilo (anteriormente, HDP 99.0003), tenofovir, tenofovir disoproxil fumarato, tenofovir alafenamida fumarato (Gilead Sciences), GS–7340 (Gilead Sciences), GS–9148 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX–001 (Chimerix) y CMX–157 (Chimerix).
11	Composición del compuesto policíclico donde el agente terapéutico adicional o agentes son seleccionados del grupo que consiste de abacavir, tenofovir, tenofovir disoproxil fumarato, y tenofovir alafenamida fumarato.

A partir de lo anterior, y suponiendo a manera de ejemplo que el compuesto policíclico estuviera en un porcentaje entre 0 y 1% p/p, las composiciones resultantes sólo contendrían otros *agentes terapéuticos,* tales como abacavir, tenofovir, tenofovir disoproxil fumarato, y tenofovir alafenamida fumarato.

En este punto debe mencionarse que en el estado de la técnica son conocidas numerosas composiciones que contienen principios activos como Zidovudina, Emtricitabina, Didanosina, Stavudina, Abacavir, Tenofovir y Lamivudina y/o combinaciones de los mismos, tal y como se demuestra a continuación:

- La publicación científica "**Combined Effect of Zidovudine (ZDV), Lamivudine (3TC) and Abacavir (ABC) Antiretroviral Therapy in Suppressing in Vitro FIV Replication.**" de Bisset et al., 2001, presenta el efecto combinado de zidovudina, lamivudina y abacavir como una terapia antiretroviral sinérgica. Veamos:

In view of close similarities at the molecular and clinical levels, feline immunodeficiency virus (FIV) infection of the domestic cat is subject of increasing attention as an animal model for human immunodeficiency virus (HIV) infection. A range of reverse transcriptase inhibitors effective against HIV are also active against FIV, allowing successful use of the cat model to investigate drug interactions and resistance development. Nevertheless, while combined nucleoside analog and protease inhibitor usage has proven remarkably effective in treating HIV infection, combination antiretroviral therapy of FIV infection has been hampered by lack of protease inhibitors specific for FIV. In an attempt to circumvent this problem, we have examined the feasibility of applying in the FIV system combination protocols lacking a protease inhibitor. We now report that, as observed during HIV infection, the nucleoside analog abacavir (ABC or 1592U89) is able to effectively block in vitro FIV-replication. Furthermore, we demonstrate that combined usage of ABC with the nucleoside analogs zidovudine (ZDV or AZT) and lamivudine (3TC) also blocks in vitro FIV replication in a synergistic manner. However, in contrast to its effect on HIV replication, the ribonucleotide reductase inhibitor hydroxyurea (HU) is unable to effectively control in vitro FIV replication.

- Por su parte, la publicación científica ""**Synergistic Activity Profile of Griffithsin in Combination with Tenofovir, Maraviroc and Enfuvirtide against HIV-1 Clade C.**" de Férir et al., 2011, menciona el uso de tenofovir en combinación con agentes de enlace de carbohidratos para el tratamiento de VIH:

Tenofovir, a well-known and highly prescribed anti-HIV-1 drug for the treatment of HIV/AIDS infections, has recently also shown its effectiveness as a potential microbicide drug in the prevention of HIV transmission.
Here, we evaluated the combination of tenofovir with various members of the class of carbohydratebinding agents (CBAs) targeting the glycans on the viral envelope gp120 for their anti-HIV efficacy. The tenofovir/CBA combinations predominantly showed synergistic antiviral activity using the median effect principle.
These findings illustrate that combination of tenofovir with CBAs may increase the antiviral potency of the individual drugs and reducing the risk on potential side-effects.

- En tercer lugar, la publicación **"Synergistic in Vitro Anti-HIV Type 1 Activity of Tenofovir with Carbohydrate-Binding Agents (CBAs)"** de Férir et al., 2011, también revela combinaciones de tenofovir y un nuevo agente anti VIH:

Griffithsin (GRFT) is possibly the most potent anti-HIV peptide found in natural sources. Due to its potent and broad-spectrum antiviral activity and unique safety profile it has great potential as topical microbicide component. Here, we evaluated various combinations of GRFT against HIV-1 clade B and clade C isolates in primary peripheral blood mononuclear cells (PBMCs) and in CD4+ MT-4 cells. In all combinations tested, GRFT showed synergistic activity profile with tenofovir, maraviroc and enfuvirtide based on the median effect principle with combination indices (CI) varying between 0.34 and 0.79 at the calculated EC95 level. Furthermore, the different glycosylation patterns on the viral envelope of clade B and clade C gp120 had no observable effect on the synergistic interactions.
Overall, we can conclude that the evaluated two-drug combination increases their antiviral potency and supports further clinical investigations in pre-exposure prophylaxis for GRFT combinations in the context of HIV-1 clade C infection.

- De otro lado, el artículo **"Dose Proportional Inhibition of HIV-1 Replication by Mycophenolic Acid and Synergistic Inhibition in Combination with Abacavir, Didanosine, and Tenofovir."** publicado por Hossain et al., 2001, revela la actividad del micofenolato mofetilo en combinación con abacavir (ABC), didanosine (DDI), lamivudine (3TC) y tenofovir (TFV):

> *Mycophenolate mofetil (MMF), a therapeutically used inhibitor of inosine monophosphate dehydrogenase is hydrolyzed to its active metabolite mycophenolic acid (MPA) in vivo. MPA exhibits anti-HIV activity in vitro. We tested MPA alone and in combination with abacavir (ABC), didanosine (DDI), lamivudine (3TC) and tenofovir (TFV) against wild-type human immunodeficiency virus type-1 (HIV-1) and nucleoside reverse transcriptase inhibitor (NRTI)-resistant HIV-1. MPA (62.5–500 nM), when combined with ABC or DDI, synergistically enhanced activity against wild-type HIV and the NRTI-resistant HIV clone DRSM34. MPA also enhanced the activity of TFV against both wild-type HXB2 and TFV-resistant strain HIVK65R, in a more than additive manner. No significant antiproliferative effect of MPA (S0.25 mM) alone or in the presence of ABC, DDI and TFV was observed. This indicates that the antiviral effects of MMF may be clinically achievable without fully blocking T-cell proliferation or inducing immunosuppression. These findings provide further rationale for the clinical testing of MMF in combination with ABC, DDI, and TFV.*

- Como quinta referencia, cabe mencionar el artículo **"Long-Term Successful Control of Super-Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection by a Novel Combination Therapy of Raltegravir, Etravirine, and Boosted-Darunavir."** publicado por Nakamura et al., 2010, revela el potencial de una combinación de retrovirales novedosos para el tratamiento de infección por VIH:

> *Drug-resistant virus infection has been a major hurdle in the management of human immunodeficiency virus type 1 (HIV-1) infection. Recently, three novel antiretrovirals [raltegravir (RAL), etravirine (ETR), and darunavir (DRV)] were introduced into the market almost simultaneously, and salvage regimens containing these three antiretrovirals have been reported to exhibit strong potency against drug-resistant HIV-1 infection. However, the sustainability of such regimens remains unclear, particularly for patients infected with multidrug-resistant viruses. Here we report a case of super-multidrug-resistant HIV-1 infection which has been successfully controlled by novel combination therapy including RAL, ETR, and DRV for over 2 years, indicating that the novel combination could become an ultimate weapon against drug-resistant HIV infection and could alter the landscape of HIV salvage therapy.*

- De igual manera, el artículo **"In Vivo Examination of Hydroxyurea and the Novel Ribonucleotide Reductase Inhibitors Trimidox and Didox in Combination with the Reverse Transcriptase Inhibitor Abacavir: Suppression of Retrovirus-Induced Immunodeficiency Disease."**publicado por Sumpter et al., 2003, revela el potencial de terapias combinadas para el tratamiento de VIH:

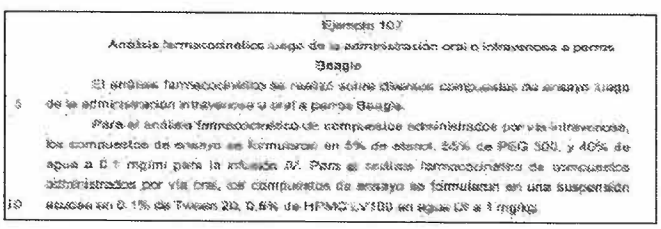
Inhibition of ribonucleotide reductase (RR) has gained attention as a potential strategy for HIV-1 therapy through the success of hydroxyurea (HU) to potentiate the activity of the nucleoside reverse transcriptase inhibitor (NRTI) didanosine (ddI) in clinical trials. However, the use of HU has been limited by its development of hematopoietic toxicity. In this study, the novel RR inhibitors didox (DX; 3,4-dihydroxybenzohydroxamic acid), and trimidox (TX; 3,4,5-trihydroxybenzamidoxime) were evaluated along with HU for anti-retroviral efficacy in LPBM5-induced retro-viral disease (MAIDS) both as monotherapeutic regimens and in combination with the guanine containing NRTI abacavir (ABC). Anti-retroviral drug efficacy was determined by measuring inhibition of splenomegaly, hypergammaglobulinemia, and splenic levels of proviral DNA. In this study, all RRIs tested showed the ability to improve the efficacy of ABC in the MAIDS model by reducing splenomegaly, hypergammaglobulinemia, and splenic proviral DNA levels.

Como se puede apreciar, las combinaciones de antivirales para el tratamiento del VIH ya era conocido en el estado de la técnica y así mismo habría sugerido a una persona versada en la materia el empleo de estas combinaciones con alta expectativa de éxito, por lo que las combinaciones reclamadas por la solicitante en el evento que el porcentaje del compuesto policíclico fuese muy bajo (cosa que es posible ya que no se revelan porcentajes preferidos en el capítulo reivindicatorio), no cumplen con el requisito de novedad ni de nivel inventivo.

Las reivindicaciones carecen de soporte y sustento en la descripción

De otra parte, el solicitante menciona que la memoria descriptiva divulga de manera suficiente las caracteristicas para desarrollar las composiciones farmacéuticas según la invención. Frente a este particular debe anotarse que las páginas 34 a 38 de la memoria descriptiva se refieren a una **información general** e insuficiente como sustento de las reivindicaciones, sobre excipientes y posibles agentes terapéuticos de combinación.

En el aparte experimental se observa que lo más cercano a una composición, es la forma líquida para administrar el policiclo a perros Beagle en el ejemplo 107:



Ejemplo 107

Análisis farmacocinéticos luego de la administración oral o intravenosa a perros Beagle

El análisis farmacocinético se realizó sobre diversos compuestos de ensayo luego de la administración intravenosa o oral a perros Beagle.

Para el análisis farmacocinético de compuestos administrados por vía intravenosa, los compuestos de ensayo se formularon en 5% de etanol, 55% de PEG 300, y 40% de agua a 0.1 mg/ml para la infusión IV. Para el análisis farmacocinético de compuestos administrados por vía oral, los compuestos de ensayo se formularon en una suspensión acuosa en 0.1% de Tween 20, 0.5% de HPMC LV100 en agua DI a 1 mg/kg.

Sin embargo, no existe información disponible sobre una formulación que contenga el policiclo en combinación con un principio activo adicional y mucho menos información que presente una evidencia clara sobre las ventajas, los efectos técnicos sorprendentes e inesperados logrados por las combinaciones reclamadas. Por lo tanto, no se puede considerar que las combinaciones reclamadas de forma específica por el nuevo capítulo reivindicatorio, es decir el compuesto policíclico + abacavir O tenofovir O tenofovir disoproxil fumarato O tenofovir alafenamida fumarato, entre otras combinaciones, presenten evidencia de dichas bondades.

Adicionalmente, las referencias mencionadas sugieren el efecto sinérgico para las combinaciones entre antivirales como los reclamados en el nuevo capítulo reivindicatorio, por lo tanto, las combinaciones objeto de estudio carecen de novedad y nivel inventivo.

Para terminar, es importante resaltar de nuevo que la anterioridad WO 2006/116764 (Johns *et al.*) citada en el escrito de oposición, enseña la posibilidad de combinación de los derivados de carbamoilpiridona allí revelados con otros agentes activos como inhibidores de la transcriptasa reversa e inhibidores de proteasa:

34. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 33, or a pharmaceutically acceptable salt, or solvate thereof.

35. A pharmaceutical composition according to Claim 34, which is an anti-HIV agent.

54. A pharmaceutical composition according to claim 34 wherein said composition comprises at least one additional therapeutic agent selected from reverse transcriptase inhibitors and protease inhibitors.

Por lo tanto, se considera que la combinación de los derivados de carbamoilpiridona con agentes terapéuticos adicionales como inhibidores de la proteasa de VIH, inhibidores no nucleósidos de la transcriptasa inversa de VIH, inhibidores nucleósidos de la transcriptasa inversa de VIH, e inhibidores nucleótidos de la transcriptasa inversa de VIH, ya habían sido anticipadas por el

Johns et al., por lo cual se considera que la formulación que contiene dicha combinación y su posible comportamiento sinérgico no es nueva ni inventiva.

En consecuencia, rogamos se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III PRUEBAS

1. Bisset, Leslie R, Hans Lutz, Jürg Böni, Regina Hofmann-Lehmann, Ruedi Lüthy, and Jörg Schüpbach. 2002. **"Combined Effect of Zidovudine (ZDV), Lamivudine (3TC) and Abacavir (ABC) Antiretroviral Therapy in Suppressing in Vitro FIV Replication."** *Antiviral Research* 53 (1): 35–45.

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Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TIVICAY safely and effectively. See full prescribing information for TIVICAY.

TIVICAY (dolutegravir tablets), for oral use
Initial U.S. Approval: 2013

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1)	11/2017
Dosage and Administration, Pregnancy Testing before Initiation of TIVICAY (2.1)	09/2018
Dosage and Administration, Adults (2.2)	11/2017
Warnings and Precautions, Hepatotoxicity (5.2)	11/2017
Warnings and Precautions, Fat Redistribution (previous 5.3)	Removed 11/2017
Warnings and Precautions, Embryo-Fetal Toxicity (5.3)	09/2018
Warnings and Precautions, Risk of Adverse Reactions or Loss of Virologic Response (5.4)	11/2017

---------- INDICATIONS AND USAGE ----------

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with:

- other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 30 kg. (1)
- rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Pregnancy Testing: Perform pregnancy testing before initiation of TIVICAY in adolescents and adults of childbearing potential. (2.1, 5.3)
- May be taken without regard to food. (2.2, 2.3)

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine[a] (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] (12.4)	50 mg twice daily

[a] Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
[b] Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: (Treatment-naïve or treatment-experienced INSTI-naïve patients weighing at least 30 kg). (2.3)

- If at least 40 kg: The recommended dose is TIVICAY 50 mg once daily.
- Patients 30 kg to less than 40 kg: The recommended dose is TIVICAY 35 mg once daily.
- If certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of TIVICAY to twice daily. (2.3, 7.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 10 mg, 25 mg, and 50 mg (3)

---------- CONTRAINDICATIONS ----------

- Previous hypersensitivity reaction to dolutegravir. (4)
- Coadministration with dofetilide. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- Hepatotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Avoid use of TIVICAY at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Advise adolescents and adults of childbearing potential to use effective contraception. (2.1, 5.3, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving TIVICAY in any one adult trial) are insomnia, fatigue, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Refer to the full prescribing information for important drug interactions with TIVICAY. (4, 7)
- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, TIVICAY and supplements containing calcium or iron can be taken together with food. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Avoid use of TIVICAY at the time of conception through the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in adolescents and adults of childbearing potential. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Pregnancy Testing before Initiation of TIVICAY
  2.2 Adults
  2.3 Pediatric Patients
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Hypersensitivity Reactions
  5.2 Hepatotoxicity
  5.3 Embryo-Fetal Toxicity
  5.4 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions
  5.5 Immune Reconstitution Syndrome
6 ADVERSE REACTIONS
  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience
7 DRUG INTERACTIONS
  7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents
  7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir
  7.3 Established and Other Potentially Significant Drug Interactions
  7.4 Drugs without Clinically Significant Interactions with Dolutegravir

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1716 of 1915

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
8.7 Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Description of Clinical Studies
14.2 Adult Subjects
14.3 Pediatric Subjects
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIVICAY is indicated in combination with:

- other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 30 kg *[see Microbiology (12.4)]*.
- rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent.

2 DOSAGE AND ADMINISTRATION

2.1 Pregnancy Testing before Initiation of TIVICAY

Perform pregnancy testing before initiation of TIVICAY in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Adults

TIVICAY tablets may be taken with or without food.

Table 1. Dosing Recommendations for TIVICAY in Adult Patients

Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirine[a]	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers *[see Drug Interactions (7.3)]*	50 mg twice daily

INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance[b] *[see Microbiology (12.4)]*	50 mg twice daily

[a] Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.

[b] Alternative combinations that do not include metabolic inducers should be considered where possible *[see Drug Interactions (7)]*.

2.3 Pediatric Patients

TIVICAY tablets may be taken with or without food.

Treatment-Naïve or Treatment-Experienced INSTI-Naïve

The recommended dose of TIVICAY in pediatric patients weighing at least 30 kg is provided in Table 2.

Table 2. Dosing Recommendations for TIVICAY in Pediatric Patients Weighing at Least 30 kg

Body Weight (kg)	Daily Dose[a] (Number of Tablets per Dose when Different Strength(s) are Required)
30 to less than 40	35 mg once daily (One 25-mg tablet and one 10-mg tablet)
40 or greater	50 mg once daily

[a] If certain UGT1A or CYP3A inducers are coadministered, then increase the weight-based dose of TIVICAY to twice daily *[see Drug Interactions (7.3) for relevant inducers]*.

Safety and efficacy of TIVICAY have not been established in pediatric patients who are INSTI-experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

3 DOSAGE FORMS AND STRENGTHS

Tablets:

10 mg: Each tablet contains 10 mg of dolutegravir (as dolutegravir sodium). Tablets are white, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "10" on the other side.

25 mg: Each tablet contains 25 mg of dolutegravir (as dolutegravir sodium). Tablets are pale yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "25" on the other side.

50 mg: Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium). Tablets are yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1718 of 1915

4 CONTRAINDICATIONS

TIVICAY is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

5.2 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.3 Embryo-Fetal Toxicity

Preliminary data from an observational study showed that TIVICAY was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of TIVICAY at the time of conception through the first trimester of pregnancy *[see Use in Specific Populations (8.1)]*.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1719 of 1915

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on TIVICAY, if possible, switch to an alternative regimen.

Perform pregnancy testing before initiation of TIVICAY in adolescents and adults of childbearing potential to exclude use of TIVICAY during the first trimester of pregnancy *[see Dosage and Administration (2.1)]*.

Advise adolescents and adults of childbearing potential to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

5.4 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of TIVICAY and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of TIVICAY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 6 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TIVICAY; review concomitant medications during therapy with TIVICAY; and monitor for the adverse reactions associated with the concomitant drugs.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TIVICAY. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.5)]*.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1720 of 1915

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Adult Subjects

Treatment-Naïve Subjects: The safety assessment of TIVICAY in HIV-1-infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving TIVICAY 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 3. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3. Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		SINGLE	
System Organ Class/ Preferred Term	TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	TIVICAY 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Psychiatric				
Insomnia	<1%	<1%	3%	3%
Depression	<1%	<1%	1%	2%
Abnormal dreams	<1%	<1%	<1%	2%

Nervous System				
Dizziness	<1%	<1%	<1%	5%
Headache	<1%	<1%	2%	2%
Gastrointestinal				
Nausea	1%	1%	<1%	3%
Diarrhea	<1%	<1%	<1%	2%
Skin and Subcutaneous Tissue				
Rash[a]	0	<1%	<1%	6%
General Disorders				
Fatigue	<1%	<1%	2%	2%
Ear and Labyrinth				
Vertigo	0	<1%	0	2%

[a] Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving TIVICAY and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for TIVICAY and ATRIPLA, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received TIVICAY 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either EPZICOM or TRUVADA). There were 484 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY and 6% in subjects receiving darunavir/ritonavir. The ARs observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent AR of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving TIVICAY 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1722 of 1915

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open-label, single-arm trial (ING112574, VIKING-3), 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects at Week 48.

Treatment-emergent ARs in VIKING-3 were generally similar compared with observations with the 50-mg once-daily dose in adult Phase 3 trials.

Virologically Suppressed Subjects: The ARs observed for TIVICAY plus rilpivirine in the Week 48 analysis of pooled data from 2 identical, international, multicenter, open-label trials (SWORD-1 and SWORD-2) of 513 HIV-1-infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine, were consistent with the AR profiles and severities for the individual components when administered with other antiretroviral agents. There were no ARs (Grades 2 to 4) with an incidence of at least 2% in either treatment arm. The rates of adverse events leading to discontinuation were 4% in subjects receiving TIVICAY plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ARs occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities:

Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented in Table 4. The mean change from baseline observed for selected lipid values is presented in Table 5. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1723 of 1915

Table 4. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	TIVICAY 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
ALT				
Grade 2 (>2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5.0 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	<1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%	7%	8%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	6%	6%	9%	6%
Grade 3 (>250 mg/dL)	<1%	2%	2%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (>3.0 x ULN)	2%	5%	5%	4%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	4%	3%	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	2%	2%	3%	3%

ULN = Upper limit of normal.

Table 5. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis[a]) and SINGLE Trials (Week 144 Analysis[a])

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	TIVICAY 50 mg + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1724 of 1915

LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: TIVICAY + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: TIVICAY n = 9, raltegravir n = 13; SINGLE: TIVICAY + EPZICOM n = 36 and ATRIPLA: n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4 of 183) of subjects had a Grade 3 to 4 treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3 of 183]) being the most frequently reported.

Virologically Suppressed Adults: Laboratory abnormalities observed in SWORD-1 and SWORD-2 were generally similar compared with observations seen in the other Phase 3 trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving TIVICAY were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with TIVICAY, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.2)]*.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1725 of 1915

96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical Trials Experience in Pediatric Subjects

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment-experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

The adverse reaction profile was similar to that for adults. Grade 2 ARs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug-related ARs reported. No ARs led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, myalgia.

Psychiatric

Anxiety

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 6) *[see Contraindications (4), Drug Interactions (7.3)]*.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1726 of 1915

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 6) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

7.3 Established and Other Potentially Significant Drug Interactions

Table 6 provides clinical recommendations as a result of drug interactions with TIVICAY. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. *[See Dosage and Administration (2), Clinical Pharmacology (12.3).]*

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1727 of 1915

Table 6. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions ***[see Dosage and Administration (2)]***

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir and/or Concomitant Drug	Clinical Comment
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of TIVICAY with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.
Protease inhibitors: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2).

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1728 of 1915

		Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Other Agents		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with TIVICAY *[see Contraindications (4)]*.
Carbamazepine[a]	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternative treatment that does not include carbamazepine where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with TIVICAY because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer TIVICAY 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins	↓Dolutegravir	Administer TIVICAY 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, TIVICAY and

containing calcium or iron[a]		supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or TIVICAY. When stopping TIVICAY, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of TIVICAY is recommended.
Rifampin[a]	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.[b]

[a] *See Clinical Pharmacology (12.3) Table 9 or Table 10 for magnitude of interaction.*

[b] The lower dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents.

7.4 Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1730 of 1915

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to TIVICAY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when TIVICAY is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of TIVICAY at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started TIVICAY after the first trimester of pregnancy *(see Data)*.

If there are plans to become pregnant or if pregnancy is confirmed while on TIVICAY during the first trimester, if possible, switch to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to TIVICAY from the time of conception through the first trimester of pregnancy.

There are insufficient human data on the use of TIVICAY during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of TIVICAY *(see Data)*.

Data

Human Data: As of May 2018, in an ongoing birth outcome surveillance study in Botswana, there have been 4 cases of neural tube defects reported out of 426 births (0.94%) to mothers who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.12% (14/11,300) in the non-dolutegravir arm and 0.09% (61/66,057) in the HIV-uninfected arm. Four cases reported with dolutegravir included one case each of encephalocele, anencephaly, myelomeningocele, and iniencephaly. No infant born to a woman who started dolutegravir during pregnancy had a neural tube defect (n = 2,812).

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1731 of 1915

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address the risk of neural tube defects with dolutegravir.

Animal Data: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation Day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether TIVICAY is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk *(see Data)*.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving TIVICAY.

Data

Animal Data: Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of TIVICAY.

Contraception

Adolescents and adults of childbearing potential should avoid use of TIVICAY at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects *[see Use in Specific Populations (8.1)]*.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1732 of 1915

Advise adolescents and adults of childbearing potential who are taking TIVICAY to consistently use effective contraception.

8.4 Pediatric Use

The safety, virologic, and immunologic responses in subjects who received TIVICAY were evaluated in 46 treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. Frequency, type, and severity of adverse reactions among the 46 pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.2)]*. In 17 subjects weighing at least 30 kg, pharmacokinetic parameters of dolutegravir were comparable to adults receiving 50 mg once daily *[see Clinical Pharmacology (12.3)]*.

Safety and efficacy of TIVICAY have not been established in pediatric patients weighing less than 30 kg or in any pediatric patients who are INSTI-experienced.

8.5 Geriatric Use

Clinical trials of TIVICAY did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TIVICAY in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, TIVICAY is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1733 of 1915

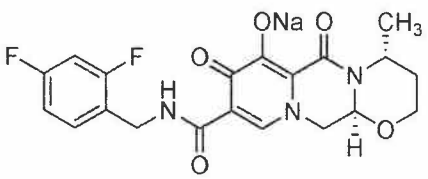
antiretroviral agents *[see Clinical Pharmacology (12.3)]*. Dolutegravir has not been studied in patients on dialysis.

10 OVERDOSAGE

There is no known specific treatment for overdose with TIVICAY. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

11 DESCRIPTION

TIVICAY contains dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Each film-coated tablet of TIVICAY for oral administration contains 10.5, 26.3, or 52.6 mg of dolutegravir sodium, which is equivalent to 10, 25, or 50 mg dolutegravir free acid, respectively, and the following inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide yellow (25-mg and 50-mg tablets only), macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir is an HIV-1 antiretroviral agent *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1734 of 1915

random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). TIVICAY did not prolong the QTc interval over 24 hours postdose.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV-1-infected subjects (Table 7) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV–1–Infected Adults

Parameter	50 mg Once Daily Geometric Mean[a] (%CV)	50 mg Twice Daily Geometric Mean[b] (%CV)
$AUC_{(0-24)}$ (mcg.h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

[a] Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.

[b] Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

Absorption

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\,h}$ ranging from 1.2 to 1.5.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1735 of 1915

Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg. Dolutegravir is a P-gp substrate in vitro. The absolute bioavailability of dolutegravir has not been established.

Effect of Food: TIVICAY may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

Metabolism: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

Polymorphisms in Drug-Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

Excretion: After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose).

Specific Populations

Pediatric Patients: The pharmacokinetics of dolutegravir in HIV-1-infected children (n = 17) weighing at least 30 kg (dosed by weight bands, receiving either 35 mg or 50 mg) were similar to those observed in HIV-1-infected adults who received dolutegravir 50 mg once daily (Table 8) *[see Clinical Studies (14.2)]*.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1736 of 1915

Table 8. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	Dose of TIVICAY	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		Cmax (mcg/mL)	AUC(0-24) (mcg.h/mL)	C24 (mcg/mL)
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)
≥30 to <40 kg (n = 3)	35 mg once daily	4.40 (54)	64.6 (64)	1.33 (93)

Geriatric Patients: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Patients with Hepatic Impairment: In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Patients with Renal Impairment: In a trial comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir were lower by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir. Dolutegravir has not been studied in patients requiring dialysis.

HBV or HCV Co-infected Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender and Race: Population analyses using pooled pharmacokinetic data from adult trials indicated gender and race had no clinically relevant effect on the exposure of dolutegravir.

Drug Interaction Studies

Drug interaction trials were performed with TIVICAY and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 9 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 10.

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with TIVICAY are provided in Table 6 *[see Dosage and Administration (2.2), Drug Interactions (7.3)]*.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1737 of 1915

Table 9. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a] The number of subjects represents the maximum number of subjects that were evaluated.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1738 of 1915

Table 10. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1739 of 1915

Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

12.4 Microbiology

Mechanism of Action

Dolutegravir 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. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1740 of 1915

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subjects in the dolutegravir 50-mg once-daily treatment arms of treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1741 of 1915

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Virologically Suppressed Subjects: SWORD-1 and SWORD-2 are identical trials in virologically suppressed subjects receiving 2 NRTIs plus either an INSTI, an NNRTI, or a PI, that switched to dolutegravir plus rilpivirine (n = 513) or remained on their current antiviral regimen (n = 511). Two subjects in each treatment arm had confirmed virologic failure at any time through Week 48. The 2 subjects in the dolutegravir/rilpivirine arm had detectable resistance substitutions at rebound. One subject had the NNRTI-resistance-associated substitution K101K/E with no decreased susceptibility to rilpivirine (fold-change = 1.2) at Week 36, had no INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir (fold-change less than 2), and had HIV-1 RNA less than 50 copies per mL at the withdrawal visit. The other subject had the dolutegravir resistance-associated substitution G193E at baseline (by exploratory HIV proviral DNA archive sequencing) and at Week 24 (by conventional sequencing) without decreased susceptibility to dolutegravir (fold-change = 1.02) at Week 24. No resistance-associated substitutions were observed for the other 2 subjects in the comparative current antiretroviral regimen arm.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir or raltegravir) containing regimen. Use of TIVICAY in INSTI-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of TIVICAY 50 mg twice daily is reduced in patients with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K, and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions,

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1742 of 1915

phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an "as-treated" analysis at Week 48 (n = 175) (Table 11). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions (see Table 11). In addition, a diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table 11. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Genotype	Week 48 (<50 copies/mL) n = 175
Overall Response	66% (116/175)
No Q148 substitution[a]	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitution[b]	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutions[b,c]	29% (6/21)

[a] Includes INSTI-resistance substitutions Y143R/C/H and N155H.

[b] INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).

[c] The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 16).

Response by Baseline Phenotype

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 12). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1743 of 1915

Table 12. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	Response at Week 48 (<50 copies/mL) Subset n = 163
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI-resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 61-fold (range: 0.75 to 209) for isolates with emergent INSTI-resistance substitutions (n = 33).

Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) of subjects in the Week 48 resistance analysis.

In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8. Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M,

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1744 of 1915

E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

Mutagenesis

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Impairment of Fertility

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

The efficacy and safety of TIVICAY were evaluated in the studies summarized in Table 13.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1745 of 1915

Table 13. Trials Conducted with TIVICAY in HIV-1-Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)
Adults: Treatment-naïve	SPRING-2 (ING113086) (NCT01227824)	TIVICAY + 2 NRTIs (n = 403) Raltegravir +3 NRTIs (n = 405)	96
	SINGLE (ING114467) (NCT01263015)	TIVICAY + EPZICOM (n = 414) ATRIPLA (n = 419)	144
	FLAMINGO (ING114915) (NCT01449929)	TIVICAY + NRTI BR (n = 243) Darunavir/ritonavir + NRTI BR (n = 242)	96
Treatment-experienced, INSTI-naïve	SAILING (ING111762) (NCT01231516)	TIVICAY + BR (n = 354) Raltegravir + BR (n = 361)	48
INSTI-experienced	VIKING-3 (ING112574) (NCT01328041)	TIVICAY + OBT (n = 183)	48
Virologically suppressed	SWORD-1 (NCT02429791) SWORD-2 (NCT02422797)	Pooled presentation TIVICAY + Rilpivirine (n = 513) CAR (n = 511)	48
Pediatrics: 6 years and older without INSTI resistance	IMPAACT P1093 (NCT01302847)	TIVICAY + BR (n = 46)	48

BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy

14.2 Adult Subjects

Treatment-Naïve Subjects

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm^3, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1746 of 1915

100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 14. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 14. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

	SPRING-2 Week 96		SINGLE Week 144	
	TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**TIVICAY 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
HIV-1 RNA <50 copies/mL	82%	78%	71%	63%
Treatment difference[a]	4.9% (95% CI: -0.6%, 10.3%)[d]		8.3% (95% CI: 2.0%, 14.6%)[e]	
Virologic nonresponse	5%	10%	10%	7%
Data in window not <50 copies/mL	1%	3%	4%	<1%
Discontinued for lack of efficacy	2%	3%	3%	3%
Discontinued for other reasons while not suppressed	<1%	3%	3%	4%
Change in ART regimen	<1%	<1%	0	0
No virologic data	12%	12%	18%	30%
Reasons				
Discontinued study/study drug due to adverse event or death[b]	2%	2%	4%	14%
Discontinued study/study drug for other reasons[c]	8%	9%	12%	13%
Missing data during window but on study	2%	<1%	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	84%	83%	73%	64%
>100,000	79%	63%	69%	61%

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1747 of 1915

Gender				
Male	84%	79%	72%	66%
Female	70%	68%	69%	48%
Race				
White	83%	78%	72%	71%
African-American/African Heritage/Other	77%	75%	71%	47%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.

[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).

[e] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of EPZICOM or TRUVADA as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm^3 in the group receiving TIVICAY and 264 cells per mm^3 for the raltegravir group at 96 weeks.

There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

SINGLE: Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race.

The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

There was no treatment-emergent resistance to dolutegravir, abacavir, or lamivudine.

FLAMINGO: In FLAMINGO, 485 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily (n = 243) or darunavir + ritonavir 800 mg/100 mg once daily (n = 242), both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir and lamivudine [EPZICOM] or fixed-dose emtricitabine/tenofovir disoproxil fumarate [TRUVADA]). There were 484 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years, 15% female, 28% non-white, 10% had hepatitis B and/or C virus co-infection, 3% were CDC Class C (AIDS), 25% had HIV-1 RNA

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1748 of 1915

greater than 100,000 copies per mL, and 35% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. Overall response rates by Snapshot algorithm through Week 96 were 80% for TIVICAY and 68% for darunavir/ritonavir. The proportion of subjects who were non-responders (HIV-1 RNA greater than or equal to 50 copies per mL) at Week 96 was 8% and 12% in the arms receiving TIVICAY and darunavir + ritonavir, respectively; no virologic data were available for 12% and 21% for subjects treated with TIVICAY and darunavir + ritonavir, respectively. The adjusted overall response rate difference in proportion and 95% CI was 12.4% (4.7%, 20.2%). No treatment-emergent primary resistance substitutions were observed in either treatment group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

In the international, multicenter, double-blind trial (SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least 1 fully active agent. There were 715 subjects included in the efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA greater than 100,000 copies per mL, and 72% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups. All subjects had at least 2-class antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral treatment resistance at baseline. Week 48 outcomes for SAILING are shown in Table 15.

Table 15. Virologic Outcomes of Randomized Treatment in SAILING at 48 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Once Daily + BR[a] (n = 354)	**Raltegravir 400 mg Twice Daily + BR[a] (n = 361)**
HIV-1 RNA <50 copies/mL	71%	64%
Adjusted[b] treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death	3%	4%
Discontinued study/study drug for other reasons[c]	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	75%	71%
>50,000 copies/mL	62%	47%

Background regimen		
No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

[a] BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.

[b] Adjusted for pre-specified stratification factors.

[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age.

The mean changes in CD4+ cell counts from baseline were 162 cells per mm^3 in the group receiving TIVICAY and 153 cells per mm^3 in the raltegravir group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects

VIKING-3 examined the effect of TIVICAY 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy (OBT) with continued treatment of TIVICAY 50 mg twice daily.

In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV-1-infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days, then received TIVICAY with OBT from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI resistance at screening and 50 subjects with only historical evidence of resistance (and not at screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus co-infection. Median baseline CD4+ cell count was 140 cells per mm^3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79% had greater than or equal to 2 NRTI, 75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 $\log_{10}$ (95% CI: 1.3 $\log_{10}$, 1.5 $\log_{10}$). Response at Week 48 was affected by baseline INSTI substitutions *[see Microbiology (12.4)]*.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1750 of 1915

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Week 48 virologic outcomes for VIKING-3 are shown in Table 16.

Table 16. Virologic Outcomes of Treatment of VIKING-3 at 48 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Twice Daily + OBT (n = 183)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data Reasons Discontinued study/study drug due to adverse event or death	3%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category	
Gender Male Female	 63% 64%
Race White African-American/African Heritage/Other	 63% 64%

Subjects harboring virus with Q148 and with additional Q148-associated secondary substitutions also had a reduced response at Week 48 in a stepwise fashion *[see Microbiology (12.4)]*.

The median change in CD4+ cell count from baseline was 80 cells per mm^3 at Week 48.

Virologically Suppressed Subjects

SWORD-1 and SWORD-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. A total of 1,024 adult HIV-1-infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI) for at least 6 months (HIV-1 RNA less than 50 copies per mL), with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine received treatment in the trials. Subjects were randomized 1:1 to continue their current antiretroviral regimen or be switched to TIVICAY 50 mg plus rilpivirine 25 mg administered once daily. The primary efficacy endpoint for the SWORD trial was the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Week 48. The proportion of subjects with HIV-1 RNA less than 50 copies per mL at Week 48 was 95% for both treatment groups; treatment difference and 95% CI was -0.2% (-3.0%, 2.5%). The proportion of subjects with HIV-1 RNA greater than or equal to 50 copies per mL (virologic failure) at Week 48 was 0.6% and 1.2% for the dolutegravir plus rilpivirine treatment group and the current antiretroviral regimen treatment groups, respectively; treatment difference and 95% CI was -0.6% (-1.7%, 0.6%). Refer

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1751 of 1915

to the Prescribing Information for JULUCA (dolutegravir and rilpivirine) tablet for complete virologic outcome information.

14.3 Pediatric Subjects

IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY in combination treatment regimens in HIV–1-infected infants, children, and adolescents. Subjects were stratified by age, enrolling adolescents first (Cohort 1: aged 12 to less than 18 years) and then younger children (Cohort 2A: aged 6 to less than 12 years). All subjects received a weight-based dose of TIVICAY *[see Dosage and Administration (2.2)]*.

These 46 subjects had a mean age of 12 years (range: 6 to 17), were 54% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 $\log_{10}$ copies per mL, median CD4+ cell count was 639 cells per mm^3 (range: 9 to 1,700), and median CD4+% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 33% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (50%) or 1 PI (70%).

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 70% (16/23) and 61% (14/23), respectively. At Week 48, the proportion of subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (14/23). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least 40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (12/19) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

The median CD4+ cell count increase from baseline to Week 48 was 84 cells per mm^3 in Cohort 1. For Cohort 2A, the median CD4+ cell count increase from baseline to Week 24 was 209 cells per mm^3.

16 HOW SUPPLIED/STORAGE AND HANDLING

TIVICAY tablets, 10 mg, are white, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "10" on the other side. Bottle of 30 tablets with child-resistant closure and containing a desiccant. NDC 49702-226-13.

Store and dispense the 10-mg tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

TIVICAY tablets, 25 mg, are pale yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "25" on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-227-13.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1752 of 1915

TIVICAY tablets, 50 mg, are yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-228-13.

Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

TIVICAY may interact with other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Drug Interactions (7)]*.

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking TIVICAY and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea-colored urine, pale-colored stools or bowel movements, nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on the right side below the ribs) *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir *[see Warnings and Precautions (5.2)]*. Advise patients that laboratory monitoring for hepatoxicity during therapy with TIVICAY is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential to avoid use of TIVICAY at the time of conception through the first trimester of pregnancy. Advise adolescents and adults of childbearing potential to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with TIVICAY *[see Warnings and Precaution (5.3)]*.

Advise adolescents and adults of childbearing potential taking TIVICAY to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1753 of 1915

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when TIVICAY is started *[see Warnings and Precautions (5.5)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to TIVICAY during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dosage

Instruct patients that if they miss a dose of TIVICAY, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Storage

Instruct patients to store the TIVICAY 10-mg tablets in the original package, keep the bottle tightly closed, and protect from moisture. Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

TIVICAY, EPZICOM, JULUCA, and TRIUMEQ are trademarks owned by or licensed to the ViiV Healthcare group of companies.

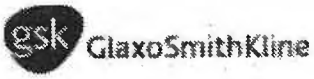
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Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

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1754 of 1915



GlaxoSmithKline
Research Triangle Park, NC 27709

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PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

TIVICAY (TIV-eh-kay)
(dolutegravir tablets)

What is TIVICAY?

TIVICAY is a prescription medicine that is used to treat Human Immunodeficiency Virus-1 (HIV-1) infection together with:

- other antiretroviral medicines in adults and children who weigh at least 66 pounds (30 kg).
- rilpivirine in adults to replace their current anti-HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

It is not known if TIVICAY is safe and effective in children who weigh less than 66 pounds (30 kg) or in children who have received certain types of medicine for HIV-1 infection.

Do not take TIVICAY if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir.
- take dofetilide.

Before you take TIVICAY, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had an allergic reaction to dolutegravir.
- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY may harm your unborn baby.
  - **You should not take TIVICAY at the time of becoming pregnant or during the first 12 weeks of pregnancy.** Your healthcare provider may change your medicine during this time in your pregnancy.
  - If you can become pregnant, your healthcare provider will perform a pregnancy test before you start treatment with TIVICAY.
  - If you can become pregnant, you should consistently use effective birth control (contraception) during treatment with TIVICAY.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TIVICAY.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY, during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take TIVICAY.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if TIVICAY can pass to your baby in your breast milk.

  Talk with your healthcare provider about the best way to feed your baby.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1756 of 1915

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with TIVICAY. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TIVICAY.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take TIVICAY with other medicines.

How should I take TIVICAY?

- **Take TIVICAY exactly as your healthcare provider tells you to take it.**
- Take TIVICAY with or without food.
- Do not change your dose or stop taking TIVICAY without talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TIVICAY should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with TIVICAY:
  - If you take TIVICAY with food, you may take these supplements at the same time that you take TIVICAY.
  - If you do not take TIVICAY with food, take TIVICAY at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of TIVICAY.
- If you miss a dose of TIVICAY, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- Stay under the care of a healthcare provider during treatment with TIVICAY.
- Do not run out of TIVICAY. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TIVICAY, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TIVICAY?

- **TIVICAY can cause serious side effects including:**
- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with TIVICAY. **Stop taking TIVICAY and get medical help right away if you develop a rash with any of the following signs or symptoms:**
  - fever
  - generally ill feeling
  - tiredness
  - muscle or joint aches
  - blisters or sores in mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the mouth, face, lips, or tongue
  - problems breathing

- **Liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with TIVICAY. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver. **Call your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking TIVICAY.
- **The most common side effects of TIVICAY include:**
  - trouble sleeping
  - tiredness
  - headache

These are not all the possible side effects of TIVICAY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIVICAY?

- Store TIVICAY at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TIVICAY 10-mg tablets in the original bottle. Keep the bottle tightly closed and protected from moisture.
- The bottle of TIVICAY (10-mg tablets) contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep TIVICAY and all medicines out of the reach of children.

General information about the safe and effective use of TIVICAY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TIVICAY for a condition for which it was not prescribed. Do not give TIVICAY to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TIVICAY that is written for health professionals. For more information, go to www.TIVICAY.com or call 1-877-844-8872.

What are the ingredients in TIVICAY?

Active ingredient: dolutegravir.

Inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients iron oxide yellow (for the 25-mg and 50-mg tablets only), macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Manufactured for: by:

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1758 of 1915

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIUMEQ safely and effectively. See full prescribing information for TRIUMEQ.

TRIUMEQ (abacavir, dolutegravir, and lamivudine) tablets, for oral use
Initial U.S. Approval: 2014

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

See full prescribing information for complete boxed warning.

Hypersensitivity Reactions

- **Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products. (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **TRIUMEQ is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients. (4)**
- **Discontinue TRIUMEQ as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue TRIUMEQ if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to TRIUMEQ, NEVER restart TRIUMEQ or any other abacavir-containing product. (5.1)**

Lactic Acidosis and Severe Hepatomegaly with Steatosis

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)**

Exacerbations of Hepatitis B

- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of TRIUMEQ. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)**

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	11/2017
Dosage and Administration, Recommended Dosage (2.2)	11/2017
Warnings and Precautions, Hepatotoxicity (5.3)	11/2017
Warnings and Precautions, Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions (5.6)	11/2017
Warnings and Precautions, Related Products that are Not Recommended (previous 5.8)	Removed 11/2017

---------- INDICATIONS AND USAGE----------

TRIUMEQ, a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) is indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 40 kg. (1)

Limitations of Use:

- TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Before initiating TRIUMEQ, screen for the HLA-B*5701 allele because TRIUMEQ contains abacavir. (2.1).
- Adults and pediatric patients weighing at least 40 kg: One tablet daily. May be taken with or without food. (2.2)
- If dosing with certain UGT1A or CYP3A inducers, then the recommended dolutegravir dosage regimen is 50 mg twice daily. An additional 50-mg dose of dolutegravir, separated by 12 hours from TRIUMEQ, should be taken. (2.3)
- Because TRIUMEQ is a fixed-dose tablet and cannot be dose adjusted, TRIUMEQ is not recommended in patients requiring dosage adjustment or patients with hepatic impairment. (2.4, 4)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. (3)

---------- CONTRAINDICATIONS ----------

- Presence of HLA-B*5701 allele. (4)
- Prior hypersensitivity reaction to abacavir, dolutegravir, or lamivudine. (4)
- Coadministration with dofetilide. (4)
- Moderate or severe hepatic impairment. (4, 8.7)

---------- WARNINGS AND PRECAUTIONS ----------

- Hepatotoxicity has been reported in patients receiving a dolutegravir-containing regimen. Monitoring for hepatotoxicity is recommended. (5.3)
- Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue TRIUMEQ as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.7)
- Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy. (5.8, 5.9)

---------- ADVERSE REACTIONS ----------

The most commonly reported adverse reactions of at least moderate intensity and incidence at least 2% (in those receiving TRIUMEQ) were insomnia, headache, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

Coadministration of TRIUMEQ with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of TRIUMEQ. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Breastfeeding is not recommended due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients weighing less than 40 kg. (8.4)
- TRIUMEQ is not recommended in patients with creatinine clearance less than 50 mL per min. (8.6)
- If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment, then the individual components should be used. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS B
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Screening for HLA-B*5701 Allele prior to Starting TRIUMEQ
2.2 Recommended Dosage
2.3 Dosage Recommendation with Certain Concomitant Medications
2.4 Not Recommended Due to Lack of Dosage Adjustment
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis
5.3 Hepatotoxicity
5.4 Posttreatment Exacerbations of Hepatitis in Patients with Hepatitis B Co-infection
5.5 Emergence of Lamivudine-Resistant HBV
5.6 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

Reference ID: 4184712

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1760 of 1915

5.7 Use with Interferon- and Ribavirin-Based Regimens
5.8 Immune Reconstitution Syndrome
5.9 Fat Redistribution
5.10 Myocardial Infarction
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents
7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir
7.3 Established and Other Potentially Significant Drug Interactions
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Impaired Renal Function
8.7 Patients with Impaired Hepatic Function
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Adult Subjects
14.2 Pediatric Subjects
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, and EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions

Serious and sometimes fatal hypersensitivity reactions, with multiple organ involvement, have occurred with abacavir, a component of TRIUMEQ (abacavir, dolutegravir, and lamivudine). Patients who carry the HLA-B*5701 allele are at a higher risk of a hypersensitivity reaction to abacavir; although, hypersensitivity reactions have occurred in patients who do not carry the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.

TRIUMEQ is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients *[see Contraindications (4), Warnings and Precautions (5.1)]*. All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ or reinitiation of therapy with TRIUMEQ, unless patients have a previously documented HLA-B*5701 allele assessment. Discontinue TRIUMEQ immediately if a hypersensitivity reaction is suspected, regardless of HLA-B*5701 status and even when other diagnoses are possible *[see Contraindications (4), Warnings and Precautions (5.1)]*.

Following a hypersensitivity reaction to TRIUMEQ, NEVER restart TRIUMEQ or any other abacavir-containing product because more severe symptoms, including death can occur within hours. Similar severe reactions have also occurred rarely following the reintroduction of abacavir-containing products in patients who have no history of abacavir hypersensitivity *[see Warnings and Precautions (5.1)]*.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including abacavir, lamivudine, and other antiretrovirals. Discontinue TRIUMEQ if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur [see Warnings and Precautions (5.2)].

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1761 of 1915

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of TRIUMEQ. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue TRIUMEQ and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted ***[see Warnings and Precautions (5.4)]*****.**

1 INDICATIONS AND USAGE

TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 40 kg.

Limitations of Use:

- TRIUMEQ alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in TRIUMEQ is insufficient in these subpopulations. See full prescribing information for TIVICAY (dolutegravir).

2 DOSAGE AND ADMINISTRATION

2.1 Screening for HLA-B*5701 Allele prior to Starting TRIUMEQ

Screen for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ *[see Boxed Warning, Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

TRIUMEQ is a fixed-dose combination product containing 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. The recommended dosage regimen of TRIUMEQ in adults and in pediatric patients weighing at least 40 kg is one tablet once daily orally with or without food.

2.3 Dosage Recommendation with Certain Concomitant Medications

The dolutegravir dose (50 mg) in TRIUMEQ is insufficient when coadministered with medications listed in Table 1 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1762 of 1915

Table 1. Dosing Recommendations for TRIUMEQ with Coadministered Medications

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, carbamazepine, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from TRIUMEQ, should be taken.

2.4 Not Recommended Due to Lack of Dosage Adjustment

Because TRIUMEQ is a fixed-dose tablet and cannot be dose adjusted, TRIUMEQ is not recommended in:

- patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.
- patients with mild hepatic impairment. TRIUMEQ is contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

TRIUMEQ tablets are purple, biconvex, oval, and debossed with "572 Tri" on one side. Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine *[see Description (11)]*.

4 CONTRAINDICATIONS

TRIUMEQ is contraindicated in patients:

- who have the HLA-B*5701 allele *[see Warnings and Precautions (5.1)]*.
- with prior hypersensitivity reaction to abacavir, dolutegravir *[see Warnings and Precautions (5.1)]*, or lamivudine.
- receiving dofetilide, due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions (7)]*.
- with moderate or severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with the use of abacavir or dolutegravir, components of TRIUMEQ.

Abacavir

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1763 of 1915

Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing regimens. See full prescribing information for ZIAGEN (abacavir).

Abacavir hypersensitivity reactions have included multi-organ failure and anaphylaxis and typically occurred within the first 6 weeks of treatment with abacavir (median time to onset was 9 days); although abacavir hypersensitivity reactions have occurred any time during treatment *[see Adverse Reactions (6.1)]*. Patients who carry the HLA-B*5701 allele are at a higher risk of abacavir hypersensitivity reactions; although, patients who do not carry the HLA-B*5701 allele have developed hypersensitivity reactions. Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when subjects carrying the HLA-B*5701 allele were excluded. In any patient treated with abacavir, the clinical diagnosis of hypersensitivity reaction must remain the basis of clinical decision making.

Due to the potential for severe, serious, and possibly fatal hypersensitivity reactions with abacavir:

- All patients should be screened for the HLA-B*5701 allele prior to initiating therapy with TRIUMEQ or reinitiation of therapy with TRIUMEQ, unless patients have a previously documented HLA-B*5701 allele assessment.
- TRIUMEQ is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.
- Before starting TRIUMEQ, review medical history for prior exposure to any abacavir-containing product. NEVER restart TRIUMEQ or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status.
- To reduce the risk of a life-threatening hypersensitivity reaction, regardless of HLA-B*5701 status, discontinue TRIUMEQ immediately if a hypersensitivity reaction is suspected, even when other diagnoses are possible (e.g., acute onset respiratory diseases such as pneumonia, bronchitis, pharyngitis, or influenza; gastroenteritis; or reactions to other medications). Clinical status, including liver chemistries, should be monitored and appropriate therapy initiated.
- If a hypersensitivity reaction cannot be ruled out, do not restart TRIUMEQ or any other abacavir-containing products because more severe symptoms, which may include life-threatening hypotension and death, can occur within hours.
- Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir. Therefore, never restart TRIUMEQ or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with TRIUMEQ due to a hypersensitivity reaction.
- If a hypersensitivity reaction is ruled out, patients may restart TRIUMEQ. Rarely, patients

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1764 of 1915

who have stopped abacavir for reasons other than symptoms of hypersensitivity have also experienced life-threatening reactions within hours of reinitiating abacavir therapy. Therefore, reintroduction of TRIUMEQ, or any other abacavir-containing product, is recommended only if medical care can be readily accessed.

- A Medication Guide and Warning Card that provide information about recognition of abacavir hypersensitivity reactions should be dispensed with each new prescription and refill.

Dolutegravir

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue TRIUMEQ and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TRIUMEQ or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

Clinically, it is not possible to determine whether a hypersensitivity reaction with TRIUMEQ would be caused by abacavir or dolutegravir. Therefore, never restart TRIUMEQ or any other abacavir- or dolutegravir-containing product in patients who have stopped therapy with TRIUMEQ due to a hypersensitivity reaction.

5.2 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretrovirals. See full prescribing information for ZIAGEN (abacavir) and EPIVIR (lamivudine). Treatment with TRIUMEQ should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.3 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen *[see Adverse Reactions (6.1)]*. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TRIUMEQ *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity including elevated serum liver biochemistries, hepatitis, and acute liver failure have also been reported in patients receiving a dolutegravir-containing regimen who had no pre-existing hepatic disease or other identifiable

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1765 of 1915

risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ. Monitoring for hepatotoxicity is recommended.

5.4 Posttreatment Exacerbations of Hepatitis in Patients with Hepatitis B Co-infection

Clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of lamivudine. See full prescribing information for EPIVIR (lamivudine). Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

5.5 Emergence of Lamivudine-Resistant HBV

Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in subjects dually infected with HIV-1 and HBV. Emergence of hepatitis B virus variants associated with resistance to lamivudine has been reported in HIV-1-infected subjects who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus. See full prescribing information for EPIVIR-HBV (lamivudine).

5.6 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of TRIUMEQ and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of TRIUMEQ and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TRIUMEQ; review concomitant medications during therapy with TRIUMEQ; and monitor for the adverse reactions associated with the concomitant drugs.

5.7 Use with Interferon- and Ribavirin-Based Regimens

Patients receiving interferon alfa with or without ribavirin and TRIUMEQ should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. See full prescribing information for EPIVIR (lamivudine). Discontinuation of TRIUMEQ should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6) (see full prescribing information for interferon and ribavirin).

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TRIUMEQ. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1766 of 1915

response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.9 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.10 Myocardial Infarction

In a published prospective, observational, epidemiological trial designed to investigate the rate of myocardial infarction (MI) in patients on combination antiretroviral therapy, the use of abacavir within the previous 6 months was correlated with an increased risk of MI. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in abacavir-treated subjects as compared with control subjects. In totality, the available data from the observational cohort and from clinical trials are inconclusive.

As a precaution, the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reaction *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.5)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and Hepatitis C *[see Warnings and Precautions (5.7)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.8)]*.
- Fat redistribution *[see Warnings and Precautions (5.9)]*.

- Myocardial infarction *[see Warnings and Precautions (5.10)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials in Adults

Serious and Fatal Abacavir-Associated Hypersensitivity Reactions: In clinical trials, serious and sometimes fatal hypersensitivity reactions have occurred with abacavir, a component of TRIUMEQ *[see Boxed Warning, Warnings and Precautions (5.1)]*. These reactions have been characterized by 2 or more of the following signs or symptoms: (1) fever; (2) rash; (3) gastrointestinal symptoms (including nausea, vomiting, diarrhea, or abdominal pain); (4) constitutional symptoms (including generalized malaise, fatigue, or achiness); (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Almost all abacavir hypersensitivity reactions include fever and/or rash as part of the syndrome.

Other signs and symptoms have included lethargy, headache, myalgia, edema, arthralgia, and paresthesia. Anaphylaxis, liver failure, renal failure, hypotension, adult respiratory distress syndrome, respiratory failure, myolysis, and death have occurred in association with these hypersensitivity reactions. Physical findings have included lymphadenopathy, mucous membrane lesions (conjunctivitis and mouth ulcerations), and maculopapular or urticarial rash (although some patients had other types of rashes and others did not have a rash). There were reports of erythema multiforme. Laboratory abnormalities included elevated liver chemistries, elevated creatine phosphokinase, elevated creatinine, and lymphopenia and abnormal chest x-ray findings (predominantly infiltrates, which were localized).

Serious Dolutegravir Hypersensitivity Reactions: In clinical trials, hypersensitivity reactions have occurred with dolutegravir, a component of TRIUMEQ *[see Warnings and Precautions (5.1)]*. These hypersensitivity reactions have been characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

Additional Treatment-Emergent Adverse Drug Reactions (ADRs) with Use of TRIUMEQ: The safety assessment of TRIUMEQ is primarily based on the analyses of data from a randomized, international, multicenter, double-blind, active-controlled trial, SINGLE (ING114467) and supported by data in treatment-experienced, INSTI-naïve subjects from SAILING (ING111762) and by data from other treatment-naïve trials. See full prescribing information for TIVICAY.

Treatment-Naïve Subjects: In SINGLE, 833 adult subjects were randomized and received at least one dose of either dolutegravir (TIVICAY) 50 mg with fixed-dose abacavir and lamivudine (EPZICOM) once daily (n = 414) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (n = 419) (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rate of adverse events leading to

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1768 of 1915

discontinuation was 4% in subjects receiving TIVICAY + EPZICOM and 14% in subjects receiving ATRIPLA once daily.

Treatment-emergent ADRs of moderate to severe intensity observed in at least 2% of subjects in either treatment arm of SINGLE are provided in Table 2.

Table 2. Treatment-Emergent Adverse Drug Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SINGLE (Week 144 Analysis)

Adverse Reaction	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Psychiatric		
Insomnia	3%	3%
Depression	1%	2%
Abnormal dreams	<1%	2%
Nervous System		
Dizziness	<1%	5%
Headache	2%	2%
Gastrointestinal		
Nausea	<1%	3%
Diarrhea	<1%	2%
General Disorders		
Fatigue	2%	2%
Skin and Subcutaneous Tissue		
Rash[a]	<1%	6%
Ear and Labyrinth		
Vertigo	0	2%

[a] Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

Treatment-Experienced Subjects: SAILING is an international, double-blind trial in INSTI-naïve, antiretroviral treatment-experienced adult subjects. Subjects were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rate of adverse events leading to discontinuation was consistent with that seen in the overall treatment-naïve patient population. See full prescribing information for TIVICAY.

The ADRs observed in the subset of subjects who received TIVICAY + EPZICOM were generally consistent with those seen in the overall treatment-naïve patient population.

Less Common Adverse Reactions Observed in Clinical Trials: The following adverse reactions occurred in less than 2% of treatment-naïve or treatment-experienced subjects in any one trial. These events have been included because of their seriousness and/or assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal distention, abdominal discomfort, dyspepsia, flatulence, gastroesophageal reflux disease, upper abdominal pain, vomiting.

General Disorders: Fever, lethargy.

Hepatobiliary Disorders: Hepatitis.

Metabolism and Nutrition Disorders: Anorexia, hypertriglyceridemia.

Musculoskeletal Disorders: Arthralgia, myositis.

Nervous System Disorders: Somnolence.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness. Nightmare and sleep disorder.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities: Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects in SINGLE are presented in Table 3. The mean change from baseline observed for selected lipid values is presented in Table 4.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SINGLE (Week 144 Analysis)

Laboratory Abnormality	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
ALT		
Grade 2 (>2.5-5.0 x ULN)	3%	5%
Grade 3 to 4 (>5.0 x ULN)	1%	<1%
AST		
Grade 2 (>2.5-5.0 x ULN)	3%	4%
Grade 3 to 4 (>5.0 x ULN)	1%	3%
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	8%
Hyperglycemia		

Grade 2 (126-250 mg/dL)	9%	6%
Grade 3 (>250 mg/dL)	2%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	11%	11%
Grade 3 to 4 (>3.0 ULN)	5%	4%
Total neutrophils		
Grade 2 (0.75-0.99 x 10^9)	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	3%	3%

ULN = Upper limit of normal.

Table 4. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SINGLE (Week 144 Analysis[a])

Lipid	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
Cholesterol (mg/dL)	24.0	26.7
HDL cholesterol (mg/dL)	5.4	7.2
LDL cholesterol (mg/dL)	16.0	14.6
Triglycerides (mg/dL)	13.6	31.9

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (TIVICAY + EPZICOM n = 30 and ATRIPLA n = 27). Seventy-two subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (TIVICAY + EPZICOM: n = 36 and ATRIPLA: n = 36).

Treatment-Experienced Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve trials.

Hepatitis C Virus Co-infection: In SINGLE, the pivotal Phase 3 trial, subjects with hepatitis C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal; subjects with hepatitis B co-infection were excluded. Overall, the safety profile in subjects with hepatitis C virus co-infection was similar to that observed in subjects without hepatitis C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis C virus co-infection for both treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis C co-infected compared with HIV mono-infected subjects receiving TRIUMEQ were observed in 15% and 2% (vs. 24% and 4% of subjects treated with ATRIPLA) (Week 96 analysis), respectively *[see Warnings and Precautions (5.3)]*. See also full prescribing information for TIVICAY.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first

4 weeks of treatment and remained stable through 144 weeks. In SINGLE, a mean change from baseline of 0.14 mg per dL (range: -0.25 mg per dL to 0.81 mg per dL) was observed after 144 weeks of treatment. Creatinine increases were similar in treatment-experienced subjects.

Abacavir and Lamivudine: Laboratory abnormalities observed in clinical trials of ZIAGEN (in combination with other antiretroviral treatment) were anemia, neutropenia, liver function test abnormalities, and elevations of CPK, blood glucose, and triglycerides. Additional laboratory abnormalities observed in clinical trials of EPIVIR (in combination with other antiretroviral treatment) were thrombocytopenia and elevated levels of bilirubin, amylase, and lipase.

Clinical Trials Experience in Pediatric Subjects

Abacavir and Lamivudine: The safety of once-daily compared with twice-daily dosing of abacavir and lamivudine, administered as either single products or as EPZICOM, was assessed in the ARROW trial (n = 336). Primary safety assessment in the ARROW (COL105677) trial was based on Grade 3 and Grade 4 adverse events. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator. No additional safety issues were identified in pediatric subjects compared with historical data in adults.

Dolutegravir: IMPAACT P1093 is a 48-week multicenter, open-label, non-comparative trial of approximately 160 HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years, of which, 23 treatment-experienced, INSTI-naïve subjects aged 12 to less than 18 years were enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)]*.

The ADR profile was similar to that for adults. Grade 2 ADRs reported by more than one subject were decreased neutrophil count (n = 2). No Grade 3 or 4 ADRs were reported. No ADRs led to discontinuation. The Grade 3 laboratory abnormalities reported in 1 subject each were elevated total bilirubin, elevated lipase, and decreased white blood cell count. There was one Grade 4 decreased neutrophil count. The changes in mean serum creatinine were similar to those observed in adults.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use with one or more of the components of TRIUMEQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Digestive

Stomatitis.

Gastrointestinal

Pancreatitis.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1772 of 1915

General

Weakness.

Blood and Lymphatic Systems

Aplastic anemia, anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

Hepatobiliary Disorders

Acute liver failure, liver transplant.

Hypersensitivity

Sensitization reactions (including anaphylaxis), urticaria *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

Metabolism and Nutrition Disorders

Hyperlactemia.

Musculoskeletal

CPK elevation, muscle weakness, myalgia, rhabdomyolysis.

Nervous

Paresthesia, peripheral neuropathy, seizures.

Psychiatric

Anxiety.

Respiratory

Abnormal breath sounds/wheezing.

Skin

Alopecia, erythema multiforme. Suspected Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving abacavir primarily in combination with medications known to be associated with SJS and TEN, respectively. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS and TEN, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases *[see Adverse Reactions (6.1)]*.

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters (OCT)2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE)1 (IC_{50} = 6.34 microM). In

vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin) *[see Contraindications (4), Drug Interactions (7.3)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

In drug interaction trials, dolutegravir did not have a clinically relevant effect on the pharmacokinetics of the following drugs: daclatasvir, tenofovir, methadone, midazolam, rilpivirine, and oral contraceptives containing norgestimate and ethinyl estradiol. Using cross-study comparisons to historical pharmacokinetic data for each interacting drug, dolutegravir did not appear to affect the pharmacokinetics of the following drugs: atazanavir, darunavir, efavirenz, etravirine, fosamprenavir, lopinavir, ritonavir, and boceprevir.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentrations and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentrations.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 5) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

Darunavir/ritonavir, lopinavir/ritonavir, rilpivirine, tenofovir, boceprevir, daclatasvir, prednisone, rifabutin, and omeprazole had no clinically significant effect on the pharmacokinetics of dolutegravir.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1774 of 1915

7.3 Established and Other Potentially Significant Drug Interactions

There were no drug-drug interaction trials conducted with the abacavir, dolutegravir, and lamivudine fixed-dose combination tablets.

Information regarding potential drug interactions with dolutegravir (Table 5) and abacavir are provided below. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. *[See Contraindications (4), Clinical Pharmacology (12.3).]*

Table 5. Established and Other Potentially Significant Drug Interactions for Dolutegravir: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
HIV-1 Antiviral Agents		
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with TRIUMEQ *[see Contraindications (4)]*.
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓Dolutegravir	Use of TRIUMEQ with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with TRIUMEQ because there are insufficient data to make dosing recommendations.
Protease inhibitor: Fosamprenavir/ritonavir[a] Tipranavir/ritonavir[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from TRIUMEQ.
Other Agents		
Carbamazepine[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from TRIUMEQ.

Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with TRIUMEQ because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium and iron supplements, including multivitamins containing calcium or iron[a]	↓Dolutegravir	Administer TRIUMEQ 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, TRIUMEQ and supplements containing calcium or iron can be taken together with food.
Metformin[a]	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or TRIUMEQ. When stopping TRIUMEQ, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of TRIUMEQ is recommended.
Rifampin[a]	↓Dolutegravir	Adjust dolutegravir dose to 50 mg twice daily. An additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from TRIUMEQ.

[a] *See Clinical Pharmacology (12.3) Table 8 or Table 9 for magnitude of interaction.*

Methadone

Abacavir: In a trial of 11 HIV-1–infected subjects receiving methadone-maintenance therapy with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased *[see Clinical Pharmacology (12.3)]*. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1776 of 1915

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRIUMEQ during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of TRIUMEQ during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Given the limited number of pregnancies exposed to dolutegravir-based regimens reported to the APR, no definitive conclusions can be drawn on the safety of TRIUMEQ in pregnancy, and continued monitoring is ongoing through the APR.

Available data from the APR show no difference in the overall risk of birth defects for abacavir or lamivudine compared with the background rate for birth defects of 2.7% in the Metropolitan Atlanta Congenital Defects Program (MACDP) reference population *(see Data)*. The APR uses the MACDP as the U.S. reference population for birth defects in the general population. The MACDP evaluates women and infants from a limited geographic area and does not include outcomes for births that occurred at less than 20 weeks' gestation. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%. The background risk for major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir *(see Data)*. During organogenesis in the rat and rabbit and a rat pre/postnatal developmental study, systemic exposures (AUC) to dolutegravir were less than (rabbits) and approximately 50 times (rats) the exposure in humans at the recommended human dose (RHD). Oral administration of abacavir to pregnant rats during organogenesis resulted in fetal malformations and other embryonic and fetal toxicities at exposures 35 times the human exposure (AUC) at the RHD. No adverse developmental effects were observed following oral administration of abacavir to pregnant rabbits during organogenesis at exposures approximately 9 times the human exposure (AUC) at the RHD. Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at a human exposure (AUC) similar to the RHD; however, no adverse development effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (C_{max}) 35 times the RHD *(see Data)*.

Data

Human Data: Abacavir: Based on prospective reports to the APR of over 2,000 exposures to abacavir during pregnancy resulting in live births (including over 1,000 exposed in the first

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1777 of 1915

trimester), there was no difference between the overall risk of birth defects for abacavir compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 2.9% (95% CI: 2.0% to 4.1%) following first trimester exposure to abacavir-containing regimens and 2.7% (95% CI: 1.9% to 3.7%) following second/third trimester exposure to abacavir-containing regimens.

Abacavir has been shown to cross the placenta and concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery *[see Clinical Pharmacology (12.3)]*.

Lamivudine: Based on prospective reports to the APR of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,500 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 3.1% (95% CI: 2.6% to 3.6%) following first trimester exposure to lamivudine-containing regimens and 2.8% (95% CI: 2.5%, 3.3%) following second/third trimester exposure to lamivudine-containing regimens.

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks' gestation using 150 mg lamivudine twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of lamivudine were 3.9 (1.2 to 12.8)–fold greater compared with paired maternal serum concentration (n = 8).

Animal Data: Dolutegravir: Dolutegravir was administered orally to pregnant rats and rabbits (up to 1,000 mg per kg per day) on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation Day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the RHD and in rats were approximately 50 times the exposure in humans at the RHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 50 times human exposure at the RHD).

Abacavir: Abacavir was administered orally to pregnant rats (at 100, 300, and 1,000 mg per kg per day) and rabbits (at 125, 350, or 700 mg per kg per day) during organogenesis (on gestation Days 6 through 17 and 6 through 20, respectively). Fetal malformations (increased

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1778 of 1915

incidences of fetal anasarca and skeletal malformations) or developmental toxicity (decreased fetal body weight and crown-rump length) were observed in rats at doses up to 1,000 mg per kg per day, resulting in exposures approximately 35 times the human exposure (AUC) at the RHD. No developmental effects were observed in rats at 100 mg per kg per day, resulting in exposures (AUC) 3.5 times the human exposure at the recommended daily dose. In a fertility and early embryo-fetal development study conducted in rats (at 60, 160, or 500 mg per kg per day), embryonic and fetal toxicities (increased resorptions, decreased fetal body weights) or toxicities to the offspring (increased incidence of stillbirth and lower body weights) occurred at doses up to 500 mg per kg per day. No developmental effects were observed in rats at 60 mg per kg per day, resulting in exposures (AUC) approximately 4 times the human exposure at the RHD. Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. In pregnant rabbits, no developmental toxicities and no increases in fetal malformations occurred at up to the highest dose evaluated, resulting in exposures (AUC) approximately 9 times the human exposure at the RHD.

Lamivudine: Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg per kg per day) and rabbits (at 90, 300 and 1,000 mg per kg per day and at 15, 40, and 90 mg per kg per day) during organogenesis (on gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (C_{max}) approximately 35 times higher than human exposure at the RHD. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similar to those observed in humans, but there was no indication of this effect in the rat at plasma concentrations (C_{max}) 35 times higher than human exposure at the RHD. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg per kg per day (from prior to mating through postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, were not affected by the maternal administration of lamivudine.

8.2 Lactation

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Abacavir and lamivudine are present in human milk. When administered to lactating rats, dolutegravir was present in milk *(see Data)*. There is no information on the effects of TRIUMEQ or its components on the breastfed infant or the effects of the drug on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving TRIUMEQ.

Data

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1779 of 1915

Animal Data: Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours' post-dose.

8.4 Pediatric Use

The clinical data supporting use of TRIUMEQ in HIV-1 infected pediatric patients weighing at least 40 kg is derived from the following previously conducted pediatric trials using the individual components of TRIUMEQ:

- The safety and efficacy of once-daily abacavir and lamivudine were established with a randomized, multicenter trial (ARROW [COL105677]) in HIV-1–infected, treatment-naïve subjects aged 3 months to 17 years with a first-line regimen containing abacavir and lamivudine, using either the combination of EPIVIR and ZIAGEN or EPZICOM *[see Adverse Reactions (6.2), Clinical Studies (14.2)]*.
- The safety and antiviral activity (efficacy) of dolutegravir was established through a 48-week, open-label, multicenter, dose-finding clinical trial (IMPAACT P1093), in which treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years were treated with dolutegravir (TIVICAY) plus optimized background therapy *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

TRIUMEQ is a fixed-dose combination tablet which cannot be adjusted for patients weighing less than 40 kg *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical trials of abacavir, dolutegravir, or lamivudine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TRIUMEQ in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Impaired Renal Function

TRIUMEQ is not recommended for patients with creatinine clearance less than 50 mL per min because TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, a component of TRIUMEQ, is required for patients with creatinine clearance less than 50 mL per min, then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Impaired Hepatic Function

TRIUMEQ is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of abacavir, a component of TRIUMEQ, is required for patients with mild hepatic impairment (Child-Pugh Score A), then the individual components should be used *[see Clinical Pharmacology (12.3)]*.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1780 of 1915

The safety, efficacy, and pharmacokinetic properties of abacavir have not been established in patients with moderate (Child-Pugh Score B) or severe (Child-Pugh Score C) hepatic impairment; therefore, TRIUMEQ is contraindicated in these patients *[see Contraindications (4)]*.

10 OVERDOSAGE

There is no known specific treatment for overdose with TRIUMEQ. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Dolutegravir

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

Abacavir

It is not known whether abacavir can be removed by peritoneal dialysis or hemodialysis.

Lamivudine

Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event.

11 DESCRIPTION

TRIUMEQ

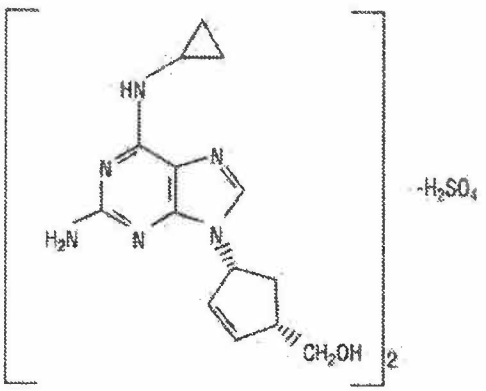
TRIUMEQ contains an INSTI (dolutegravir) and 2 nucleoside analogues (abacavir and lamivudine) with inhibitory activity against HIV.

Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine. TRIUMEQ tablets are purple, biconvex, oval, debossed with "572 Tri" on one side and contain the inactive ingredients D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film-coating (OPADRY II Purple 85F90057) contains the inactive ingredients iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide.

Abacavir Sulfate

The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 g per mol. It has the following structural formula:

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1781 of 1915



Abacavir sulfate is a white to off-white solid and is soluble in water.

Dolutegravir

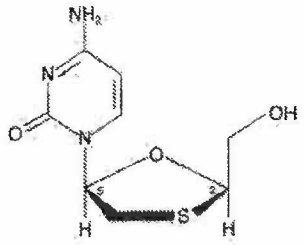
The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Lamivudine

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 g per mol. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid and is soluble in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

TRIUMEQ is an HIV-1 antiretroviral agent *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects on Electrocardiogram

A thorough QT trial has been conducted for dolutegravir. Neither the effects of abacavir nor lamivudine as single entities or the combination of abacavir, dolutegravir, and lamivudine on the QT interval have been evaluated.

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours' post-dose.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1783 of 1915

12.3 Pharmacokinetics

Pharmacokinetics in Adults

One TRIUMEQ tablet was bioequivalent to one dolutegravir (TIVICAY) tablet (50 mg) plus one abacavir and lamivudine fixed-dose combination tablet (EPZICOM) under fasted conditions in healthy subjects (n = 62).

Abacavir: Following oral administration, abacavir is rapidly absorbed and extensively distributed. After oral administration of a single dose of 600 mg of abacavir in 20 subjects, C_{max} was 4.26 ± 1.19 mcg per mL (mean ± SD) and AUC_{∞} was 11.95 ± 2.51 mcg•hour per mL. Binding of abacavir to human plasma proteins is approximately 50% and was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5′-carboxylic acid and glucuronyl transferase to form the 5′-glucuronide. In single-dose trials, the observed elimination half-life ($t_{½}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L per hour per kg (mean ± SD).

Dolutegravir: Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and $C_{24\ h}$ ranging from 1.2 to 1.5. Dolutegravir is a P-gp substrate in vitro. The absolute bioavailability of dolutegravir has not been established. Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A. After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose is excreted unchanged in the feces. Thirty-one percent of the total oral dose is excreted in the urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was less than 1% of the dose. Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1–infected subjects.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1784 of 1915

Table 6. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1–Infected Adults

Parameter	50 mg Once Daily Geometric Mean (%CV)
$AUC_{(0\text{-}24)}$ (mcg•h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

Cerebrospinal Fluid (CSF): In 11 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 18 ng per mL (range: 4 ng per mL to 23.2 ng per mL) 2 to 6 hours postdose after 2 weeks of treatment. The clinical relevance of this finding has not been established.

Lamivudine: Following oral administration, lamivudine is rapidly absorbed and extensively distributed. After multiple-dose oral administration of lamivudine 300 mg once daily for 7 days to 60 healthy subjects, steady-state C_{max} ($C_{max,ss}$) was 2.04 ± 0.54 mcg per mL (mean ± SD) and the 24-hour steady-state AUC ($AUC_{24,ss}$) was 8.87 ± 1.83 mcg•hour per mL. Binding to plasma protein is low. Approximately 70% of an intravenous dose of lamivudine is recovered as unchanged drug in the urine. Metabolism of lamivudine is a minor route of elimination. In humans, the only known metabolite is the trans-sulfoxide metabolite (approximately 5% of an oral dose after 12 hours). In most single-dose trials in HIV-1–infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1–infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD).

Effect of Food on Oral Absorption

TRIUMEQ may be taken with or without food. Overall, when compared with fasted conditions, administration of TRIUMEQ to healthy adult subjects with a high-fat meal (53% fat, 869 calories) resulted in decreased C_{max} for abacavir and increased C_{max} and AUC for dolutegravir. Lamivudine exposures were not affected by food. With a high-fat meal, the C_{max} of abacavir decreased 23% and the C_{max} and AUC of dolutegravir increased 37% and 48%, respectively.

Specific Populations

Patients with Renal Impairment: The effect of renal impairment on the combination of abacavir, dolutegravir, and lamivudine has not been evaluated (see the U.S. prescribing information for the individual abacavir, dolutegravir and lamivudine components).

Patients with Hepatic Impairment: The effect of hepatic impairment on the combination of abacavir, dolutegravir, and lamivudine has not been evaluated (see the U.S. prescribing information for the individual abacavir, dolutegravir, and lamivudine components).

Pediatric Patients: The pharmacokinetics for the individual components of TRIUMEQ (abacavir, dolutegravir, and lamivudine) have been evaluated in pediatric subjects.

Dolutegravir: The pharmacokinetics of dolutegravir in HIV-1–infected children (n = 14) weighing at least 40 kg were similar to those observed in HIV-1–infected adults who received dolutegravir 50 mg once daily (Table 7) *[see Clinical Studies (14.2)]*.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

		Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
Weight (n)	**Dose of TIVICAY**	**C_{max} (mcg/mL)**	**$AUC_{(0\text{-}24)}$ (mcg.h/mL)**	**C_{24} (mcg/mL)**
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)

Abacavir and Lamivudine: The pharmacokinetic data for abacavir and lamivudine once daily following administration of EPZICOM in pediatric subjects weighing at least 40 kg are limited. The dosing recommendations in this population are based on the safety and efficacy established in a controlled trial conducted using either the combination of EPIVIR and ZIAGEN or EPZICOM. Refer to the prescribing information for EPIVIR and ZIAGEN for pharmacokinetic information on the individual products in pediatric patients *[see Dosage and Administration (2.2), Clinical Studies (14.2)]*.

Geriatric Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir. The pharmacokinetics of abacavir or lamivudine have not been studied in subjects older than 65 years.

Male and Female Patients: There are no significant or clinically relevant gender differences in the pharmacokinetics of the individual components (dolutegravir, abacavir, or lamivudine) based on the available information that was analyzed for each of the individual components.

Racial Groups: There are no significant or clinically relevant racial differences in pharmacokinetics of the individual components (dolutegravir, abacavir, or lamivudine) based on the available information that was analyzed for each of the individual components.

Drug Interaction Studies

The drug interaction trials described were conducted with dolutegravir, abacavir, and/or lamivudine as single entities; no drug interaction trials have been conducted using the combination of abacavir, dolutegravir, and lamivudine. No clinically significant drug interactions are expected between dolutegravir, abacavir, and lamivudine.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1786 of 1915

Dosing recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir or abacavir are provided in Section 7.3 *[see Drug Interactions (7)]*.

Table 8. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)

[a] The number of subjects represents the maximum number of subjects that were evaluated.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1787 of 1915

Table 9. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg /100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Boceprevir 800 mg every 8 h	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1788 of 1915

Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

[c] The number of subjects represents the maximum number of subjects that were evaluated.

Abacavir or Lamivudine: The drug interactions described are based on trials conducted with abacavir or lamivudine as single entities.

Ethanol: Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects.

Methadone: In a trial of 11 HIV-1-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of abacavir twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI: 6% to 42%) *[see Drug Interactions (7.3)]*. The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.7)]*.

Abacavir, Lamivudine, Zidovudine: Fifteen HIV-1–infected subjects were enrolled in a crossover-designed drug interaction trial evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Lamivudine and Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

The effects of other coadministered drugs on abacavir or lamivudine are provided in Table 10.

Table 10. Effect of Coadministered Drugs on Abacavir or Lamivudine

Coadministered Drug and Dose	Drug and Dose	n	Concentrations of Abacavir or Lamivudine		Concentration of Coadministered Drug
			AUC	Variability	
Ethanol 0.7 g/kg	Abacavir Single 600 mg	24	↑41%	90% CI: 35% to 48%	↔[a]
Nelfinavir 750 mg every 8 h x 7 to 10 days	Lamivudine Single 150 mg	11	↑10%	95% CI: 1% to 20%	↔
Trimethoprim 160 mg/ Sulfamethoxazole 800 mg daily x	Lamivudine Single 300 mg	14	↑43%	90% CI: 32% to 55%	↔

5 days					

↑ = Increase; ↔ = no significant change; AUC = area under the concentration versus time curve; CI = Confidence interval.

[a] The drug-drug interaction was only evaluated in males.

12.4 Microbiology

Mechanism of Action

Dolutegravir: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified recombinant HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine-5′-triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity in Cell Culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a median EC_{50} value of 0.54 nM (range: 0.41 to 0.60 nM) in a viral susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates with median EC_{50} values of 0.18 nM (n = 3, range: 0.09 to 0.5 nM), 0.08 nM (n = 5, range: 0.05 to 2.14 nM) 0.12 nM (n = 4, range: 0.05 to 0.51 nM), 0.17 nM (n = 3, range: 0.16 to 0.35 nM), 0.24 nM (n = 3, range: 0.09 to 0.32 nM), 0.17 nM (range: 0.07 to 0.44 nM), 0.2 nM (n = 3, range: 0.02 to 0.87 nM), and 0.42 nM (n = 3, range: 0.41 to 1.79 nM) for clades A, B, C, D, E, F, and G, and group O viruses, respectively. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Abacavir: The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC_{50} values ranged from 3.7 to 5.8 microM (1 microM = 0.28 mcg per mL) and 0.07 to 1.0 microM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and the mean EC_{50} value was 0.26 ± 0.18 microM against 8 clinical

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1791 of 1915

isolates. The median EC_{50} values of abacavir were 344 nM (range: 14.8 to 676 nM), 16.9 nM (range: 5.9 to 27.9 nM), 8.1 nM (range: 1.5 to 16.7 nM), 356 nM (range: 35.7 to 396 nM), 105 nM (range: 28.1 to 168 nM), 47.6 nM (range: 5.2 to 200 nM), 51.4 nM (range: 7.1 to 177 nM), and 282 nM (range: 22.4 to 598 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B), respectively. The EC_{50} values against HIV-2 isolates (n = 4), ranged from 0.024 to 0.49 microM.

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 microM (1 microM = 0.23 mcg per mL). The median EC_{50} values of lamivudine were 60 nM (range: 20 to 70 nM), 35 nM (range: 30 to 40 nM), 30 nM (range: 20 to 90 nM), 20 nM (range: 3 to 40 nM), 30 nM (range: 1 to 60 nM), 30 nM (range: 20 to 70 nM), 30 nM (range: 3 to 70 nM), and 30 nM (range: 20 to 90 nM) against HIV-1 clades A-G and group O viruses (n = 3 except n = 2 for clade B) respectively. The EC_{50} values against HIV-2 isolates (n = 4) from 0.003 to 0.120 microM in PBMCs. Ribavirin (50 microM) used in the treatment of chronic HCV infection decreased the anti-HIV-1 activity of lamivudine by 3.5-fold in MT-4 cells.

Antiviral Activity in Combination with Other Antiviral Agents

Neither dolutegravir, abacavir, nor lamivudine were antagonistic to all tested anti-HIV agents. See full prescribing information for ZIAGEN (abacavir), TIVICAY (dolutegravir), and EPIVIR (lamivudine).

Resistance in Cell Culture

Dolutegravir: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Abacavir and Lamivudine: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions K65R, L74V, Y115F, and M184V/I in HIV-1 RT. M184V or I substitutions resulted in high-level resistance to lamivudine and approximately 2-fold decrease in susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184V or I conferred a 7- to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility.

Resistance in Clinical Subjects

Dolutegravir: No subjects in the treatment arm receiving dolutegravir + EPZICOM of SINGLE (treatment-naïve trial) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 11 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had

treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to abacavir and lamivudine, components of TRIUMEQ, was observed in the arm receiving dolutegravir + EPZICOM in the SINGLE trial through Week 144.

Cross-Resistance

Dolutegravir: The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Abacavir and Lamivudine: Cross-resistance has been observed among NRTIs. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with a K65R substitution with or without an M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutation (TAM) substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Dolutegravir: Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 26-fold higher than those in humans at the recommended dose of 50 mg once daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 17-fold and 30-fold higher in males and females, respectively, than those in humans at the recommended dose of 50 mg once daily.

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition,

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1793 of 1915

non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 7 to 28 times the human exposure at the recommended dose of 600 mg.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 12 times (mice) and 57 times (rats) the human exposures at the recommended dose of 300 mg.

Mutagenicity

Dolutegravir: Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay. Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility

Dolutegravir, abacavir, or lamivudine did not affect male or female fertility in rats at doses associated with exposures approximately 44, 9, or 112 times (respectively) higher than the exposures in humans at the doses of 50 mg, 600 mg, and 300 mg (respectively).

13.2 Animal Toxicology and/or Pharmacology

Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 21 times the expected systemic exposure in humans at a dose of 600 mg. The clinical relevance of this finding has not been determined.

14 CLINICAL STUDIES

14.1 Adult Subjects

The efficacy of TRIUMEQ is supported by data from a randomized, controlled trial (double-blind through 96 weeks and open-label phase from 96 to 144 weeks) in antiretroviral treatment-naïve subjects, SINGLE (ING114467, NCT01263015) and other trials in treatment-naïve subjects. See full prescribing information for TIVICAY. The efficacy of dolutegravir, in

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1794 of 1915

combination with at least two active background regimens in treatment-experienced, INSTI-naïve subjects is supported by data from SAILING (ING111762, NCT01231516) (refer to the prescribing information for TIVICAY).

Treatment-Naïve Subjects

In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily with fixed-dose abacavir and lamivudine (EPZICOM) or fixed-dose efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment groups.

Week 144 (open-label-phase analysis which followed the Week 96 double-blind phase) outcomes for SINGLE are provided in Table 11.

Table 11. Virologic Outcomes of Randomized Treatment in SINGLE at 144 Weeks (Snapshot Algorithm)

	TIVICAY + EPZICOM Once Daily (n = 414)	ATRIPLA Once Daily (n = 419)
HIV-1 RNA <50 copies/mL	71%	63%
Treatment difference[a]	8.3% (95% CI: 2.0%, 14.6%)[d]	
Virologic nonresponse	10%	7%
Data in window not <50 copies/mL	4%	<1%
Discontinued for lack of efficacy	3%	3%
Discontinued for other reasons while not suppressed	3%	4%
No virologic data	18%	30%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	4%	14%
Discontinued study/study drug for other reasons[c]	12%	13%
Missing data during window but on study	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	73%	64%
>100,000	69%	61%
Gender		
Male	72%	66%
Female	69%	48%
Race		

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1795 of 1915

White	72%	71%
African-American/African Heritage/Other	71%	47%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.

[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race. The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm^3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm^3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm^3 (15.6 cells per mm^3, 78.2 cells per mm^3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).

Treatment-Experienced

In SAILING, there were 715 subjects included in the efficacy and safety analyses (see full prescribing information for TIVICAY). At Week 48, 71% of subjects randomized to TIVICAY plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV-1 RNA less than 50 copies per mL (treatment difference and 95% CI: 7.4% [0.7%, 14.2%]).

14.2 Pediatric Subjects

The efficacy of the individual components of TRIUMEQ for the treatment of HIV-1 infection was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847) or the ARROW trial (NCT02028676), as summarized below.

- Abacavir and lamivudine once daily, in combination with a third antiretroviral drug, were evaluated in a randomized, multicenter trial (ARROW) in HIV-1–infected, treatment-naïve subjects. Subjects randomized to once-daily dosing (n = 336) and who weighed at least 25 kg received abacavir 600 mg and lamivudine 300 mg, as either the single entities or as EPZICOM. At Week 96, 67% of subjects receiving abacavir and lamivudine once-daily in combination with a third antiretroviral drug, had HIV-1 RNA less than 80 copies per mL.
- Dolutegravir, in combination with other antiretroviral drugs was evaluated in treatment-experienced, INSTI-naïve, HIV-1–infected subjects aged 6 to less than 18 years in a 48-week open-label, multicenter, dose-finding clinical trial, IMPAACT P1093. Subjects aged 12 to less than 18 years were enrolled in Cohort 1 and subjects aged 6 to less than 12 years were

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1796 of 1915

enrolled in Cohort IIA. At 48 weeks, 61% (14/23) of subjects aged 12 to less than 18 years treated with TIVICAY once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies per mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% (16/24) of subjects weighing at least 40 kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRIUMEQ tablets, 600 mg of abacavir as abacavir sulfate, 50 mg of dolutegravir as dolutegravir sodium, and 300 mg lamivudine, are purple, oval, film-coated, biconvex tablets debossed with "572 Tri" on one side.

Bottle of 30 with child-resistant closure NDC 49702-231-13.

Store and dispense in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug Interactions

TRIUMEQ may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Drug Interactions (7)]*.

Hypersensitivity Reaction

Inform patients:

- that a Medication Guide and Warning Card summarizing the symptoms of the abacavir hypersensitivity reaction and other product information will be dispensed by the pharmacist with each new prescription and refill of TRIUMEQ, and instruct the patient to read the Medication Guide and Warning Card every time to obtain any new information that may be present about TRIUMEQ. The complete text of the Medication Guide is reprinted at the end of this document.
- to carry the Warning Card with them.
- how to identify a hypersensitivity reaction *[see Warnings and Precautions (5.1), Medication Guide]*.
- that if they develop symptoms consistent with a hypersensitivity reaction they should call their healthcare provider right away to determine if they should stop taking TRIUMEQ.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1797 of 1915

- that a hypersensitivity reaction can worsen and lead to hospitalization or death if TRIUMEQ is not immediately discontinued.
- to not restart TRIUMEQ or any other abacavir-containing product following a hypersensitivity reaction because more severe symptoms can occur within hours and may include life-threatening hypotension and death.
- that if they have a hypersensitivity reaction, they should dispose of any unused TRIUMEQ to avoid restarting abacavir.
- that a hypersensitivity reaction is usually reversible if it is detected promptly and TRIUMEQ is stopped right away.
- that if they have interrupted TRIUMEQ for reasons other than symptoms of hypersensitivity (for example, those who have an interruption in drug supply), a serious or fatal hypersensitivity reaction may occur with reintroduction of abacavir.
- to not restart TRIUMEQ or any other abacavir-containing product without medical consultation and only if medical care can be readily accessed by the patient or others.
- to not restart TRIUMEQ or any other dolutegravir-containing product following a hypersensitivity reaction to TRIUMEQ.

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including TRIUMEQ, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir, a component of TRIUMEQ *[see Warnings and Precautions (5.3), Adverse Reactions (6.1)]*. Inform patients that monitoring for hepatotoxicity during therapy with TRIUMEQ is recommended.

Posttreatment Exacerbations of Hepatitis in Patients with Hepatitis B Co-infection

Advise patients co-infected with HIV-1 and HBV that worsening of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.4)]*.

Use with Interferon- and Ribavirin-Based Regimens in Patients with Hepatitis C Co-infection

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs and symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when TRIUMEQ is started *[see Warnings and Precautions (5.8)]*.

Redistribution/Accumulation of Body Fat

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.9)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRIUMEQ during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dose

Instruct patients that if they miss a dose of TRIUMEQ, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Availability of Medication Guide

Instruct patients to read the Medication Guide before starting TRIUMEQ and to re-read it each time the prescription is renewed. Instruct patients to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Storage

Instruct patients to store TRIUMEQ in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

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EPIVIR-HBV is a trademark owned by or licensed to the GSK group of companies.

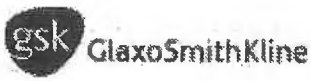
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Manufactured for:



ViiV Healthcare
Research Triangle Park, NC 27709

by:



GlaxoSmithKline
Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from

Shire Pharmaceuticals Group plc
Basingstoke, UK

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TRM:xPI

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1800 of 1915

MEDICATION GUIDE

TRIUMEQ (TRI-u-meck)

(abacavir, dolutegravir, and lamivudine)

tablets

What is the most important information I should know about TRIUMEQ?

TRIUMEQ can cause serious side effects, including:

- **Serious allergic reactions (hypersensitivity reaction)** that can cause death have happened with TRIUMEQ and other abacavir-containing products. Your risk of this allergic reaction to abacavir is much higher if you have a gene variation called HLA-B*5701. Your healthcare provider can determine with a blood test if you have this gene variation.

  If you get a symptom from 2 or more of the following groups while taking TRIUMEQ, call your healthcare provider right away to find out if you should stop taking TRIUMEQ.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, sore throat

A list of these symptoms is on the Warning Card your pharmacist gives you. **Carry this Warning Card with you at all times.**

If you stop TRIUMEQ because of an allergic reaction, never take TRIUMEQ (abacavir, dolutegravir and lamivudine) or any other medicine that contains abacavir or dolutegravir (EPZICOM, TIVICAY, TRIZIVIR, or ZIAGEN) again.

- If you have an allergic reaction, dispose of any unused TRIUMEQ. Ask your pharmacist how to properly dispose of medicines.
- If you take TRIUMEQ or any other abacavir-containing medicine again after you have had an allergic reaction, **within hours** you may get **life-threatening symptoms** that may include **very low blood pressure** or **death.**
- If you stop TRIUMEQ for any other reason, even for a few days, and you are not allergic to TRIUMEQ, talk with your healthcare provider before taking it again. Taking TRIUMEQ again can cause a serious allergic or life-threatening reaction, even if you never had an allergic reaction to it before.

If your healthcare provider tells you that you can take TRIUMEQ again, start taking it when you are around medical help or people who can call a healthcare provider if you need one.

- **Build-up of acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1801 of 1915

take TRIUMEQ. Lactic acidosis is a serious medical emergency that can cause death. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**

- feel very weak or tired
- unusual (not normal) muscle pain
- trouble breathing
- stomach pain with nausea and vomiting
- feel cold, especially in your arms and legs
- feel dizzy or lightheaded
- have a fast or irregular heartbeat

- **Serious liver problems** can happen in people who take TRIUMEQ. In some cases, these serious liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis). **Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light colored stools (bowel movements)
  - loss of appetite
  - nausea or vomiting
  - pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or serious liver problems if you are female, very overweight (obese), or have been taking nucleoside analogue medicines for a long time.

- **Other Serious Liver problems:** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver function tests during treatment with TRIUMEQ. Liver problems including liver failure have also happened with TRIUMEQ in people without a history of liver disease or other risk factors. Liver failure resulting in liver transplant has been reported with TRIUMEQ. Your healthcare provider may do blood tests to check your liver function. **Call your healthcare provider right away if you develop any of the signs or symptoms of liver problems listed above.**
- **Worsening of hepatitis B virus in people who have HIV-1 infection.** If you have Human Immunodeficiency Virus type 1 (HIV-1) and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking TRIUMEQ. A "flare-up" is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease can be serious and may lead to death.
  - Do not run out of TRIUMEQ. Refill your prescription or talk to your healthcare provider before your TRIUMEQ is all gone.
  - Do not stop TRIUMEQ without first talking to your healthcare provider.
  - If you stop taking TRIUMEQ, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.
- **Resistant Hepatitis B Virus (HBV).** If you have HIV-1 and hepatitis B, the hepatitis B virus can change (mutate) during your treatment with TRIUMEQ and become harder to treat (resistant).
- **Use with interferon and ribavirin-based regimens.** Worsening of liver disease that has caused death has happened in people infected with both HIV-1 and hepatitis C virus who were taking

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1802 of 1915

antiretroviral medicines and were also being treated for hepatitis C with interferon with or without ribavirin. If you are taking TRIUMEQ and interferon with or without ribavirin, tell your healthcare provider if you have any new symptoms.

What is TRIUMEQ?

TRIUMEQ is a prescription HIV-1 (Human Immunodeficiency Virus type 1) medicine used to treat HIV-1 infection in adults and children who weight at least 88 pounds (40 kg).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

TRIUMEQ contains 3 prescription medicines, abacavir (ZIAGEN), dolutegravir (TIVICAY) and lamivudine (EPIVIR).

- TRIUMEQ is not for use by itself in people who have or have had resistance to abacavir, dolutegravir, or lamivudine.

It is not known if TRIUMEQ is safe and effective in children who weigh less than 88 pounds (40 kg).

Do not take TRIUMEQ if you:

- if you have a certain type of gene variation called the HLA-B*5701 allele. Your healthcare provider will test you for this before prescribing treatment with TRIUMEQ.
- are allergic to abacavir, dolutegravir, lamivudine, or any of the ingredients in TRIUMEQ. See the end of this Medication Guide for a complete list of ingredients in TRIUMEQ.
- take dofetilide (TIKOSYN). Taking TRIUMEQ and dofelitide (TIKOSYN) can cause serious side effects that may be serious or life-threatening.
- have certain liver problems.

Before you take TRIUMEQ, tell your healthcare provider about all of your medical conditions, including if you:

- have been tested and know whether or not you have a particular gene variation called HLA-B*5701.
- have or have had liver problems, including hepatitis B or C virus infection.
- have kidney problems.
- have heart problems, smoke, or have diseases that increase your risk of heart disease such as high blood pressure, high cholesterol, or diabetes.
- drink alcohol or take medicines that contain alcohol.
- are pregnant or plan to become pregnant. It is not known if TRIUMEQ will harm your unborn baby.

  Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medications, including TRIUMEQ during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take TRIUMEQ.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - Two of the medicines in TRIUMEQ (abacavir and lamivudine) pass into your breastmilk.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1803 of 1915

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines interact with TRIUMEQ. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TRIUMEQ.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take TRIUMEQ with other medicines.

How should I take TRIUMEQ?

- **Take TRIUMEQ exactly as your healthcare provider tells you to take it.**
- Do not change your dose or stop taking TRIUMEQ without talking with your healthcare provider.
- TRIUMEQ may be taken with or without food.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TRIUMEQ should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with TRIUMEQ:
  - If you take TRIUMEQ with food, you may take these supplements at the same time that you take TRIUMEQ.
  - If you do not take TRIUMEQ with food, take TRIUMEQ at least 2 hours before or 6 hours after you take these supplements.
- If you miss a dose of TRIUMEQ, take it as soon as you remember. Do not take 2 doses at the same time or take more than your healthcare provider tells you to take.
- Stay under the care of a healthcare provider during treatment with TRIUMEQ.
- Do not run out of TRIUMEQ. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TRIUMEQ, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TRIUMEQ?

TRIUMEQ can cause serious side effects including:

- **See "What is the most important information I should know about TRIUMEQ?"**
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking TRIUMEQ.
- **Changes in body fat** can happen in people who take HIV-1 medicines. These changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may happen. The exact cause and long-

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1804 of 1915

term health effects of these conditions are not known.

- **Heart attack (myocardial infarction).** Some HIV-1 medicines including TRIUMEQ may increase your risk of heart attack.
- **The most common side effects of TRIUMEQ include:**
  - trouble sleeping
  - tiredness
  - headache

These are not all the possible side effects of TRIUMEQ. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRIUMEQ?

- Store TRIUMEQ at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TRIUMEQ in the original bottle.
- Keep the bottle of TRIUMEQ tightly closed and protect it from moisture.
- The bottle of TRIUMEQ contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep TRIUMEQ and all medicines out of the reach of children.

General information about the safe and effective use of TRIUMEQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRIUMEQ for a condition for which it was not prescribed. Do not give TRIUMEQ to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TRIUMEQ that is written for health professionals.

What are the ingredients in TRIUMEQ?

Active ingredients: abacavir, dolutegravir, and lamivudine

Inactive ingredients: D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Tablet film-coating contains: iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide.

Manufactured for:

ViiV Healthcare

Research Triangle Park, NC 27709

by:

GlaxoSmithKline

Research Triangle Park, NC 27709

Lamivudine is manufactured under agreement from Shire Pharmaceuticals Group plc, Basingstoke, UK

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1805 of 1915

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For more information go to www.TRIUMEQ.com or call 1-877-844-8872.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 11/2017

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1806 of 1915

(Front of card)

WARNING CARD

TRIUMEQ® (abacavir, dolutegravir, and lamivudine) tablets

Patients taking TRIUMEQ may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking TRIUMEQ, call your healthcare provider right away to find out if you should stop taking this medicine.

	Symptom(s)
Group 1	Fever
Group 2	Rash
Group 3	Nausea, vomiting, diarrhea, or abdominal (stomach area) pain
Group 4	Generally ill feeling, extreme tiredness, or achiness
Group 5	Shortness of breath, cough, or sore throat

Always carry this Warning Card with you to help recognize symptoms of this allergic reaction.

(Back of Card)

WARNING CARD

TRIUMEQ® (abacavir, dolutegravir, and lamivudine) tablets

If you must stop treatment with TRIUMEQ because you have had an allergic reaction to abacavir, **NEVER** take TRIUMEQ or any other abacavir-containing medicine (ZIAGEN®, EPZICOM®, or TRIZIVIR®) again. If you have an allergic reaction, dispose of any unused TRIUMEQ. Ask your pharmacist how to properly dispose of medicines. If you take TRIUMEQ or another abacavir-containing medicine again after you have had an allergic reaction, **WITHIN HOURS** you may get **life-threatening symptoms** that may include **very low blood pressure** or **death**.

Please read the Medication Guide for additional information on TRIUMEQ.

03/2017 TRM:XWC

Reference ID: 4184712

Electronic Patent Application Fee Transmittal					
Application Number:	15346335				
Filing Date:	08-Nov-2016				
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus				
First Named Inventor/Applicant Name:	Benjamin Micah Collman				
Filer:	Donna Johnson Gressler/Trent Bastian				
Attorney Docket Number:	1147.P2C				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	1900	1900
		Total in USD ($)		**1900**

Electronic Acknowledgement Receipt	
EFS ID:	36741799
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
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.P2C
Receipt Date:	31-JUL-2019
Filing Date:	08-NOV-2016
Time Stamp:	17:18:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1900
RAM confirmation Number	E20197UH18384339
Deposit Account	071250
Authorized User	Trent Bastian
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 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)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	1147P2C_2019-07-31_RCE.PDF	84254 3f7fd434e2d8717f7fbde57823ec1f25c0489130	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Transmittal Letter	1147P2C_2019-07-31_Supplemental_IDS.PDF	136509 f1abadfc4ad2bdd5ffb2394c8a249c90d76807c5	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	1147P2C_2019-07-31_Supplemental_SB08.PDF	109314 a264a52bba2a399a9fe17c913f5f3cfdd33e2067c	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Foreign Reference	WO2008043829.PDF	166030 1a5688d7994e707c4314f15fe226feeb3a318b47a	no	5
Warnings:					
Information:					
5	Non Patent Literature	IN_ExamReport_201817013772.pdf	124102 814e4e1a8f1034e822f78605ed4f3d4a6c592e76	no	6
Warnings:					
Information:					
6	Non Patent Literature	BO_Office_Action_SP260_2016.PDF	905298 48aa0a7ea4c712ddc4706378a7a0ab56cdd4c081e	no	10

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Information:					
7	Non Patent Literature	SV_Office_Action_2018005682.PDF	1247658 c486a13a13c4b963e5ff9d95dc46e35af27e9e8	no	18
Warnings:					
Information:					
8	Non Patent Literature	EA_OfficeAction_201890654.pdf	670881 9858e459e45d8c9c0ea3cda17a64df2a1e8016a0c	no	12
Warnings:					
Information:					
9	Non Patent Literature	CO_Opposition_CO15-265717.PDF	1359863 f4eae8369638f300f00c7c9eab467eeb68a8564af	no	45
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The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
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Warnings:					
Information:					
11	Non Patent Literature	TRIUMEQ_Prescribing_Information.PDF	754639 ee3851f752d72e41c64a2fac3e8c1f57d9ad6b44	no	48
Warnings:					
Information:					
12	Fee Worksheet (SB06)	fee-info.pdf	30882 51be1eab6102fab6c982ebcacd6431d5cd9e1178	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6222908		

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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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

25000 7590 08/15/2019
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER
WORSHAM, JESSICA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/15/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	11/15/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25000 7590 08/15/2019
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

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APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	11/15/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
WORSHAM, JESSICA N	1615	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively.
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1815 of 1915

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 08/15/2019

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

EXAMINER
WORSHAM, JESSICA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/15/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 30 minutes to complete, including gathering, preparing, and submitting the completed application 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
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.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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 inspection 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.

Notice of Allowability	Application No. 15/346,335	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--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE filed 31 July 2019.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 7/31/19.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1818 of 1915

Continuation of 3. The allowed claim(s) is/are: 1-5,26-27,52-53 and 55

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

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 31 July 2019 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. See attached copy of PTO-1449.

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 31 July 2019 has been entered.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: The closest prior art of Carra et al. (WO2015/196116 and U.S. Patent Application Publication No. 2016/0016973) were published after the effective filing date of the instant application and have a common assignee. The next closest prior art of WO2014/100323 comprises administering the compound of Formula

1 at a different time than additional drugs such as tenofovir or emtricitabine. The prior art does not teach all three drugs within the same tablet. Applicants have shown a 30% higher exposure of bictegravir in a fixed dose combination of bictegravir, emtricitabine, and tenofovir alafenamide relative to its exposure when co-administered as a single agent of bictegravir with a fixed dose combination of emtricitabine and tenofovir alafenamide.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

4. 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 on 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 an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC											
Symbol									Type	Version
A61K	/	9	/	209					F	2013-01-01
A61K	/	9	/	2054					I	2013-01-01
A61K	/	31	/	513					I	2013-01-01
A61K	/	31	/	553					I	2013-01-01
A61K	/	31	/	675					I	2013-01-01
A61K	/	9	/	0053					I	2013-01-01
A61K	/	9	/	2013					I	2013-01-01
A61K	/	9	/	2095					I	2013-01-01
A61K	/	9	/	28					I	2013-01-01
A61K	/	31	/	5365					I	2013-01-01
A61K	/	9	/	2086					I	2013-01-01
A61P	/	31	/	18					I	2018-01-01

CPC Combination Sets											
Symbol									Type	Set	Ranking	Version
A61K	/	31	/	513					I	1	1	2013-01-01
A61K	/	2300	/	00					A	1	2	2013-01-01
A61K	/	31	/	553					I	2	1	2013-01-01
A61K	/	2300	/	00					A	2	2	2013-01-01
A61K	/	31	/	675					I	3	1	2013-01-01
A61K	/	2300	/	00					A	3	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	08 August 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20190808

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	5365
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	08 August 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20190808

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1824 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		10		19		28		37		46	10	55		
2	2		11		20		29		38		47				
3	3		12		21		30		39		48				
4	4		13		22		31		40		49				
5	5		14		23		32		41		50				
	6		15		24		33		42		51				
	7		16		25		34		43	8	52				
	8		17	6	26		35		44	9	53				
	9		18	7	27		36		45		54				

NONE		Total Claims Allowed:
(Assistant Examiner)	(Date)	10
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	08 August 2019	O.G. Print Claim(s) / O.G. Print Figure
(Primary Examiner)	(Date)	1 / None

U.S. Patent and Trademark Office

Part of Paper No.: 20190808

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner
No classified search performed.		

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
No classified search performed.		

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No classified search performed.		

* 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: EAST, PALM	05/03/2018	JW
EAST: See attached	05/03/2018	JW
SciFinder: See attached	05/03/2018	JW

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(tenofovir adj alafenamide and emtricitabine and bictegravir).clm.	04/23/2019	JW

/JESSICA N WORSHAM/ Primary Examiner, Art Unit 1615	

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1826 of 1915

PTO/SB/08a (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	WO-2008/043829-A2	04-17-2008	Boehringer Ingelheim Int		

Examiner Signature	/JESSICA WORSHAM/	Date Considered	08/08/2019

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Dated: July 31, 2019 Signature: /Donna Johnson Gressler/ (Donna Johnson Gressler)

1073907.2

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	2	of	2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Exam Report dated 2019-07-26 for Indian Appl. No. 201817013772	
	CB	Office Action dated 2019-03-25 for Bolivian Appl. No. SP260-2016	x
	CC	Office Action received 2019-05-27 for Salvadoran Appl. No. 2018005682	x
	CD	Office Action received 2019-07-01 for Eurasian Appl. No. 201890654	x
	CE	Opposition dated 2017-06-20 for Colombian Appl. No. 15-265.717	x
	CF	TIVICAY Product Label (Revised September 2018) GlaxoSmithKline, 44 Pages.	
	CG	TRIUMEQ Product Label (Revised November 2017) GlaxoSmithKline, 48 Pages.	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	08/08/2019

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
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15346335	NOA	08/15/2019	1147.P2C
	1449	08/15/2019	1147.P2C

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Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. [ ] Other _____
   - b. [X] Enclosed
     - i. [ ] Amendment/Reply
     - ii. [ ] Affidavit(s)/ Declaration(s)
     - iii. [X] Information Disclosure Statement (IDS)
     - iv. [X] Other SB08
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. [ ] Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 07-1250
     - i. [X] RCE fee required under 37 CFR 1.17(e)
     - ii. [ ] Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
   - c. [ ] Payment by credit card (Form PTO-2038 enclosed)
   - d. [X] Payment by EFS-Web

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Donna Johnson Gressler/	Date	October 21, 2019
Name (Print/Type)	Donna Johnson Gressler	Registration No.	45,544

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office (USPTO), deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the USPTO on the date shown below.

Signature	/Trent Bastian/		
Name (Print/Type)	Trent Bastian	Date	October 21, 2019

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Dated: October 21, 2019
Electronic Signature for Trent Bastian: /Trent Bastian/

Docket No.: 1147.P2C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/346,335 | Confirmation No.: 1307

Filed: November 8, 2016 | Art Unit: 1615

For: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus | Examiner: J. N. Worsham

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

A translation of the non-English language reference is attached.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

The Director is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 07-1250, under Order No. 1147.P2C.

Dated: October 21, 2019

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

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1832 of 1915

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Sheet 1 of 2

Complete if Known	
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First Named Inventor	Benjamin Micah Collman
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Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-7,390,791	06-24-2008	Becker et al.	
	AB	US-7,803,788	09-28-2010	Becker et al.	
	AC	US-8,754,065	06-17-2014	Liu et al.	
	AD	US-9,296,769	03-29-2016	Liu et al.	
	AE	US-10,098,886	10-16-2018	Carra et al.	
	AF	US-10,385,067	08-20-2019	Carra et al.	
	AG	US-2002-0119443-A1	08-29-2002	Becker et al.	
	AH	US-2003-0219727-A1	11-27-2003	Becker et al.	
	AI	US-2005-0124583-A1	06-09-2005	Becker et al.	
	AJ	US-2005-0124584-A1	06-09-2005	Becker et al.	
	AK	US-2005-0124585-A1	06-09-2005	Becker et al.	
	AL	US-2006-0024659-A1	02-02-2006	Becker et al.	
	AM	US-2018-0215769-A1	08-02-2018	Jin et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

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Dated: _October 21, 2019_____ Signature: _/Donna Johnson Gressler/_____ (Donna Johnson Gressler)

PTO/SB/08b (07-09)
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(Use as many sheets as necessary)

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Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Notice of Preliminary Rejection dated 2019-09-04 for Korean Appl. No. 10-2018-7015929.	√
	CB	SAX, P. et al. (2014) "Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study" *J Acquir Immune Defic Syndr* 67(1):52-58.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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Korean Patent Application No. 10-2018-7015929
Your Ref.: 1147.KR
Enclosure Page 1

KIPO'S NOTICE OF PRELIMINARY REJECTION
(ENGLISH TRANSLATION)

RESULTS OF KIPO EXAMINATION -- SUMMARY

- Examined Claims: Claims 1-11
- Rejected Portions and Relevant Provisions

No.	Rejected Portions	Relevant Provisions - Grounds
1	All claims	Article 29(2) – Inventiveness
2	Claims 4, 8, and 9	Article 42(4)(ii) – Clarity

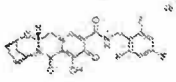
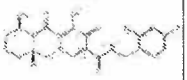
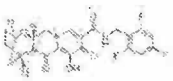
EXAMINER'S DETAILED GROUNDS FOR REJECTION

1. The present application cannot be allowed under Article 29(2) of the Korean Patent Act because all the claims lack inventiveness, as set forth below.

Cited Reference 1: WO 2015/022351 (February 19, 2015)
Cited Reference 2: WO 2014/100323 (June 26, 2014)
Cited Reference 3: *J. Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp52-58 (September 1, 2014)

1-1. **Claim 1** is directed to 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.

Claim 1 is compared with Cited References 1-3 in the table below.

Type	Claim 1	Cited Reference 1	Cited Reference 2	Cited Reference 3
Active ingredient	50 mg 	50 mg  (dolutegravir)	 Compound 42	150 mg elvitegravir
	25 mg tenofovir alafenamide salt	300 mg tenofovir disoproxil fumarate	(-)	10 mg tenofovir alafenamide fumarate

	200 mg emtricitabine	200 mg emtricitabine	(-)	200 mg emtricitabine
dosage form	tablet	tablet	(-)	tablet

First, upon comparison between Claim 1 and Cited Reference 1, the two inventions are identical in that they both provide a tablet containing an HIV inhibitor having an integrase inhibitory activity, a tenofovir precursor, and emtricitabine, and they are also identical in terms of the amounts of the HIV inhibitor and the emtricitabine. Claim 1 only differs from Cited Reference 1 in limiting the integrase inhibitor to a compound of Formula I and using tenofovir alafenamide as a tenofovir precursor.

However, Cited Reference 2 discloses a compound of Formula I as an integrase inhibitor (*see* Compound 42) and teaches that the inhibitor has properties suitable for drug development, such as excellent HIV inhibitory activity, low cytotoxicity, good bioavailability, and the like (*see* Tables 1-4, etc.). Accordingly, a person of ordinary skill in the art would have no difficulty in selecting a compound of Formula I and substituting dolutegravir of Cited Reference 1 with the selected compound. Cited Reference 3 also discloses a tablet containing elvitegravir as an integrase inhibitor, a tenofovir precursor, and emtricitabine. Cited Reference 3 discloses that the tablet comprises 10 mg tenofovir alafenamide fumarate (TAF) which is more safe and effective than tenofovir disoproxil fumarate and, in the presence of cobicistat which boosts absorption, 10 mg TAF is equivalent to 25mg TAF (*see* page 53, left column, paragraphs 2-4). Accordingly, a person of ordinary skill in the art could easily substitute the tenofovir disoproxil fumarate of Cited Reference 1 with 25 mg TAF.

With regard to the effect of Claim 1, the specification only shows the formulation of a single tablet containing three types of active ingredients, and there is no ground supporting that the tablet exhibits an excellent anti-HIV effect and the like that a person of ordinary skill in the art could not predict from Cited References 1 to 3.

Thus, Claim 1 could have readily been conceived from Cited References 1 to 3 by a person of ordinary skill in the art.

1-2. Claims 2-11 directly or indirectly refer to Claim 1.
The technical feature of **Claim 2** is not different from that of Claim 1.
The amounts limited in **Claim 3** can be naturally derived by selecting the active ingredients in salt form.
The total weight and shape of the tablet limited in **Claims 4-7** merely correspond to the property and shape of a conventional tablet.
The amount of the compound of Formula I limited in **Claims 8 and 9** could be easily selected by a person of ordinary skill in the art during a formulation process through repetitive experiments depending on the therapeutic dose and physical properties of the compound.

Claim 10 is directed to a film coated bilayer tablet and limits the types and amounts of excipients. However, selecting the shape of a preparation and the types and amounts of excipients suitable therefor is conventionally carried out in the course of formulating pharmaceutical ingredients, and the shape and the types and amounts of excipients selected above are widely used for tablets.
The use in the therapeutic treatment of an HIV infection limited in **Claim 11** also merely corresponds to the use disclosed in Cited Reference 1.

That is, all the features further comprised or limited in Claims 2-11 could have been easily derived from Cited References 1 to 3 by a person of ordinary skill in the art. Further, there is no ground supporting that Claims 2-11 exhibit an unexpectedly and remarkably excellent effect. Thus, Claims 2-11 could have been easily derived from Cited References 1 to 3 by a person of ordinary skill in the art.

2. The present application cannot be allowed because Claims 4, 8, and 9 fail to meet the requirements under Article 42(4)(ii) of the Korean Patent Act, as set forth below.

Claims 4, 8, and 9 describe the numerical ranges using the expression 'about~' and thus are not recognized as clearly describing the subject matter to be protected by the invention.

[Documents Annexed]

1. WO 2015/022351(February 19, 2015)
2. WO 2014/100323(June 26, 2014)
3. *J. Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp52-58 (September 1, 2014)

/ === End of Translation === /

발송번호: 9-5-2019-063389847
발송일자: 2019.09.02.
제출기일: 2019.11.02.

수신 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
양영준

03170

YOUR INVENTION PARTNER

특 허 청

의견제출통지서

출원인	성명	길리애드 사이언시즈, 인코포레이티드 (특허고객번호: 519990290219)
	주소	미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브 333
대리인	성명	양영준 외 1 명
	주소	서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
발명자	성명	홍, 레이
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발명자	성명	콜맨, 벤자민, 미카
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
발명자	성명	코지아라, 조안나 엠.
	주소	미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 길리애드 사이언시즈, 인코포레이티드 내
출원번호		10-2018-7015929
출원일자		2018.06.05.
발명의 명칭		인간 면역결핍 바이러스의 치료를 위한 치료 조성물

1. 이 출원에 대한 심사결과 다음과 같은 거절이유가 있어 특허법 제63조에 따라 이를 통지하오니 의견이 있거나 보정이 필요할 경우에는 상기 제출기일(2019.11.02.)까지 의견(답변, 소명)서[특허법시행규칙 별지 제24호서식] 또는/및 보정서[특허법시행규칙 별지 제9호서식]를 제출하여 주시기 바랍니다.

2. 상기 제출기일(2019.11.02.)을 연장하려는 경우에는 지정기간연장신청을 통해 그 제출기일을 4개월까지 연장할 수 있습니다. 이 경우 연장신청은 1개월 단위로 해야 하며, 필요 시 4개월을 초과하지 않는 범위에서 2개월 이상을 일괄하여 연장신청할 수 있습니다. 불가피한 사유의 발생(하단의 안내참조)으로 4개월을 초과하여 지정기간을 연장받고자 하는 때에는 그 사유를 기재한 소명서를 추가로 첨부해서 연장신청을 해야 합니다.

[심사결과]

☐ 심사 대상 청구항 : 제1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11항

☐ 이 출원의 거절이유가 있는 부분과 관련 법조항

순번	거절이유가 있는 부분	관련 법조항

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1838 of 1915

1	청구항 전항	특허법 제29조제2항
2	청구항 제4항, 제8항, 제9항	특허법 제42조제4항제2호

[구체적인 거절이유]

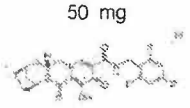
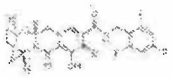
1. 이 출원의 청구범위의 청구항 전항에 기재된 발명은 아래와 같이 그 출원 전에 이 발명이 속하는 기술분야에서 통상의 지식을 가진 사람이 쉽게 발명할 수 있는 것이므로 특허법 제29조제2항에 따라 특허를 받을 수 없습니다.

- 아 래 -

인용발명 1 : 국제공개공보 WO2015/022351 (2015. 2. 19.)
인용발명 2 : 국제공개공보 WO2014/100323 (2014. 6. 26.)
인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014. 9. 1.)

1-1. 제1항은 (a) 50 mg의 화학식 I 화합물 또는 그의 제약상 허용되는 염, (b) 25 mg의 테노포비르 알라페나미드 또는 그의 제약상 허용되는 염, 및 (c) 200 mg의 엠트리시타빈 또는 그의 제약상 허용되는 염을 포함하는 정제입니다.

제1항을 인용발명 1 내지 3과 대비하면 다음과 같습니다.

구분	제1항	인용발명 1	인용발명 2	인용발명 3
활성 성분	50 mg 	50 mg  (돌루테그라비르)	 화합물 42	150 mg 엘비테그라비르
	25 mg 테노포비르 알라페나미드의 염	300 mg 테노포비르 디소프록실 푸마레이트	(-)	10 mg 테노포비르 알라페나미드 푸마레이트
	200 mg 엠트리시타빈	200 mg 엠트리시타빈	(-)	200 mg 엠트리시타빈
제형	정제	정제	(-)	정제

먼저, 제1항을 인용발명 1과 대비하면, 인테그라아제 억제 활성을 가지는 HIV 억제용 물질, 테노포비르의 전구체 및 엠트리시타빈을 함유하는 정제인 점이 공통되고, HIV 억제제와 엠트리시타빈의 함량도 동일합니다.

다만, 제1항은 인테그라아제 억제 활성 물질이 화학식 I의 화합물인 점 및 테노포비르 전구체로 테노포비르 알라페나미드를 사용하는 점에서 인용발명 1과 차이가 있습니다.

그런데, 인용발명 2에 화학식 I의 화합물이 인테그리아제 억제 물질로 개시되어(화합물 42 참조) 있어 살펴보면, 위 물질이 우수한 HIV 억제 활성, 낮은 세포독성, 양호한 생체 이용률 등 의약품 개발에 적절한 성질을 가지는 물질이라는 것을 알 수 있으므로(표 1 내지 4 등 참조), 이 기술분야에서 통상의 지식을 가진 자(이하 '통상의 기술자' 라 함)가 화학식

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1839 of 1915

I 화합물을 선택하여 인용발명 1의 돌루테그라비르를 치환하는 것에 어려움이 없다고 판단됩니다.

또한, 인용발명 3에도 인테그라아제 억제 물질인 엘비테그라비르, 테노포비르 전구체 및 엠트리시타빈을 함유하는 정제가 개시되어 있는데, 그 정제는 테노포비르 디소프록실 푸마레이트에 비하여 안전하고 효과적인 테노포비르 알라페니미드 푸마레이트(TAF)를 10 mg 포함하고 있고, 흡수촉진제인 코비시스타트가 부가될 때 10 mg의 TAF는 25mg의 TAF와 동등하다고 기재되어 있으므로(제53면, 좌측열 단락 2 내지 4 참조), 통상의 기술자가 인용발명 1의 테노포비르 디소프록실 푸마레이트를 TAF 25 mg으로 쉽게 치환할 수 있습니다.

그리고 제1항의 효과를 살펴보아도, 발명의 설명으로부터 세 종류의 약물을 단일 정제로 제조할 수 있다는 것을 알 수 있을 뿐이고, 통상의 기술자가 인용발명 1 내지 3으로부터 예측하기 어려운 현저히 우수한 항-HIV 효과 등을 나타낸다고 인정할 근거가 없습니다.

따라서 제1항은 통상의 기술자가 인용발명 1 내지 3으로부터 쉽게 발명할 수 있는 것입니다.

1-2. 제2항 내지 제11항은 제1항을 직·간접적으로 인용하는 종속항으로서,

제2항의 기술적 특징은 제1항과 차이가 없고,

제3항의 함량도 염 형태의 활성성분을 선택함에 따라 당연히 도출되는 것이며,

제4항 내지 제7항에서 한정한 정제의 총중량과 형태도 통상적인 정제가 가지는 성질과 형태에 불과하고,

제8항 및 제9항에서 화학식 I 화합물의 함량을 한정한 것도 제제화 과정에서 화합물의 약용량과 물성에 따라 통상의 기술자가 반복된 실험을 통하여 쉽게 선택할 수 있는 것입니다.

또한, 제10항은 필름 코팅된 2층 정제로서 그 부형제의 종류와 함량을 한정한 것이나, 제제의 형태와 그에 적합한 부형제 종류와 함량을 선택하는 것은 약효성분의 제형화 과정에서 통상적으로 수행되는 것인데, 그 선택된 형태 및 부형제 종류와 함량은 정제에 널리 사용되는 범주에 해당하고,

제11항의 HIV 감염 치료 용도도 인용발명 1에 개시된 용도를 단순히 부가한 것입니다.

즉, 제2항 내지 제11항에서 부가 또는 한정된 구성을 모두 통상의 기술자가 인용발명 1 내지 3으로부터 쉽게 도출할 수 있는 것이고, 제2항 내지 제11항이 통상의 기술자가 예측하기 어려운 현저히 우수한 효과를 나타낸다고 인정할 근거도 없으므로, 제2항 내지 제11항은 인용발명 1 내지 3으로부터 통상의 기술자가 쉽게 도출할 수 있는 것으로 인정됩니다.

2. 이 출원은 청구범위의 청구항 제4항, 제8항, 제9항의 기재가 아래에 지적한 바와 같이 불비하여 특허법 제42조제4항제2호에 따른 요건을 충족하지 못하므로 특허를 받을 수 없습니다.

- 아 래 -

제4항, 제8항 및 제9항은 수치의 범위를 기재하면서 '약~'이라고 표현하고 있어서, 발

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1840 of 1915

명이 보호받고자 하는 사항을 명확하게 기재하지 않은 것으로 인정됩니다.

[첨 부]
첨부1 국제공개공보 WO2015/022351(2015.02.19.) 1부.
첨부2 국제공개공보 WO2014/100323(2014.06.26.) 1부.
첨부3 J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014. 9. 1.) 1부.
끝.

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1841 of 1915

2019.09.02.

특허청 특허심사2국

약품화학심사과 심사관 김경미 김 경미

<< 안내 >>

1. 특허법 제47조제2항에 따라 특허출원서에 최초로 첨부된 명세서 또는 도면에 기재된 사항의 범위 안에서 명세서 또는 도면을 보정할 수 있음을 알려드립니다.

2. 출원일이 2013년 7월 1일 이후인 출원에 대해서는, 하나의 의견제출통지에 따른 지정기간 내에 보정서를 2회 이상 제출한 경우에는, 마지막 보정 이외의 모든 보정은 취하간주되오니 주의하시기 바랍니다.

3. 보정료 납부안내
 o 명세서 또는 도면을 보정하기 위하여 명세서등 보정서를 전자문서로 제출할 경우 매건 4,000원, 서면으로 제출할 경우 매건 14,000원의 보정료를 납부하여야 합니다.
 o 보정료는 접수번호를 부여받아 이를 납부자번호로 "특허료등의 징수규칙" 별지 제1호서식에 기재하여, 접수번호를 부여받은 날의 다음 날까지 납부하여야 합니다. 다만, 납부일이 공휴일(토요휴무일을 포함한다)에 해당하는 경우에는 그날 이후의 첫 번째 근무일까지 납부하여야 합니다.
 o 보정료는 국고수납은행(대부분의 시중은행)에 납부하거나, 인터넷지로(www.giro.or.kr)로 납부할 수 있습니다. 다만, 보정서를 우편으로 제출하는 경우에는 보정료에 상응하는 동상환을 동봉하여 제출하시면 특허청에서 납부해드립니다.

4. 지정기간연장 안내 : 연장가능기간(4개월)을 초과하여 지정기간을 연장하고자 소명서를 첨부하여 지정기간연장신청서를 제출한 경우 심사관은 아래의 사유에 해당되는지를 판단하여 지정기간연장의 승인 여부 및 연장할 수 있는 기간을 정하여 통지합니다.
 【4개월을 초과하여 지정기간연장을 할 수 있는 사유】
 ① 기간만료 전 1개월 이내에 최초로 대리인을 선임하거나 선임된 대리인 모두를 해임·변경한 경우
 ② 기간만료 전 1개월 이내에 출원인변경신고서를 제출한 경우
 ③ 기간만료 전 2개월 이내에 외국특허청의 심사결과를 받은 경우로서 동 심사결과를 보정서에 반영하고자 하는 경우(이 경우 신청서 제출 시 해당 심사결과 사본 및 그 기초가 된 청구범위 사본도 같이 제출해야 함)
 ④ 의견제출통지서의 송달이 1개월 이상 지연된 경우(1개월 추가 연장 가능)
 ⑤ 원출원 또는 분할출원이 심판이나 소송에 계류 중인 경우
 ⑥ 거절이유와 관련된 시험 및 결과측정에 기간이 더 필요한 경우
 ⑦ 기타 불가피하게 기간연장이 필요하다고 인정되는 경우
 단, 제3자가 심사청구한 때에는 ①~⑤의 경우라도 불승인

5. 온라인 영상면담 및 보정안 리뷰(심층면담) 서비스 안내
 o 심사관에게 방문면담을 신청할 경우 특허청(대전)에서 출원발명에 관한 상담 서비스를 받을 수 있고, 영상면담을 신청할 경우에는 특허청(대전) 방문 없이도 상담이 가능합니다(영상면담 장소: 특허청 서울사무소와 강원, 경남, 경북, 광주, 부산, 울산, 인천, 전남지역지식재산센터).
 o 보정안 리뷰를 신청할 경우 심층면담을 통해 거절이유 해소 여부 등 보정안에 대한 보다 체계적인 사전검토 서비스를 받을 수 있습니다(특허로(www.patent.go.kr) - 출원신청 메뉴).

6. 출원인의 명세서 작성 및 보정에 이해를 돕고자 아래 사이트에서 명세서작성사례 및 기술분야별 보정매뉴얼 등을 제공하고 있습니다. 인터넷 접속이 어려울 경우, 담당 심사관에게 연락주시면 명세서작성사례 등을 우편으로 송부해드리겠습니다.
 o 특허로(www.patent.go.kr)-명세서작성관련 유용한 Tip

※ 「특허로」 고객센터에서 알림서비스를 신청하시면 담당 심사관 지정 알림, 마감기한 알림 등 각종 민원처리 사항을 이메일과 휴대폰(SMS)로 받아 보실 수 있습니다.

※ 이 통지서의 내용에 대해 문의사항이 있으시면 특허청 ☎ 042-481-5412(담당심사관 김경미)로, 서식 또는 절차에 대하여는 특허고객상담센터 ☎1544-8080로 문의하시기 바랍니다.

※ 우 35208 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1842 of 1915

Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study

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Objectives: To evaluate the safety and efficacy of the novel tenofovir prodrug, tenofovir alafenamide (TAF), as part of a single-tablet regimen (STR) for the initial treatment of HIV-1 infection.

Design: Phase 2, randomized, double-blind, double-dummy, multicenter, active-controlled study.

Methods: Antiretroviral naive adults with HIV-1 RNA ≥5000 copies per milliliter and a CD4 count ≥50 cells per microliter were randomized 2:1 to receive an STR of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF), plus placebo for 48 weeks.

Results: Patients on both E/C/F/TAF (n = 112) and E/C/F/TDF (n = 58) had high rates of virologic suppression (<50 HIV copies per milliliter) at week 24 (86.6%; 89.7%) and at week 48 (88.4%; 87.9%), and had similar improvements in CD4 at week 48 (177; 204), respectively. Both treatments were well tolerated, and most adverse events were self-limiting and of mild to moderate severity. Compared with patients on E/C/F/TDF, patients on E/C/F/TAF had smaller reductions in estimated creatinine clearance (−5.5 vs. −10.1 mL/min, $P = 0.041$), significantly less renal tubular proteinuria, and smaller changes in bone mineral density for hip (−0.62% vs. −2.39%, $P < 0.001$) and spine (−1.00% vs. −3.37%, $P < 0.001$). Patients on E/C/F/TAF had higher increases in total cholesterol, low-density lipoprotein, and high-density lipoprotein, but the total cholesterol/high-density lipoprotein ratio was unchanged for both.

Conclusions: Treatment-naive patients given the STR that contained either TAF or TDF achieved a high rate of virologic success. Compared with those receiving TDF, patients on E/C/F/TAF experienced significantly smaller changes in estimated creatinine clearance, renal tubular proteinuria, and bone mineral density.

Key Words: tenofovir alafenamide, GS-7340, elvitegravir, stribild, clinical trials

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P.E.S., A.Z., I.B., R.E., and R.O. enrolled patients and reviewed and interpreted analyses of data. S.M., M.W.F., C.C., and H.W. designed the study. Data collection was overseen by H.W., C.C., H.M., M.W.F., and S.M. H.W. analyzed data, which were reviewed and interpreted by C.C., H.M., M.F., and S.M. The first draft of this report was written by P.E.S., H.M., M.F., and S.M. The draft report was edited by P.E.S., A.Z., I.B., R.E., and R.O.

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INTRODUCTION

Currently available antiretroviral regimens have led to marked declines in the morbidity and mortality of patients living with HIV-1[1–3] and decreased risk of HIV-1 transmission.[4–6] This success has shifted clinical attention toward antiretroviral drug regimens that optimize tolerability, long-term safety, and durable efficacy. Morbidity and mortality are increasingly driven by non-AIDS associated comorbidities, which are observed earlier than in age-matched controls, despite durable suppression with the best available antiretroviral therapy (ART).[1,2,7–10] Current guidelines recommend that patients begin ART earlier and stay on it continuously,[11] so the contribution of specific antiretroviral agents to long-term morbidity and mortality is increasingly important. In regimens of comparable efficacy, pill burden, dose frequency, safety, and tolerability are significant factors affecting maximal adherence over the long term.[12–14] Single-tablet regimens (STRs) represent a simple and convenient way for patients to maximize adherence and to control their HIV for many years.

Current Department of Health and Human Services guidelines recommend tenofovir disoproxil fumarate (TDF) as a preferred component of the nucleotide reverse-

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Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1843 of 1915

transcriptase inhibitor (NRTI) backbone for HIV-1–positive treatment-naive patients.[11] Despite a favorable safety and tolerability profile, TDF has been associated with nephrotoxicity,[15,16] requires dose adjustment as creatinine clearance falls <50 mL/min,[17] and has been shown to result in a greater decline in bone mineral density (BMD) relative to some other NRTIs.[18,19]

Tenofovir (TFV) is a nucleotide analog HIV-1 reverse transcriptase inhibitor. TDF, the first-generation prodrug of TFV, undergoes rapid metabolism in the plasma after oral administration.[20] TFV is then distributed intracellularly, where it is phosphorylated to the active moiety TFV diphosphate (TFV-DP). TFV alafenamide (TAF, formerly GS-7340) is a next-generation oral prodrug of TFV that may offer improved safety and efficacy. Relative to TDF, TAF is more stable in plasma and is predominantly metabolized intracellularly to TFV by cathepsin A.[20–22] This intracellular drug metabolism results in higher intracellular levels of the active metabolite TFV-DP and lower plasma levels of TFV, relative to TDF.[20,21]

Both nonhuman primate studies and human clinical studies have shown a relationship between plasma TFV levels and renal toxicity.[23–25] Because TFV (but not TAF) actively enters renal tubular cells via organic anion transporters 1 and 3, the reduced TFV levels that occur with TAF may be clinically manifest as reduced nephrotoxicity.[26,27] The higher intracellular TFV-DP levels may result in improved antiviral potency. In a 10-day monotherapy study in HIV-1–positive patients, those who received 25 mg of TAF had an approximately 0.5 $\log_{10}$ greater decline in plasma HIV-1 RNA than did patients who received the standard 300-mg dose of TDF.[28] In vitro, higher intracellular TFV-DP levels enable TAF to retain activity against viruses that have reduced susceptibility to TDF,[29] suggesting the potential use of TAF in a broader range of patients.

Because cobicistat increases the bioavailability of TAF by approximately 2.2-fold via the inhibition of P-glycoprotein intestinal secretion, the 10-mg dose of TAF delivered by the E/C/F/TAF STR is equivalent to the 25-mg dose of TAF.[28,30,31] To confirm the antiviral activity and safety profile of TAF compared with that of TDF, we conducted a randomized, double-blind Phase 2 clinical trial of 2 STRs—elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and TAF 10 mg (E/C/F/TAF) compared with elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and TDF 300 mg (E/C/F/TDF), licensed as Stribild (Gilead Sciences, Foster City, CA). The primary objective of this study, GS-292-0102, was to evaluate the efficacy and safety of TAF relative to TDF, both as part of an elvitegravir-based STR in treatment-naive patients at 24 weeks, with a particular focus on virologic, renal, and bone endpoints. Here, we report the efficacy and safety data from this study through 48 weeks.

METHODS

Study Design

Study 292-0102 is an ongoing randomized, double-blind, double dummy, active controlled, Phase 2 study being conducted in the United States that was approved by the US Food and Drug Administration and by institutional review boards at all sites. HIV-positive treatment-naive adults were considered eligible if they were ≥18 years of age with a plasma HIV-1 RNA ≥5000 copies per milliliter, a $CD4^+$ cell count >50 cells per microliter, an HIV-1 genotype showing sensitivity to TFV and emtricitabine (FTC), and an estimated glomerular filtration rate (eGFR; Cockcroft–Gault) of ≥70 mL/min. Patients were excluded if they were hepatitis B or C coinfected, had a new AIDS-defining condition within 30 days of screening, or were pregnant. The study was conducted from December 2011 through April 2013 (week 48 endpoint) and is posted on clinicaltrials.gov (NCT01497899).

Eligible participants were randomized centrally by a third party interactive voice/web response system, stratified by screening HIV-1 RNA (≤ or >,100,000 copies per milliliter), in a 2:1 fashion to receive treatment with either E/C/F/TAF or E/C/F/TDF administered once daily with food; all patients also received matching placebo tablets.

Randomized patients were seen at screening, baseline, and at weeks 2, 4, 8, 12, 16, and then every 8 weeks through week 48. Laboratory analyses (hematology, serum chemistries, $CD4^+$ cell count, and urinalysis; Covance Laboratories, Indianapolis, IN), HIV-1 RNA (TaqMan 2.0; Roche Diagnostics, Indianapolis, IN), and physical examinations were performed at all visits. HIV-1 genotype (reverse transcriptase and protease) was tested at screening (GenoSure MG, Monogram Biosciences, South San Francisco, CA). Any patient with confirmed virologic failure (2 consecutive viral load samples >50 copies/mL) and an HIV RNA >400 copies/mL at week 8 or later had the second, confirmatory, sample sent for resistance analysis by GeneSeq Integrase, PhenoSense GT, and PhenoSense Integrase (Monogram Biosciences).

Trough pharmacokinetic (PK) samples were collected at weeks 8, 24, and 48 visits, and population PK samples were collected at weeks 2, 4, 12, 16, 24, and 40. An intensive PK substudy was performed on a subset of patients at week 4 or 8 and included peripheral blood mononuclear cell (PBMC) sampling for intracellular TFV-DP levels.

Dual energy x-ray absorptiometry (DEXA) was used to measure BMD only at the hip and lumbar spine before study drug administration at baseline and every 24 weeks. These were read centrally by BioClinica (Newtown, PA), with investigators and patients blinded to the results. Patients were scanned with the same machine throughout the study, and phantom scans were used for quality assurance across sites. Blood and urine for selected bone and renal biomarkers were collected and analyzed at baseline and weeks 24 and 48.

Statistical Methods

The primary objective was to determine the efficacy of a regimen containing E/C/F/TAF vs. E/C/F/TDF in HIV-1 treatment-naive adults at week 24 (primary endpoint) and week 48 (secondary endpoint) according to US Food and Drug Administration snapshot analysis (the proportion of patients with HIV-1 RNA <50 copies per milliliter).[32] The sample size of 150 patients (100 in the E/C/F/TAF arm) was chosen to estimate the response rate of HIV-1 RNA <50

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1844 of 1915

copies per milliliter at week 24 and to have 76% power to detect a 1.5% (standard deviation of 3.2%) difference in hip BMD in the E/C/F/TAF arm relative to the E/C/F/TDF treatment group. The safety and tolerability of the 2 treatment arms through 48 weeks of treatment were assessed as secondary endpoints.

An individual patient was considered a treatment success if he or she had HIV-1 RNA <50 copies per milliliter at week 24 without virologic failure (confirmed >50 copies per milliliter in week 24 window). These criteria were also used for the week 48 secondary analysis. Safety analyses included available data from all participants who consented to participate, and who received at least 1 dose of study medication; patients who discontinued were followed up for 30 days after drug discontinuation. Demographic and baseline characteristics were summarized using standard descriptive methods.

RESULTS

Of 233 patients screened, 171 were randomized, and 170 received at least 1 dose of study drug (E/C/F/TAF, n = 112, E/C/F/TDF, n = 58). Baseline characteristics are outlined in Table 1. Patients were primarily male, and approximately 30% were black or African American; most had no prior AIDS-defining condition. The median viral load at baseline was 4.6 $\log_{10}$ copies per milliliter, and the median CD4$^+$ cell count was 391 cells per microliter. Overall, 21% had baseline HIV-1 RNA >100,000 copies per milliliter, and 15% had a baseline CD4 count <200 cells per microliter (E/C/F/TAF, 12.5%; E/C/F/TDF, 18.9%). The median eGFR at baseline was 114 mL/min. Through week 48, 4 patients in the E/C/F/TAF arm and 0 in the E/C/F/TDF arm discontinued due to adverse events; 3 of the discontinuations due to unrelated illness (coxsackie infection, dual cytomegalovirus/*Mycobacterium avium* infection on day 13, acute promyelocytic leukemia) and 1 due to flushing that was considered drug related.

At week 24, virologic success was attained in 87.5% of those on the E/C/F/TAF arm and 89.7% for those receiving E/C/F/TDF [weighted difference −3.7%, 95% confidence interval −14.4 to 7.0, $P = 0.48$]. At week 48, there was virologic success in 88.4% (99/112) of patients who received E/C/F/TAF and 87.9% (51/58) who received E/C/F/TDF (weighted difference −1.0%, 95% confidence interval −12.1 to 10.0, $P = 0.84$). An analysis of virologic response using different virologic endpoints (missing = failure) demonstrated that 79% of patients in the E/C/F/TAF arm had HIV-1 RNA <20 copies per milliliter compared with 74% on E/C/F/TDF ($P = 0.56$), whereas no RNA signal was detectable in 59% of those on E/C/F/TDF vs. 53% on E/C/F/TDF. Median adherence to study treatment was equivalent in the 2 treatment arms (98%). Two patients in the E/C/F/TDF arm and none in the E/C/F/TAF arm discontinued their treatment due to the loss of efficacy. The mean CD4$^+$ cell count increase from baseline was 177 cells per microliter in the E/C/FTAF arm vs. 204 cells per microliter in the E/C/F/TDF arm ($P = 0.41$).

Six patients, 3 in each treatment arm (3/112 = 2.7% for E/C/F/TAF, 3/58 = 5.2% for E/C/F/TDF), met the criteria for virologic resistance testing. No resistance was detected in the E/C/F/TAF arm.

Resistance was detected in 2 patients in the E/C/F/TDF arm: 1 developed NRTI resistance with M184V and K70E and 1 developed both NRTI and Integrase Strand Transfer Inhibitor (INSTI) resistance with M184V and E92Q.

In patients in the intensive PK substudy (n = 26), plasma TFV exposure was 91% lower for patients taking E/C/F/TAF than for patients taking E/C/F/TDF, as measured by AUC_{tau}. Conversely, intracellular TFV-DP levels in PBMCs were 5.3-fold higher for patients in the E/C/F/TAF arm.

The 48-week safety profile of E/C/F/TAF was generally similar to that of E/C/F/TDF, with 94.6% (106) vs. 94.8% (55) patients reporting any treatment-emergent adverse event, and 9.8% (11) vs. 5.2% (3) reporting a grade 3 or 4 adverse event. The most common treatment-emergent adverse events were nausea and diarrhea, where nausea was reported in 21% on E/C/F/TAF and 12% of those on E/C/F/TDF. Of the 23 patients reporting nausea in the E/C/F/TAF treatment arm, 18 of these were grade 1, and 5 were grade 2, 15 resolved within 2 weeks, and none led to treatment discontinuation. A total of 7% in each arm reported vomiting. Diarrhea was reported in 16% in each treatment arm. No patient in either arm discontinued treatment due to any of these gastrointestinal events. Adverse events reported in at least 5% of participants in either arm are shown in Table 2.

All postbaseline grade 3 or 4 laboratory abnormalities are shown in Table 3. Grade 3 or 4 low-density lipoprotein (LDL) cholesterol elevations were more common in the E/C/F/TAF than in the E/C/F/TDF arm (9% vs. 3%). Fasting metabolic assessments showed that the median increase in LDL cholesterol was 17 mg/dL for E/C/F/TAF vs. 11 mg/dL for E/C/F/TDF ($P = 0.11$). There were statistically significant differences between groups in the median changes in total cholesterol (30 vs. 17 mg/dL, $P = 0.007$) and high-density lipoprotein (HDL) cholesterol (7 vs. 3 mg/dL, $P = 0.023$), whereas total cholesterol/HDL cholesterol ratio remained unchanged (median increase 0.2 vs. 0.1, $P = 0.34$). However, categorical analysis at week 48 by National Cholesterol Education Program Adult Treatment Panel III[33] classification showed no differences between the 2 treatment arms for total cholesterol ($P = 0.54$) or for LDL cholesterol

TABLE 1. Baseline Characteristics

Characteristic	E/C/F/TAF (n = 112)	E/C/F/TDF (n = 58)
Age (yrs), median	34	38
Male (%)	96	98
Race (%)		
White	67	69
Black/African descent	30	28
Hispanic/Latino	22	19
Asymptomatic HIV infection (%)	88	91
HIV-1 RNA ($\log_{10}$ copies/mL), median	4.55	4.58
>100,000 copies/mL	17%	28%
CD4 cell count (cells/mm^3), median	385	397
≤ 200 cells/mm^3	13%	19%
Estimated GFR, median, (Cockcroft–Gault), mL/min	115	113

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1845 of 1915

TABLE 2. Adverse Events

Adverse Event (Any Grade) Occurring in At Least 5% of Patients, % (n)	E/C/F/TAF (n = 112)	E/C/F/TDF (n = 58)
Nausea	21% (23)	12% (7)
Diarrhea	16% (18)	16% (9)
Upper respiratory tract infection	15% (17)	21% (12)
Fatigue	14% (16)	9% (5)
Headache	10% (11)	14% (8)
Cough	10% (11)	10% (6)
Pharyngitis	8% (9)	3% (2)
Rash	8% (9)	5% (3)
Vomiting	7% (8)	7% (4)
Influenza	7% (8)	0
Bronchitis	6% (7)	5% (3)
Nasopharyngitis	6% (7)	3% (2)
Depression	6% (7)	3% (2)
Conjunctivitis	6% (7)	0
Anogenital warts	5% (6)	5% (3)
Abnormal dreams	5% (6)	2% (1)
Flatulence	5% (6)	3% (2)
Insomnia	4% (4)	7% (4)
Sinusitis	4% (5)	5% (3)
Seasonal allergies	3% (3)	5% (3)
Back pain	3% (3)	10% (6)
Paresthesia	3% (3)	7% (4)
Neck pain	3% (3)	5% (3)
Syphilis	3% (3)	5% (3)
Anxiety	2% (2)	9% (5)
Pain in extremities	1% (1)	5% (3)
Skin papilloma	0	5% (3)

($P = 0.37$), and there were no differences in change in triglycerides or serum glucose between treatment arms.

There was a rise in serum creatinine and consequent decline in creatinine clearance in both arms. Compared with baseline, the median change in serum creatinine at week 48 was 0.07 mg/dL for E/C/F/TAF vs. 0.10 mg/dL for E/C/F/TDF ($P = 0.077$), and the median change in eGFR by Cockcroft–Gault was −5.5 mL/min for E/C/F/TAF vs. −10.1 mL/min for E/C/F/TDF ($P = 0.041$). The median changes in serum creatinine generally occurred by week 4 for both treatment arms and then stabilized for the duration of the study.

TABLE 3. Grade 3 or 4 Laboratory Abnormalities

Maximum Toxicity Grade Postbaseline % (n)	E/C/F/TAF (n = 112)	E/C/F/TDF (n = 58)
Any grade 3 or grade 4 abnormality	25% (28)	17% (10)
LDL	9% (10)	3% (2)
Creatine phosphokinase	6% (7)	3% (2)
Neutropenia	5% (6)	2% (1)
Amylase	3% (3)	3% (2)
Urine RBC	2% (2)	0
Total cholesterol	2% (2)	0
ALT	1% (1)	2% (1)
AST	1% (1)	0
GGT	1% (1)	2% (1)
White blood cells	1% (1)	0
Hypophosphatemia	1% (1)	0
Urine protein	1% (1)	0
Glucose	1% (1)	2% (1)
Triglycerides	1% (1)	2%(1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; RBC, red blood cells.

There were no clinically defined cases of proximal renal tubulopathy in either arm, and there were no treatment discontinuations due to laboratory or clinical renal events. Less proteinuria (urine protein/creatinine ratio) and albuminuria (urine albumin/creatinine ratio) were observed with E/C/F/TAF, but the differences were not statistically significant (Fig. 1). Renal tubular proteinuria [urine retinol-binding protein (RBP)/creatinine ratio and urine β-2 microglobulin/creatinine ratio] was significantly lower in patients who received E/C/F/TAF (Fig. 1).

Changes in BMD, expressed as the median percent change from baseline, are shown in Figure 2. There was significantly less change in the E/C/F/TAF arm in BMD as measured by using DEXA at both the hip (−0.62% vs. −2.39%, $P < 0.001$) and lumbar spine (−1.00% vs. −3.37%, $P < 0.001$) at week 48, which were also significant at week 24. In the E/C/F/TAF arm, 32% of the patients had no decrease seen in hip BMD vs. 7% in the E/C/F/TDF arm ($P < 0.001$), and no decrease at the lumbar spine was seen in 37% of the patients who received E/C/F/TAF vs. 11% who received E/C/F/TDF ($P < 0.001$). Conversely, a change in BMD >3% from baseline at the hip was observed 11.5% vs. 40.0% and at the lumbar spine in 24.8% vs. 55.3% (E/C/F/TAF vs. E/C/F/TDF, respectively, $P < 0.001$ for both). At weeks 24 and 48, markers of bone turnover were lower in patients on E/C/F/TAF than on E/C/F/TDF. At week 48, procollagen type 1 N-terminal propeptide, a marker of bone formation, increased 9% from baseline for E/C/F/TAF vs. 69% for E/C/F/TDF ($P < 0.001$), whereas C-terminal telopeptide (CTx), a marker of bone resorption, increased 19% from baseline for E/C/F/TAF vs. 78% for E/C/F/TDF ($P < 0.001$). There were no fragility fractures in either arm of the study.

DISCUSSION

TDF is a preferred NRTI in the initial therapy based on its favorable efficacy and safety data in randomized clinical trials and widespread use in clinical practice.[11] However, TDF may be associated with renal toxicity,[15,16] and comparative studies demonstrate that TDF treatment is linked to a greater loss in bone density as compared with other NRTI options.[18,34] Given the prolonged survival of patients with HIV with effective therapy, and the need for indefinite treatment, there is a need for an NRTI option that provides antiviral activity comparable with TDF with an improved safety profile.

In this Phase 2, randomized clinical trial, HIV-positive treatment-naive adults received STRs of E/C/F/TAF or E/C/F/TDF. Both E/C/F/TAF and E/C/F/TDF demonstrated high and comparable rates of virologic suppression, with expected rises in the $CD4^+$ cell count through 48 weeks of therapy. Both regimens were well tolerated, with few discontinuations due to adverse events. Although nausea occurred more

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1846 of 1915

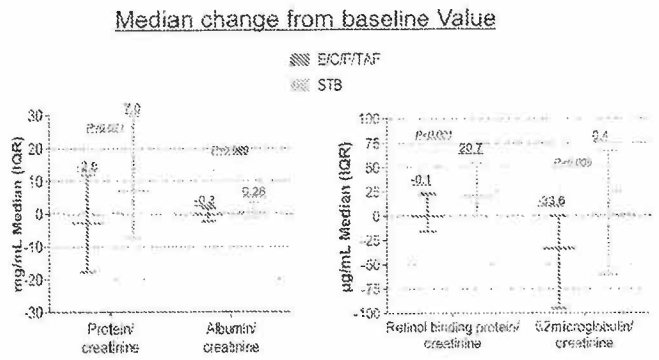
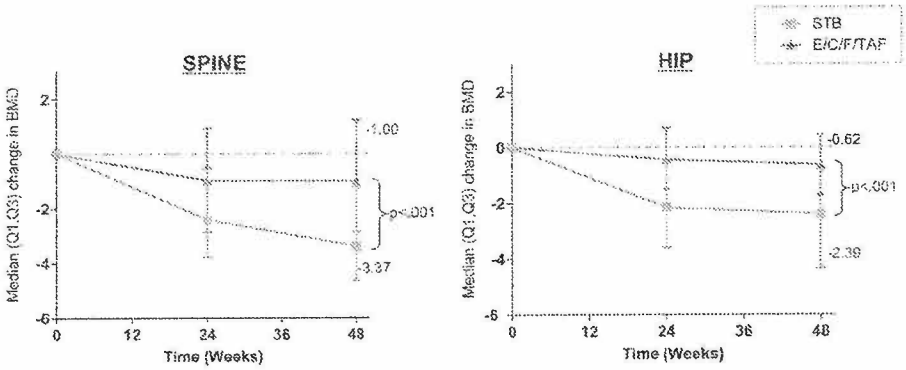


FIGURE 1. Urine tubular proteins: median change from the baseline value.

frequently in the E/C/F/TAF than in the E/C/F/TDF arm, the nausea reported was all grade 1 and grade 2 in severity, did not lead to drug discontinuation in any patient, and was comparable with the rate of nausea in the phase 3 studies of E/C/F/TDF.[35,36]

Because the 2 treatment regimens in this study differed only in whether patients received TAF or TDF, the study offered an opportunity to compare the pharmacokinetics, renal, and bone effects of the 2 prodrugs. Plasma concentrations of TFV were substantially (91%) lower with E/C/F/TAF than with E/C/F/TDF, and the TAF regimen delivered 5.3 times the intracellular, physiologically active metabolite, TFV-DP, to PBMCs, which could translate into less end-organ toxicity and/or improved virologic control. Although the effect of these differences did not translate into an observed significant difference in antiviral activity between the 2 regimens, the study had not been powered to demonstrate differences in virologic endpoints, and this is being further explored in the E/C/F/TAF Phase 3 program. In addition, no genotypic resistance emerged in the E/C/F/TAF group for the 3 patients with virologic failure and who met criteria for resistance analysis.

There were significant differences between the E/C/F/TAF and E/C/F/TDF treatment groups in specified renal, bone, and lipid endpoints. Early small increases in creatinine were seen in both arms, which were expected to be due to the known nonpathologic inhibitory effect of cobicistat on tubular creatinine secretion.[37] However, after week 2, patients on TAF had a lower magnitude increase in serum creatinine than did patients on TDF despite receiving the same other components of combination ART. The mechanism for this



No decrease in hip BMD: 32% E/C/F/TAF vs 7% STB (p<.001)

W48 Median Value of Bone Biomarkers as % of Baseline: E/C/F/TAF vs. STB	
Procollagen Type 1 N-terminal propeptide (P1NP):	109% vs 189% (p<0.001)
C-terminal telopeptide (CTx):	119% vs. 178% (p<0.001)

FIGURE 2. Percent change in the spine and hip BMD as determined using DEXA.

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1847 of 1915

difference is currently unknown but potentially may be related to the 91% lower plasma TFV exposure observed when TFV is delivered as TAF compared with TDF, because higher plasma TFV levels have been associated with an increased risk of renal impairment in other studies.[24,25] TFV in plasma is actively transported into the proximal renal tubular cell via organic anion transporter (OAT) 1 and OAT 3, but TAF is not a substrate for these transporters.[27] Thus, the intracellular concentration of TFV within proximal tubules is lower in patients treated with TAF compared with those treated with TDF, and decreased cytotoxicity of TAF in isolated human renal cells was recently demonstrated.[27]

The effect of TAF vs. TDF on proximal renal function was assessed using standard clinical measures of proteinuria and albuminuria, and markers of proximal renal tubular cell dysfunction, RBP, and β-2 microglobulin. These low molecular weight proteins are freely filtered at the glomerulus, and hence are almost entirely removed from the ultrafiltrate and catabolized in the proximal renal tubules.[38,39] The presence of these proteins in increased amounts in the urine may indicate subclinical renal tubular cell dysfunction.[38,39] In this study, urinary RBP/creatinine and β-2 microglobulin/creatinine ratios were significantly lower in the E/C/F/TAF arm, which suggests that TAF has a lesser effect than TDF on the proximal renal tubular cell. Whether this translates into long-term clinical benefit in renal function must be explored in larger studies with a longer follow-up. Nonetheless, these data are encouraging, as they demonstrate that TAF has a reduced effect on serum creatinine and is associated with reduced tubular proteinuria, both of which are important clinical markers of chronic kidney disease.

Patients with HIV have a lower BMD than age-matched HIV-uninfected controls, and they also experience higher fracture rates.[10,19] In addition, several studies have shown that TDF-containing regimens lead to a greater decline in bone density than in the case of comparator drugs.[18,34] In this study, patients who received E/C/F/TAF had smaller decreases in BMD through 48 weeks than those receiving E/C/F/TDF. It is noteworthy that the magnitude of BMD change that was observed for patients on the E/C/F/TAF arm was the lowest magnitude BMD change reported to date for treatment-naive study patients receiving NRTIs who had bone density assessed with bone DEXA scans. For example, the ASSERT study compared patients treated with TDF/FTC vs. ABC/3TC, each combined with efavirenz, and found a loss of BMD in both groups after the initiation of ART. However, there was a statistically greater loss of BMD at the hip and spine in patients treated with TDF/FTC than in those given ABC/3TC.[18] Although cross-study comparisons should only be made cautiously, the STR E/C/F/TAF demonstrated less loss of BMD than seen with ABC/3TC + EFV demonstrated in the ASSERT study (hip: −0.62% vs. −1.9%; spine: −1.0% vs. −1.6% for E/C/F/TAF and ABC/3TC + EFV, respectively). The DEXA results in this study were supported by changes in markers of bone turnover, with significantly less change in markers of bone formation (procollagen type 1 N-terminal propeptide) and bone resorption (CTX) among patients on E/C/F/TAF compared with those on E/C/F/TDF.

There were significantly greater increases in total and HDL cholesterol in the E/C/F/TAF than in the E/C/F/TDF study arm. By contrast, the total cholesterol/HDL ratio, triglycerides, and glucose were not significantly different, and there were no differences in National Cholesterol Education Program risk classification. The likely cause of these differences may relate to the previously reported lipid-lowering effect of TFV,[40,41] and the markedly lower plasma concentrations of TFV in the E/C/F/TAF compared with that in the E/C/F/TDF arm.

CONCLUSIONS

Treatment-naive patients given either TAF or TDF as part of an STR containing emtricitabine, cobicistat, and elvitegravir achieved a high rate of virologic suppression, with comparably low rates of adverse events and adverse event-related drug discontinuation in both arms. Nausea was more common in those receiving E/C/F/TAF than in those receiving E/C/F/TDF in this study, though it was mild and did not lead to study drug discontinuation. Pharmacokinetic data demonstrated that TAF delivers the parent drug TFV into PBMCs, where the active, phosphorylated metabolite, TFV-DP, achieves a concentration 5- to 7-fold higher than TDF, with 91% lower plasma TFV levels. The E/C/F/TAF-treatment group had a significantly higher eGFR and significantly less tubular proteinuria than E/C/F/TDF; further, changes in BMD significantly favored E/C/F/TAF. These promising results await confirmation in fully powered Phase 3 randomized controlled clinical trials comparing TAF with TDF, which are underway.

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Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1848 of 1915

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1849 of 1915

Electronic Patent Application Fee Transmittal					
Application Number:	15346335				
Filing Date:	08-Nov-2016				
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus				
First Named Inventor/Applicant Name:	Benjamin Micah Collman				
Filer:	Donna Johnson Gressler/Trent Bastian				
Attorney Docket Number:	1147.P2C				
Filed as Large Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	1900	1900
		Total in USD ($)		**1900**

Electronic Acknowledgement Receipt	
EFS ID:	37510235
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
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.P2C
Receipt Date:	21-OCT-2019
Filing Date:	08-NOV-2016
Time Stamp:	13:59:02
Application Type:	Utility under 35 USC 111(a)

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2	Transmittal Letter	1147P2C_2019-10-21_IDS.PDF	83937 4c6e09c9551843979 33a65715d0eec771001 e329a	no	2
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3	Information Disclosure Statement (IDS) Form (SB08)	1147P2C_2019-10-21_SB08.PDF	106678 ba2d506c47a569bc6859777e38c3126cc97 c3ea7	no	2
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25000 7590 10/29/2019

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

EXAMINER	
WORSHAM, JESSICA N	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/29/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	01/29/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

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PTOL-85 (Rev. 02/11)

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(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	01/29/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
WORSHAM, JESSICA N	1615	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

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(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

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❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1856 of 1915

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 10/29/2019

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

EXAMINER
WORSHAM, JESSICA N

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/29/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 30 minutes to complete, including gathering, preparing, and submitting the completed application 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
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.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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 inspection 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.

Notice of Allowability	Application No. 15/346,335	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--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE filed 21 October 2019.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/21/19.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Continuation of 3. The allowed claim(s) is/are: 1-5,26-27,52-53 and 55

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

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 21 October 2019 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. See attached copy of PTO-1449.

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 21 October 2019 has been entered.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: The closest prior art of Carra et al. (WO2015/196116, U.S. Patent Application Publication No. 2016/0016973, and U.S. Patent Nos. 10,098,886 and 10,385,067) were published after the effective filing date of the instant application and have a common assignee. The next closest prior art of WO2014/100323 comprises

administering the compound of Formula I at a different time than additional drugs such as tenofovir or emtricitabine. The prior art does not teach all three drugs within the same tablet. Applicants have shown a 30% higher exposure of bictegravir in a fixed dose combination of bictegravir, emtricitabine, and tenofovir alafenamide relative to its exposure when co-administered as a single agent of bictegravir with a fixed dose combination of emtricitabine and tenofovir alafenamide.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

4. 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 on 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 an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner
No classified search performed.		

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
No classified search performed.		

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No classified search performed.		

* 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: EAST, PALM	05/03/2018	JW
EAST: See attached	05/03/2018	JW
SciFinder: See attached	05/03/2018	JW

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(tenofovir adj alafenamide and emtricitabine and bictegravir).clm.	04/23/2019	JW

/JESSICA N WORSHAM/ Primary Examiner, Art Unit 1615	

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1864 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC Symbol					Type	Version
A61K	/	9	/	209	F	2013-01-01
A61K	/	9	/	2054	I	2013-01-01
A61K	/	31	/	513	I	2013-01-01
A61K	/	31	/	675	I	2013-01-01
A61K	/	31	/	553	I	2013-01-01
A61K	/	9	/	2086	I	2013-01-01
A61P	/	31	/	18	I	2018-01-01
A61K	/	9	/	0053	I	2013-01-01
A61K	/	9	/	2013	I	2013-01-01
A61K	/	9	/	2095	I	2013-01-01
A61K	/	9	/	28	I	2013-01-01
A61K	/	31	/	5365	I	2013-01-01

CPC Combination Sets							
Symbol					Type	Set	Ranking	Version
A61K	/	31	/	513	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	31	/	553	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01
A61K	/	31	/	675	I	3	1	2013-01-01
A61K	/	2300	/	00	I	3	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	24 October 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20191024

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	5365
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	24 October 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20191024

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1866 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		10		19		28		37		46	10	55		
2	2		11		20		29		38		47				
3	3		12		21		30		39		48				
4	4		13		22		31		40		49				
5	5		14		23		32		41		50				
	6		15		24		33		42		51				
	7		16		25		34		43	8	52				
	8		17	6	26		35		44	9	53				
	9		18	7	27		36		45		54				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	24 October 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20191024

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1867 of 1915

PTO/SB/08a (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-7,390,791	06-24-2008	Becker et al.	
	AB	US-7,803,788	09-28-2010	Becker et al.	
	AC	US-8,754,065	06-17-2014	Liu et al.	
	AD	US-9,296,769	03-29-2016	Liu et al.	
	AE	US-10,098,886	10-16-2018	Carra et al.	
	AF	US-10,385,067	08-20-2019	Carra et al.	
	AG	US-2002-0119443-A1	08-29-2002	Becker et al.	
	AH	US-2003-0219727-A1	11-27-2003	Becker et al.	
	AI	US-2005-0124583-A1	06-09-2005	Becker et al.	
	AJ	US-2005-0124584-A1	06-09-2005	Becker et al.	
	AK	US-2005-0124585-A1	06-09-2005	Becker et al.	
	AL	US-2006-0024659-A1	02-02-2006	Becker et al.	
	AM	US-2018-0215769-A1	08-02-2018	Jin et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER. Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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: _October 21, 2019_____ Signature: _/Donna Johnson Gressler/_____ (Donna Johnson Gressler)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

PTO/SB/08b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Notice of Preliminary Rejection dated 2019-09-04 for Korean Appl. No. 10-2018-7015929.	√
	CB	SAX, P. et al. (2014) "Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study" *J Acquir Immune Defic Syndr* 67(1):52-58.	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	10/24/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

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

Oct 29, 2019 03:45:14 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15346335	NOA	10/29/2019	1147.P2C
	1449	10/29/2019	1147.P2C

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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

PTO/SB/30 (11-17)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).
   - a. [ ] Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.
     - i. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - ii. [ ] Other _____
   - b. [X] Enclosed
     - i. [ ] Amendment/Reply
     - ii. [ ] Affidavit(s)/ Declaration(s)
     - iii. [X] Information Disclosure Statement (IDS)
     - iv. [X] Other SB08
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)
   - b. [ ] Other _____
3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   - a. [X] The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 07-1250 .
     - i. [X] RCE fee required under 37 CFR 1.17(e)
     - ii. [ ] Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
   - c. [ ] Payment by credit card (Form PTO-2038 enclosed)
   - d. [X] Payment by EFS-Web

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Donna Johnson Gressler/	Date	November 13, 2019
Name (Print/Type)	Donna Johnson Gressler	Registration No.	45,544

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being EFS-Web transmitted to the United States Patent and Trademark Office (USPTO), deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the USPTO on the date shown below.

Signature	/Trent Bastian/		
Name (Print/Type)	Trent Bastian	Date	November 13, 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: November 13, 2019
Electronic Signature for Trent Bastian: /Trent Bastian/

Docket No.: 1147.P2C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 15/346,335

Confirmation No.: 1307

Filed: November 8, 2016

Art Unit: 1615

For: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

Examiner: J. N. Worsham

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the reference listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the reference be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement, pursuant to 37 C.F.R. § 1.114(c), accompanies the Request for Continued Examination (37 C.F.R. § 1.114) submitted herewith.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith is a copy of non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance

with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed reference.

The Director is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Acount No. 07-1250, under Order No. 1147.P2C.

Dated: November 13, 2019

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

PTO/SB/08a (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER. Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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: _November 13, 2019_____ Signature: _/Donna Johnson Gressler/_____ (Donna Johnson Gressler)

PTO/SB/08b (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

	Complete if Known
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Office Action dated 2019-09-22 for Gulf Cooperation Council Appl. No. 2016-32320.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

PATENT OFFICEOF THE
COOPERATION COUNCIL FOR
THE ARAB STATES OF THE GULF

مكتب براءات الاختراع
لمجلس التعاون لدول الخليج العربية

EXAMINATION REPORT

***NAME OF THE EXAMINATION OFFICE:** GCC PATENT OFFICE

Examination Report No.		Date:22/09/2019
Applicant's or agent's file reference:		
Application No.	**Application filing date**	**Earliest Priority date**
GC 2016-32320	07/11/2016	09/11/2015

International Patent Classification (IPC) as indicated in the search report or the request , if no indication in the search report

A61K 31/513, 31/5365, 31/675, 9/00, 9/20, 9/24, 9/28

Applicant: Gilead Sciences, Inc.

Title of Invention: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF NAMUH SURIV YCNEICIFEDONUMMI

1. This is the first [X] Second [ ] Third [ ] examination report on this application.
2. This REPORT consists of a total of 3 sheets
3. This report contains indications relating to the following items:

I. [X] Basis of the report (Box I)
II. [X] Priority (Box II)
III. [ ] Non-establishment of opinion with regard to novelty, inventive step industrial applicability ; (Box III)
IV [ ] Lack of unity of invention (Box IV)
V [X] Reasoned statement with regard to novelty, inventive step or industrial applicability ; Citation and explanation supporting such statement (Box V)
VI [ ] Certain documents cited (Box VI)
VII [ ] Certain defect in the application (Box VII)
VIII [ ] Certain observations of the application (Box VIII)

4. The search report(s) used to prepare this Exam. Report is a

( ) Previous report(s) (X) New search report was prepared

The search report used was issued by the **GCC Patent Office**
and the date of completion is **15/09/2019**

Date of submission of the request to this Examination Patent Office		Date of mailing of the report
10/05/2018		
Examiner Name	Head of Section	Director of Substantive Examination Dept. **Fahed Al-Mutairi**
PH. Mohammad S. AlMousa	**PH. Majed I. AlRufayyig**	

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1876 of 1915

Box I. Basis of the report

1. This report has been drawn on the basis of

[ ] the application as originally filed.

[ ] the description, as originally filed,

[ ] the claims, as originally filed,

[ ] the drawings, as originally filed,

[X] the application modifications.

[ ] The description, filed with the letter of the applicant dated on ,

[X] The claims, filed with the letter of the applicant dated on,09/05/2018

[ ] The drawings, filed with the letter of the applicant dated on,

2. The amendments have resulted in the cancellation of : pages:
sheets of drawings/figures No:

[ ] This reports has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box

3. Additional observations, if necessary :

Box II.Priority

1. [X] Priority accepted as mentioned in page 1
2. [ ] This report has been established as if no priority had been claimed.
3. [ ] This report has been established as if no priority had been claimed due to failure to furnish :

[ ] copy of the earlier application whose priority has been claimed.
Or [ ] translation thereof it the earlier application whose priority has been claimed.

4. [ ] This report has been established as if no priority had been claimed due to the fact that the priorityclaim has been found invalid.

[ ] Thus for the purposes of this report, the filing date indicated above is considered to be the relevant date.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1877 of 1915

Box V. Reasoned statement with regard to novelty, inventive step or industrial applicability: citation and explanations supporting such statement

1. STATEMENT:

Novelty (N)	Claims	**None**	**Yes**
	Claims	**1-9**	**No**
Inventive Step(IS)	Claims	**None**	**Yes**
	Claims	**1-9**	**No**
Industrial applicability (IA)	Claims	**1-9**	**Yes**
	Claims	**None**	**No**

2. CITATIONS AND EXPLANATIONS:

The following documents have been cited in the search Report:

D1 WO2014100323A1

2.1 Novelty:

The present invention is relates to 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. The compound of formula I is known to be therapeutically effective in the treatment of HIV (see documents D1). Its combination with another anti-HIV agent including tenofovir alafenamide and emtricitabine is also suggested in D1. Therefore, the subject-matter of claims **1-9** are not novel and contrary the requirement of article 2/2 of GCC patent regulation.

2.2 Inventive Step :

As long as novelty has not been established for claims **1-9**, inventive step cannot be discussed in the sense of Article 2/3 of the GCC Patent Regulation.

2.3 Industrial Applicability:

The technical solutions of claims **1-9** are industrially applicable.

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1878 of 1915

Electronic Patent Application Fee Transmittal	
Application Number:	15346335
Filing Date:	08-Nov-2016
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus
First Named Inventor/Applicant Name:	Benjamin Micah Collman
Filer:	Donna Johnson Gressler/Trent Bastian
Attorney Docket Number:	1147.P2C
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	1900	1900
		Total in USD ($)		**1900**

Electronic Acknowledgement Receipt	
EFS ID:	37743517
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
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.P2C
Receipt Date:	13-NOV-2019
Filing Date:	08-NOV-2016
Time Stamp:	16:52:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1900
RAM confirmation Number	E2019ACG53396160
Deposit Account	071250
Authorized User	Trent Bastian
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 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)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	1147P2C_2019-11-13_RCE.pdf	73919 ea832a110f52dd17c62174accd8e266dd0e7dc51	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Transmittal Letter	1147P2C_2019-11-13_IDS.pdf	94019 fc9c1f1294722f6881d07fbd6fd42ac59d76f8c	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	1147P2C_2019-11-13_SB08.pdf	97503 0a26e053eb3d3cfbd2f9fbd4391816a72ed7e4	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Non Patent Literature	1147P2C_GC_Office_Action_2016-32320.PDF	176500 ec2e304c35422a6f0a9f0d42217039b09dd46cf2	no	3
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30882 b32f125c998ea5fcddaa6e874f24cac92c50892	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	472823		

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 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

25000 7590 11/27/2019
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER	
WORSHAM, JESSICA N	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/27/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	02/27/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1884 of 1915

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25000 7590 11/27/2019

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

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	02/27/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
WORSHAM, JESSICA N	1615	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively.
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1885 of 1915

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Collman	1147.P2C	1307

25000 7590 11/27/2019

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

EXAMINER	
WORSHAM, JESSICA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/27/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 30 minutes to complete, including gathering, preparing, and submitting the completed application 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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 disclosure of these records is required by the Freedom of Information Act.
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.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
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 inspection 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.

Notice of Allowability	Application No. 15/346,335	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--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to RCE filed 13 November 2019.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/13/19.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Continuation of 3. The allowed claim(s) is/are: 1-5,26-27,52-53 and 55

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

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 13 November 2019 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. See attached copy of PTO-1449.

Request for Continued Examination

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 13 November 2019 has been entered.

Reasons for Allowance

3. The following is an examiner's statement of reasons for allowance: The closest prior art of Carra et al. (WO2015/196116, U.S. Patent Application Publication No. 2016/0016973, and U.S. Patent Nos. 10,098,886 and 10,385,067) were published after the effective filing date of the instant application and have a common assignee. The next closest prior art of WO2014/100323 comprises

administering the compound of Formula 1 at a different time than additional drugs such as tenofovir or emtricitabine. The prior art does not teach all three drugs within the same multi-layer tablet. Applicants have shown a 30% higher exposure of bictegravir in a fixed dose combination of bictegravir, emtricitabine, and tenofovir alafenamide relative to its exposure when co-administered as a single agent of bictegravir with a fixed dose combination of emtricitabine and tenofovir alafenamide.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence

4. 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 on 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 an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC - Searched*		
Symbol	Date	Examiner
No classified search performed.		

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
No classified search performed.		

US Classification - Searched*			
Class	Subclass	Date	Examiner
	No classified search performed.		

* 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: EAST, PALM	05/03/2018	JW
EAST: See attached	05/03/2018	JW
SciFinder: See attached	05/03/2018	JW

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(tenofovir adj alafenamide and emtricitabine and bictegravir).clm.	04/23/2019	JW

/JESSICA N WORSHAM/ Primary Examiner, Art Unit 1615	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

CPC											
Symbol									Type	Version
A61K	/	9	/	209					F	2013-01-01
A61K	/	9	/	2054					I	2013-01-01
A61K	/	31	/	513					I	2013-01-01
A61K	/	31	/	675					I	2013-01-01
A61K	/	31	/	553					I	2013-01-01
A61K	/	9	/	2086					I	2013-01-01
A61P	/	31	/	18					I	2018-01-01
A61K	/	9	/	0053					I	2013-01-01
A61K	/	9	/	2013					I	2013-01-01
A61K	/	9	/	2095					I	2013-01-01
A61K	/	9	/	28					I	2013-01-01
A61K	/	31	/	5365					I	2013-01-01

CPC Combination Sets										
Symbol							Type	Set	Ranking	Version
A61K	/	31	/	513			I	1	1	2013-01-01
A61K	/	2300	/	00			I	1	2	2013-01-01
A61K	/	31	/	553			I	2	1	2013-01-01
A61K	/	2300	/	00			I	2	2	2013-01-01
A61K	/	31	/	675			I	3	1	2013-01-01
A61K	/	2300	/	00			I	3	2	2013-01-01

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	21 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20191121

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1894 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	5365
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	21 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20191121

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1895 of 1915

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/346,335	Collman et al.
	Examiner	Art Unit
	JESSICA WORSHAM	1615

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		10		19		28		37		46	10	55		
2	2		11		20		29		38		47				
3	3		12		21		30		39		48				
4	4		13		22		31		40		49				
5	5		14		23		32		41		50				
	6		15		24		33		42		51				
	7		16		25		34		43	8	52				
	8		17	6	26		35		44	9	53				
	9		18	7	27		36		45		54				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	10	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	21 November 2019	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20191121

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1040
1896 of 1915

PTO/SB/08a (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature	/JESSICA WORSHAM/	Date Considered	11/21/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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: _November 13, 2019_____ Signature: _/Donna Johnson Gressler/_____ (Donna Johnson Gressler)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

PTO/SB/08b (07-09)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	J. N. Worsham
Attorney Docket Number	1147.P2C

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Office Action dated 2019-09-22 for Gulf Cooperation Council Appl. No. 2016-32320.	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	11/21/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

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

Nov 27, 2019 03:49:35 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.
15346335	NOA	11/27/2019	1147.P2C
	1449	11/27/2019	1147.P2C

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:

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

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

25000 7590 11/27/2019
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Trent Bastian	(Typed or printed name)
/Trent Bastian/	(Signature)
December 13, 2019	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	11/08/2016	Benjamin Micah Coltman	1147.P2C	1307

TITLE OF INVENTION: Therapeutic Compositions for Treatment of Human Immunodeficiency Virus

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	02/27/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
WORSHAM, JESSICA N	1615	424-465000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively.
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Gilead Sciences, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Foster City, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 07-1250

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Donna Johnson Gressler/ Date December 13, 2019

Typed or printed name Donna Johnson Gressler Registration No. 45,544

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Cipla v. Gilead **IPR2025-00033** **Petitioner Exhibit 1040**
1900 of 1915

Electronic Patent Application Fee Transmittal				
Application Number:	15346335			
Filing Date:	08-Nov-2016			
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus			
First Named Inventor/Applicant Name:	Benjamin Micah Collman			
Filer:	Donna Johnson Gressler/Trent Bastian			
Attorney Docket Number:	1147.P2C			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1000

Electronic Acknowledgement Receipt	
EFS ID:	38023442
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
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.P2C
Receipt Date:	13-DEC-2019
Filing Date:	08-NOV-2016
Time Stamp:	12:34:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E2019BCC35068825
Deposit Account	071250
Authorized User	Trent Bastian
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37 CFR 1.19 (Document supply fees)

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37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	1147P2C_2019-12-13_Issue_Fee_Payment.PDF	148991 52a3aeea4f4c93a70b690fc868ba514ee4a2d65a	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30506 d5a119fc0174add3ec84d1d056eee30577055df1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	179497		

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.

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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.

PTO/SB/08a (07-09)
Approved for use through 07/31/2016. OMB 0651-0031
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	15/346,335
Filing Date	November 8, 2016
First Named Inventor	Benjamin Micah Collman
Art Unit	1615
Examiner Name	Jessica N. Worsham
Attorney Docket Number	1147.PC

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AT	US-2017/0000807-A1	01-05-2017	Koziara et al.	
	AU	US-8,841,310	09-23-2014	~~Janssen R & D Ireland~~	Stoffels
	AV	US-2014/0349971-A1	11-27-2014	~~Janssen R & D Ir~~eland	Stoffels
	AW	US-2008/0200435-A1	08-21-2008	~~Janssen R & D Ireland~~	Stoffels
	AX	US-2015/0283135-A1	10-08-2015	~~Janssen R & D Ireland~~	Stoffels
	AY	US-2014/0142070-A1	05-22-2014	Delaet et al.	
	AZ	US-8,598,185	12-03-2013	Dahl et al.	
	AA1	US-9.018,192	04-28-2015	Dahl et al.	
	AB1	US-9,545,414	01-17-2017	Dahl et al.	
	AC1	US-2017-0079999-A1	03-23-2017	DAHL et al.	

Change(s) applied to document, /D.C./ 6/12/2019

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BG	WO-2015/196116-A1	12-23-2015	Gilead Sciences, Inc.		
	BH	WO-2013/116720-A1	08-08-2013	Gilead Sciences, Inc		
	BI	WO-2015/022351-A1	02-19-2015	Ratiopharm Gmbh		

Examiner Signature	/JESSICA WORSHAM/	Date Considered	05/04/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

805749.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/346,335	02/04/2020	10548846	1147.P2C	1307

25000 7590 01/15/2020

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Benjamin Micah Collman, Foster City, CA;
Gilead Sciences, Inc., Foster City, CA;
Lei Hong, Cupertino, CA;
Joanna M. Koziara, Foster City, CA;

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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

Jan 16, 2020 03:46:07 AM

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

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

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Application	Document	Mailroom Date	Attorney Docket No.
15346335	ISSUE.NTF	01/15/2020	1147.P2C

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:

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

Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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: March 5, 2020 Signature: /Trent Bastian/ (Trent Bastian)

Docket No.: 1147.P2C
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Patent No.: 10,548,846

Issued: February 4, 2020

For: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.323

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted a typographical error which should be corrected.

In claim 9, column 77, last line of granted U.S. Patent 10,548,846, please correct "alafenamine" to "alafenamide".

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Applicant believes a fee is due under 37 CFR 1.20(a). Please charge our Deposit Account No. 07-1250, under Order No. 1147.P2C from which the undersigned is authorized to draw. The Director is hereby authorized to charge any additional fees which may be required with respect to this communication, or credit any overpayment, to Deposit Account No. 07-1250, under Order No. 1147.P2C.

Dated: March 5, 2020

Respectfully submitted,

Electronic signature: /Donna Johnson Gressler/
Donna Johnson Gressler
Registration No.: 45,544
GILEAD SCIENCES, INC.
(650) 574-3000
Agent For Applicant

PTO/SB/44 (09-07)
Approved for use through 01/31/2020. OMB 0651-0033
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	10,548,846
APPLICATION NO.	:	15/346,335
ISSUE DATE	:	February 4, 2020
INVENTOR(S)	:	Benjamin Micah Collman et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims:

Claim 9, column 77, last line, please replace:

"alafenamine"

With:

"alafenamide"

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Donna Gressler
GILEAD SCIENCES, INC.
333 Lakeside Drive
Foster City, California 94404

Electronic Patent Application Fee Transmittal				
Application Number:	15346335			
Filing Date:	08-Nov-2016			
Title of Invention:	Therapeutic Compositions for Treatment of Human Immunodeficiency Virus			
First Named Inventor/Applicant Name:	Benjamin Micah Collman			
Filer:	Donna Johnson Gressler/Trent Bastian			
Attorney Docket Number:	1147.P2C			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
CERTIFICATE OF CORRECTION	1811	1	150	150

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	150

Electronic Acknowledgement Receipt	
EFS ID:	38776293
Application Number:	15346335
International Application Number:	
Confirmation Number:	1307
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.P2C
Receipt Date:	05-MAR-2020
Filing Date:	08-NOV-2016
Time Stamp:	11:07:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$150
RAM confirmation Number	E202035B08009352
Deposit Account	071250
Authorized User	Trent Bastian
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 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)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	1147P2C_2020-03-03_Request_for_Certificate_of_Correction.pdf	83405 ea5089e4ee8fef072ec68553a1af0569bd82...8c5f	no	2
Warnings:					
Information:					
2	Request for Certificate of Correction	1147P2C_2020-03-05_Certificate_of_Correction.pdf	83412 6ee78901f3ad5792f5afaf72e09e876d56a8...e4af	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30481 720366deb785f7fa976d1dc4e4ab1fd8c61...172d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	197298		

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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
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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 10,548,846 B2
APPLICATION NO.	: 15/346335
DATED	: February 4, 2020
INVENTOR(S)	: Benjamin Micah Collman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Claim 9, Column 77, last line, please replace:
"alafenamine"
With:
"alafenamide"

Signed and Sealed this
Seventh Day of April, 2020

Andrei Iancu
Director of the United States Patent and Trademark Office