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03170

특 허 청 의견제출통지서

출 원 인 성 명 김리애드 사이언시즈, 인코포레이티드 (특허고객번호:
 519990290219)
 주 소 미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브
 333
 대 리 인 성 명 양영준 외 1 명
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 333 김리애드 사이언시즈, 인코포레이티드 내
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 333 김리애드 사이언시즈, 인코포레이티드 내
 발 명 자 성 명 코지아라, 조안나 엠.
 주 소 미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브
 333 김리애드 사이언시즈, 인코포레이티드 내
 출 원 번 호 10-2020-7025458
 출 원 일 자 2020.09.03.
 발 명 의 명 칭 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(2022.02.23.)까지 의견(답변, 소명)서[특허법시행규칙 별지 제24호서식] 또는/및 보정서[특허법시행규칙 별지 제9호서식]를 제출하여 주시기 바랍니다.

2. 상기 제출기일(2022.02.23.)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 : 제1항

☐ 이 출원의 거절이유가 있는 부분과 관련 법조항

순번	거절이유가 있는 부분	관련 법조항
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1	청구항 제1항	특허법 제29조제2항
2	청구항 제1항	특허법 제42조제4항제2호

[구체적인 거절이유]

1. 이 출원의 청구범위의 청구항 제1항에 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 -

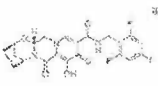
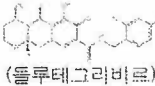
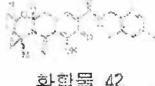
인용발명 1 : 국제공개공보 WO2015/022351(2015.02.19.)

인용발명 2 : 국제공개공보 WO2014/100323(2014.06.26.)

인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.)

1-1. 제1항은 '화학식 1의 화합물 또는 그의 제약상 허용되는 염', '테노포비르 알라페나미드 또는 그의 제약상 허용되는 염' 및 '엠트리시타빈 또는 그의 제약상 허용되는 염'을 포함하는 '고체 경구 투여 형태의 용도'입니다.

제1항을 인용발명 1 내지 3과 대비하면 다음과 같습니다.

구분	제1항	인용발명 1	인용발명 2	인용발명 3
화합물 성분		 (돌루테그리비르)	 화합물 42	엘비테그라비르
	테노포비르 알라페나미드의 염	테노포비르 디소프록살 푸마레이트	(-)	테노포비르 알라페나미드 푸마레이트
	엠트리시타빈	엠트리시타빈	(-)	엠트리시타빈
제형	고체 경구 투여 형태	정제	(-)	정제

먼저, 제1항을 인용발명 1과 대비하면, 인테그라아제 억제 활성을 가지는 HIV 억제용 물질, 테노포비르의 전구체 및 엠트리시타빈을 함유하는 제형인 점이 동일합니다.

다만, 제1항은 인테그라아제 억제 활성 물질이 화학식 1의 화합물인 점 및 테노포비르 전구체로 테노포비르 알라페나미드를 사용하는 점에서 인용발명 1과 차이가 있습니다.

그런데, 인용발명 2에 화학식 1의 화합물이 인테그라아제 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 1 화합물을 선택하여 인용발명 1의 돌루테그리비르를 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 알라페나이드 푸마레이트(TAF)를 포함하고 있고, 흡수촉진제인 코바시스타트가 부가될 때 10 mg의 TAF는 25mg의 TAF와 동등하다고 기재되어 있으므로(제53면, 좌측열 단락 2 내지 4 참조), 통상의 기술자가 인용발명 1의 테노포비르 디소프록실 푸마레이트를 TAF로 쉽게 치환할 수 있습니다.

그리고 제1항의 효과를 살펴보면, 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.

2. 이 출원은 청구범위의 청구항 제1항의 기재가 아래에 지적한 바와 같이 불비하여 특허법 제42조제4항제2호에 따른 요건을 충족하지 못하므로 특허를 받을 수 없습니다.

- 아 래 -

제1항은 청구항의 말미를 '용도'로 기재하고 있어서 특허법제2조에서 정의하고 있는 발명의 종류인 물건, 방법, 제조방법의 발명 중 어느 것에도 해당하지 않아서 발명이 보호받고자 하는 사항을 명확하고 간결하게 기재하지 않은 것입니다('의약품'을 청구하는 경우에는 이 기술분야에서 통상적으로 사용되는 ' ~ '를 유효성분으로 포함하는, ~를 치료하기 위한 약학적 조성물'과 같이 기재하여야 합니다).

【참 부】

첨부1 국제공개공보 W02015/022351(2015.02.19.) 1부.

첨부2 국제공개공보 W02014/100323(2014.06.26.) 1부.

첨부3 J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.) 1부, 끝.

2021. 12. 23.

특허청

화학생명기술심사국

약품화학심사과

심사관 곽희찬

곽희찬

<< 안내 >>

1. 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 출원인변경신청서를 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

※ 심사청구로 일부 반환 안내 : 처음으로 통지되는 의견제출통지서의 의견제출기한 만료 전까지 출원을 취하(또는 포기)하는 경우 출원인은 심사청구료의 3분의 1에 해당하는 금액을 반환신청할 수 있습니다. (2021. 11. 18.부터 시행)

※ 위에서 안내한 후속 절차 또는 신청 서식 등에 관한 사항은 특허고객상담센터 ☎1544-8080로, 이 통지서 내용에 대한 사항은 특허청 ☎042-481-3327(담당심사관 곽희찬)로 문의하시기 바랍니다.

※ 특허로(www.patent.go.kr) 또는 특허청(www.kipo.go.kr) 홈페이지를 방문하시면 심시 진행 상황, 서류 제출 및 절차에 관한 보다 많은 정보를 제공받을 수 있습니다.
(특허청) 우 35208 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)

KIPO'S NOTICE OF PRELIMINARY REJECTION
(ENGLISH TRANSLATION)

RESULTS OF KIPO EXAMINATION -- SUMMARY

- Examined Claims, Claim 1
- Rejected Portions and Relevant Provisions

No.	Rejected Portions	Relevant Provisions - Grounds
1	Claim 1	Article 29(2) - Inventiveness
2	Claim 1	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 Claim 1 lack inventiveness, as set forth below.**

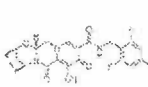
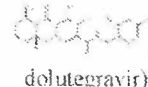
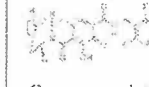
Cited Reference 1: WO 2015/022351 (February 19, 2015)

Cited Reference 2: WO 2014/100323 (June 26, 2014)

Cited Reference 3: *J. Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp 52-58
(September 1, 2014)

- 1-1. **Claim 1** is directed to 'use of a solid oral dosage form' comprising 'a compound of Formula 1 or a pharmaceutically acceptable salt thereof,' 'tenofovir alafenamide or a pharmaceutically acceptable salt thereof,' and 'emtricitabine or a pharmaceutically acceptable salt thereof.'

Claim 1 is compared with Cited References 1-3 in the table below.

	Claim 1	Cited Reference 1	Cited Reference 2	Cited Reference 3
Active ingredients		 (dolutegravir)	 Compound 42	elvitegravir
	a salt of tenofovir alafenamide	tenofovir disoproxil fumarate	(-)	tenofovir alafenamide fumarate
	emtricitabine	emtricitabine	(-)	emtricitabine
Formulation	solid oral dosage form	tablet	(-)	tablet

Firstly, Claim 1 is identical to Cited Reference 1 in that they relate to a formulation containing an HIV inhibitor having an integrase inhibitory activity, a tenofovir precursor, and emtricitabine.

Claim 1 only differs from Cited Reference 1 in using a compound of Formula I as an integrase inhibitory activity material and 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, and good bioavailability (*see* Tables 1-4, etc.). Accordingly, a person of ordinary skill in the art would not have had difficulty in selecting a compound of Formula I and substituting the dolutegravir of Cited Reference 1 with the compound.

Cited Reference 3 also discloses a tablet containing elvitegravir as an integrase inhibitor, a tenofovir precursor, and emtricitabine and describes that the tablet comprises tenofovir alafenamide fumarate (TAF) which is more safe and effective than tenofovir disoproxil fumarate and 10 mg TAF in the presence of cobicistat which boosts absorption is equivalent to 25 mg TAF (*see* p.53, left column, paragraphs 2-4). Accordingly, a person of ordinary skill in the art could have easily substituted the tenofovir disoproxil fumarate of Cited Reference 1 with TAF.

Upon review of the effect of Claim 1, it can only be known from the specification that three types of drugs can be formulated as a single tablet, and there is no ground supporting that the claimed dosage form exhibits a remarkably excellent anti-HIV effect which a person of ordinary skill in the art cannot predict from Cited References 1-3.

Thus, Claim 1 could have been easily conceived by a person of ordinary skill in the art in view of Cited References 1-3.

2. The present application cannot be allowed because Claim 1 fails to meet the requirements under Article 42(4)(ii) of the Korean Patent Act, as set forth below.

Claim 1 commences with 'use,' which does not correspond to any of the invention types defined by Article 2 of the Korean Patent Act, a product, a method, and a preparation process. Thus, said claim fails to clearly and concisely describe the subject matter seeking protection (in case of a claim claiming 'medicinal use,' the claim should be described in a commonly used format, for example, 'a pharmaceutical composition for treating ~ comprising ~ as an active ingredient').

[Documents Annexed]

1. WO 2015/022351 (February 19, 2015)
2. WO 2014/100323 (June 26, 2014)

Korean Patent Application No. 10-2020-7025458
Your Ref.: 1147-KR-P2D
Enclosure Page 3

3. *J. Acquir. Immune Defic. Syndr.*, Vol. 67, No. 1, pp 52-58 (September 1, 2014)

[==== End of Translation ====]

발송번호: 9-5-2023-027546139
 발송일자: 2023.03.23.
 제출일자: 2023.05.23.

수신 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
 양영준 귀하(귀중)

03170

특 허 청 의견제출통지서

출 원 인 성 명 김리애드 사이언스즈, 인코포레이티드 (특허고객번호: 519990290219)
 주 소 미국 캘리포니아 94404 포스터 시티 레이크사이드 드라이브 333
 대 리 인 성 명 양영준 외 1 명
 주 소 서울특별시 종로구 사직로8길 39, 세양빌딩 (내자동) 5층(김.장법률사무소)
 발 명 자 성 명 홍, 레이
 주 소 미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 김리애드 사이언스즈, 인코포레이티드 내
 발 명 자 성 명 클랜, 벤자민, 미카
 주 소 미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 김리애드 사이언스즈, 인코포레이티드 내
 발 명 자 성 명 코지아라, 조안나 램.
 주 소 미국 94404 캘리포니아주 포스터 시티 레이크사이드 드라이브 333 김리애드 사이언스즈, 인코포레이티드 내
 출 원 번 호 10-2023-7001933
 출 원 일 자 2023.01.17.
 발 명 의 명 칭 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 제출일자(2023.05.23.)까지 의견(답변, 소명)서[특허법시행규칙 별지 제24호서식] 또는/및 보정서[특허법시행규칙 별지 제9호서식]를 제출하여 주시기 바랍니다.

2. 상기 제출일자(2023.05.23.)를 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 : 제1항

☐ 이 출원의 거절이유가 있는 부분과 관련 법조항

순번	거절이유가 있는 부분	관련 법조항
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1	청구항 전항	특허법 제29조제2항
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[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 -

특허요건판단 기준일: 2015.11.09.

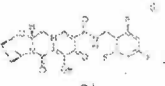
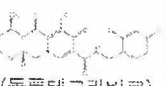
인용발명 1 : 국제공개공보 WO2015/022351(2015.02.19.)

인용발명 2 : 국제공개공보 WO2014/100323(2014.06.26.)

인용발명 3 : J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.)

1-1. 제1항은 '제약상 허용되는 염으로서, 50 mg의 화학식 1의 화합물; 제약상 허용되는 염으로서, 25 mg의 테노포비르 알라페나이드, 및 200 mg의 엠트리시타빈 또는 그의 제약상 허용되는 염을 포함하는 정제'입니다.

제1항을 인용발명 1 내지 3과 대비하면 다음과 같습니다.

구분	제1항	인용발명 1	인용발명 2	인용발명 3
활성 성분	 의 염	 (돌루테그라비르)	 화합물 42	엘비테그라비르
	테노포비르 알라페나이드의 염	테노포비르 디소포록실 푸마레이트	(-)	테노포비르 알라페나이드 푸마레이트
	엠트리시타빈	엠트리시타빈	(-)	엠트리시타빈
제형	정제	정제	(-)	정제

먼저, 제1항을 인용발명 1과 대비하면, 인테그라아제 억제 활성을 가지는 HIV 억제용 물질, 테노포비르의 전구체 및 엠트리시타빈을 함유하는 정제인 점이 같습니다.

다만, 제1항은 인테그라아제 억제 활성 물질이 ①화학식 1의 화합물인 점, ②테노포비르 전구체로 테노포비르 알라페나이드를 사용하는 점, ③각 활성성분의 함량을 특정한 점에서 인용발명 1과 차이가 있습니다.

①그런데, 인용발명 2에 화학식 1의 화합물이 인테그라아제 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

항)가 화학식 I 화합물을 선택하여 인용발명 1의 올루테그라비르를 치환하는 것에 어려움이 없다고 판단됩니다.

②또한, 인용발명 3에도 인테그라아제 억제 물질인 올비테그라비르, 테노포비르 전구체 및 엔트리카타빈을 함유하는 정제가 개시되어 있는데, 그 정제는 테노포비르 디소프록실 푸마레이트에 비하여 안전하고 효과적인 테노포비르 알라페나미드 푸마레이트(TAF)를 포함하고 있고, 흡수촉진제인 코비시스타트기 부가물 때 10 mg의 TAF는 25mg의 TAF와 동등하다고 기재되어 있으므로(제53면, 좌측열 단락 2 내지 4 참조), 통상의 기술자가 인용발명 1의 테노포비르 디소프록실 푸마레이트를 TAF로 쉽게 치환할 수 있습니다.

③그리고, 약리효과를 고려하여 단순 반복적인 시험을 통해 그 함량을 도출해 보는 것 또한 이 기술분야에서 통상적으로 시도되는 기술상식입니다.

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.

[참 부]

첨부1 국제공개공보 W02015/022351(2015.02.19.) 1부.

첨부2 국제공개공보 W02014/100323(2014.06.26.) 1부.

첨부3 J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp52-58 (2014.09.01.) 1부.
끝.

2023.03.23.

특허청

화학생명기술심사국

약품화학심사과

심사관 박희찬


 박희찬

<< 안내 >>

1. 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
- ※ 심사청구료 일부 반환 안내 : 처음으로 통지되는 의견제출통지서의 의견서제출기한 만료 전까지 출원을 취하(또는 포기)하는 경우 출원인은 심사청구료의 3분의 1에 해당하는 금액을 반환신청할 수 있습니다. (2021. 11. 18. 부당 시행)
- ※ 위에서 안내한 후속 절차 또는 신청 서식 등에 관한 사항은 특허고객상담센터 ☎1544-8080로, 이 통지서 내용에 대한 사항은 특허청 약품화학심사과 ☎042-481-5490(대표번호)로 문의하시기 바랍니다.
- ※ 특허로(www.patent.go.kr) 또는 특허청(www.kipo.go.kr) 홈페이지를 방문하시면 심시 진행 상황, 서류 제출 및 절차에 관한 보다 많은 정보를 제공받을 수 있습니다.
 (특허청) 우 35208 대전광역시 서구 청사로 189, 4동 (둔산동, 정부대전청사)

KIPO'S NOTICE OF PRELIMINARY REJECTION
(ENGLISH TRANSLATION)

RESULTS OF KIPO EXAMINATION -- SUMMARY

- Examined Claims: Claim 1
- Rejected Portions and Relevant Provisions

No.	Rejected Portions	Relevant Provisions - Grounds
1	Claim 1	Article 29(2) - Inventiveness

EXAMINER'S DETAILED GROUNDS FOR REJECTION

- 1. The present application cannot be allowed under Article 29(2) of the Korean Patent Act because Claim 1 lacks inventiveness, as set forth below.**

Reference date for judging patentability: **November 9, 2015**

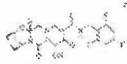
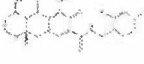
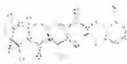
Cited Reference 1: WO 2015/022351 (February 19, 2015)

Cited Reference 2: WO 2014/100323 (June 26, 2014)

Cited Reference 3: J. Acquir. Immune Defic. Syndr., Vol. 67, No. 1, pp 52-58
(September 1, 2014)

- 1-1. **Claim 1** is directed to 'a tablet comprising 50 mg of a compound of Formula 1: as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.'

Claim 1 is compared with Cited References 1-3 in the table below.

	Claim 1	Cited Reference 1	Cited Reference 2	Cited Reference 3
Active ingredient	a salt of 	 (dolutegravir)	 compound 42	elvitegravir
	salt of tenofovir alafenamide	tenofovir disoproxil fumarate	(-)	tenofovir alafenamide fumarate
	emtricitabine	emtricitabine	(-)	emtricitabine

Formulation	tablet	tablet	(-)	tablet
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Firstly, upon comparison, **Claim 1** is identical to **Cited Reference 1** in that they relate to a tablet containing a substance for HIV inhibition having an integrase inhibitory activity, a tenofovir precursor, and emtricitabine.

Claim 1 only differs from Cited Reference 1 in that ① the substance having integrase inhibitory activity is a compound of Formula 1, ② tenofovir alafenamide is used as a tenofovir precursor, and ③ the amount of each active ingredient is specified.

① However, **Cited Reference 2** discloses a compound of Formula 1 as an integrase inhibitor (*see* compound 42), indicating that this compound has properties suitable for drug development, such as excellent HIV inhibitory activity, low cytotoxicity, and good bioavailability (*see* Tables 1-4, etc.). Accordingly, a person of ordinary skill in the art would not have difficulty in selecting a compound of formula 1 and substituting dolutegravir of Cited Reference 1 with said compound.

② **Cited Reference 3** also discloses a tablet containing elvitegravir as an integrase inhibitor, a tenofovir precursor, and emtricitabine, and describes that the tablet comprises tenofovir alafenamide fumarate (TAF) which is more safe and effective than tenofovir disoproxil fumarate and 10 mg TAF in the presence of cobicistat which boosts absorption is equivalent to 25 mg TAF (*see* p.53, left column, paragraphs 2-4). Accordingly, a person of ordinary skill in the art could have easily substituted the tenofovir disoproxil fumarate of Cited Reference 1 with 25 mg TAF.

③ In addition, deriving the amount thereof through simple and repetitive tests in consideration of pharmacological effect is conventional technical knowledge in the art.

Upon review of the effect of Claim 1, it can only be known from the specification that three types of drugs can be formulated as a single tablet, and there is no ground recognizing that said claim exhibits remarkably superior anti-HIV effects which a person of ordinary skill in the art cannot predict from Cited References 1-3.

Thus, **Claim 1** could have readily been conceived from **Cited References 1-3** by a person of ordinary skill in the art.

[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, pp 52-58 (September 1, 2014)

[=== End of Translation ===]



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NOTICE OF ALLOWANCE AND FEE(S) DUE

25000 7590 06/01/2023
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER

WORSHAM, JESSICA N

ART UNIT PAPER NUMBER

1615

DATE MAILED: 06/01/2023

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Colman	1147-US-P2C2DC	2232

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	\$1200	\$0.00	\$0.00	\$1200	09/01/2023

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize expediency.**

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

25000 7590 06/01/2023
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.
17738.803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

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	\$1200	\$0.00	\$0.00	\$1200	09/01/2023

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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, _____ 1

(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. _____ 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)

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

☐ Electronic Payment via Patent Center or 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. _____



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.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232
EXAMINER				
WORSHAM, JESSICA N				
ART UNIT			PAPER NUMBER	
1615				

DATE MAILED: 06/01/2023

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.

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. 17/738,803	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

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 April 2023.
☐ 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 52-64. 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 <u>4/20/23</u> . 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

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 20 April 2023 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.

Terminal Disclaimer

2. The terminal disclaimer filed on 5 April 2023 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **U.S. Patent No. 10,548,846** has been reviewed and is accepted. The terminal disclaimer has been recorded.

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 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 Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center

Application/Control Number: 17/738,803
Art Unit: 1615

Page 4

and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Issue Classification 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 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	/	2027	I	2013-01-01
A61K	/	9	/	2833	I	2013-01-01
A61K	/	31	/	537	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

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)	13		
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	18 May 2023	O.G. Print Claim(s)	O.G. Print Figure	
(Primary Examiner)	(Date)	1	None	

U.S. Patent and Trademark Office

Part of Paper No.: 20230518

Issue Classification 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 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)	13	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	18 May 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20230518

Issue Classification 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 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		10		19		28		37		46	4	55	13	64
	2		11		20		29		38		47	5	56		
	3		12		21		30		39		48	6	57		
	4		13		22		31		40		49	7	58		
	5		14		23		32		41		50	8	59		
	6		15		24		33		42		51	9	60		
	7		16		25		34		43	1	52	10	61		
	8		17		26		35		44	2	53	11	62		
	9		18		27		36		45	3	54	12	63		

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 13	
JESSICA WORSHAM/ Primary Examiner, Art Unit 1615 (Primary Examiner) _____ (Date) 18 May 2023		O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20230518

Search Notes 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 1615

CPC - Searched*		
Symbol	Date	Examiner
(A61K9/209 or A61K9/0053 or A61K9/2013 or A61K9/2027 or A61K9/2054 or A61K9/2086 or A61K9/2095 or A61K9/28 or A61K9/2833 or A61K31/513 or A61K31/5365 or A61K31/537 or A61K31/553 or A61K31/675 or A61P31/18 or A61K9/282 or A61K9/20 or A61K2300/00).cpc.	04/12/2023	JW

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: PE2E, PALM	12/01/2022	JW
PE2E: See attached	12/01/2022	JW
SciFinder: See attached	12/01/2022	JW
PE2E: See attached	04/12/2023	JW

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	
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Search Notes 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 1615

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(emtricitabine and tenofovir and tablet and bictegravir).clm.	04/12/2023	JW

JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	
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PTO/SB/08b (07-09)

Approved for use through 05/31/2024. 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 <i>(Use as many sheets as necessary)</i>		Complete if Known			
		Application Number	17/738,803		
		Filing Date	May 6, 2022		
		First Named Inventor	Benjamin Micah Collman		
		Art Unit	1615		
		Examiner Name	J. N. Worsham		
Sheet	2	of	2	Attorney Docket Number	1147-US-P2C2DC

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 2021-12-23 for Korean Appl. No. 10-2020-7025458, 7 pages.	√
	CB	Notice of Preliminary Rejection dated 2023-03-23 for Korean Appl. No. 10-2023-7001933, 6 pages.	√

Examiner Signature	/JESSICA WORSHAM/	Date Considered	05/18/2023
--------------------	-------------------	-----------------	------------

*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.

#5041500V1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

TO: IPDocketing@gilead.com,IPUS2@gilead.com
FROM: noreply@uspto.gov
CC: patentcenter_eofficeaction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - Correspondence Notification for Customer Number 25000

Thu Jun 01 05:29:10 EDT 2023

Dear Patent Center Customer:

Correspondence Address:

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

This is a courtesy notification regarding the following USPTO patent application(s) associated with your Customer Number, 25000, that have new outgoing correspondence. This correspondence is now available for viewing in Patent Center.

The official date of notification of the outgoing correspondence will be indicated on the form (e.g., PTOL-90) accompanying the correspondence.

Disclaimer:

The list of documents shown below are provided as a courtesy and is not part of the official file wrapper. The content of the images shown in the Image File Wrapper is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
17738803	NOA	06/01/2023	1147-US-P2C2DC
17738803	1449	06/01/2023	1147-US-P2C2DC

To view your correspondence online, please sign in to [Patent Center](#) and then select Workbench/View correspondence. To update your email address(es), select Manage/Manage customer numbers.

If you have any questions, please contact the [Patent Electronic Business Center](#) (EBC) at ebc@uspto.gov or 866-217-9197 Monday – Friday, 6 a.m. to midnight ET.

Please do not reply to this email as it was sent from an unmonitored mailbox.

Sincerely,

The Patent Center Team

Doc code: RCEX

Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)

Approved for use through 05/31/2024, OMB 0851-0031

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL (Submitted Only via EFS-Web)					
Application Number	17738803	Filing Date	2022-05-06	Docket Number (if applicable)	1147-US-P2C2DC
				Art Unit	1615
First Named Inventor	Benjamin Micah Collman			Examiner Name	J. N. Worsham
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. The Instruction Sheet for this form is located at WWW.USPTO.GOV					
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☐ 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) ☐ Other _____					
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The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed. ☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No <u>071250</u>					
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Cipla v. Gilead

IPR2025-00033

 Petitioner Exhibit 1002
 843 of 1074

Doc code: RCEX

Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)

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Cipla v. Gilead

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Petitioner Exhibit 1002
844 of 1074

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Datum/Date
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Zeichen/Reference/Référence	
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Gilead Sciences, Inc.	

Appeal number: T0355/23-3.3.07

Please find enclosed a copy of the statement setting out the grounds of Appeal filed by Opponent 01 (Teva Pharmaceutical Industries Ltd.), Opponent 02 (Dr. Richard Cooke) and Opponent 03 (Sandoz GmbH).

Any reply must be filed within **4 months** of this notification.

The Registry B. Aienza Vivancos
Tel.: 089 / 2399 - 3371

Annex(es):

- Letter of Opponent 01 dated 25.04.2023
- Letter of Opponent 02 dated 02.05.2023
- Letter of Opponent 03 dated 28.04.2023

Registered letter



EPO Form 3344

01/11



ELKINGTON + FIFE

European patent no. 3 346 995

(application no. 16798063.0)

Gilead Sciences, Inc.

Opponent: Dr Richard Cooke

Grounds of appeal

1. Requests

(01) The opposition division decided that the patent should be maintained in amended form in accordance with AR1 filed on 26.08.2022.

(02) We request that the decision be set aside and the patent be revoked in its entirety.

(03) We request oral proceedings before the board reaches any other decision.

2. Main request

(04) The opposition division refused the patentee's main request for lack of compliance with Article 123(2) EPC. For completeness, on the assumption that the patentee will also appeal, we will provide comments on this request.

2.1 Added subject-matter (Articles 123(2) and 100(a) EPC)

(05) Claim 1 of the main request relates to a tablet comprising:

- 50 mg bicitgravir or a salt thereof;
- 25 mg tenofovir alafenamide or a salt thereof; and
- 200 mg emtricitabine or a salt thereof.

(06) At the oral proceedings, the patentee's arguments were restricted to basis at claim 7 of the application as filed, which relates to a tablet including the same components but which in addition is coated.

(07) According to the patentee, a generalisation of this claim is permissible in accordance with the test in the Guidelines (H-V, 3.2.1) because the deleted feature is not related or inextricably linked to the other features of the embodiment and the overall disclosure justifies its isolation.

(08) We think that this section of the Guidelines for Examination is not pertinent, as it relates to isolating a feature from an embodiment in the application and introducing that feature to a more generally defined claim. However, the present situation involves deleting a feature from an embodiment, which is discussed in a different part of the Guidelines for Examination (H-V, 3.1). This passage of the Guidelines for Examination refers to the three-part test (T 331/87), with some

minor modifications, but then notes that regardless of the outcome of that test any amendment must comply with the gold standard. The general recent position of the boards appears to be that the three-part test is necessary but not sufficient for compliance with Article 123(2) EPC, and therefore added subject-matter should be assessed only by reference to the gold standard (Case Law, II.E.1.4.4).

(09) In the present case, the gold standard is not satisfied. The application teaches the skilled person that when the tablet includes the claimed amounts of the compounds and their salts, that the tablets must in addition have a coating (claim 7). The patentee referred to the passage of the description which states that in certain embodiments the tablets are coated and in other embodiments the tablets are not coated (paragraph 71). However, this does not assist the patentee, because the embodiment described by claim 7 is one in which the tablet is coated.

(10) The skilled person would understand that the coating was required in the embodiment of claim 7, and therefore the requirements of Article 123(2) EPC are not fulfilled.

2.2 Novelty and inventive step (Articles 100(a), 54 and 56 EPC)

(11) The main request is broader than AR1 and therefore lacks novelty and inventive step for the same reasons at least. Therefore, we refer to our arguments for that request.

3. Auxiliary request 1

(12) AR1 includes two independent claims. Claim 1 is limited, relative to claim 1 as granted, in that bictegravir and tenofovir alafenamide are present as salts, and emtricitabine is present as the free compound (i.e., is not a salt). Claim 4 is limited, relative to claim 1 as granted, in that the tablet must be coated.

3.1 Lack of novelty over D1 (Articles 100(a) and 54 EPC)

(13) As the decision notes, D1 (WO 2015/196116) was filed on 19.06.2015, before the earliest priority date of the patent (09.11.2015), and validly entered the European regional phase (D1a). Thus, D1 is relevant for the consideration of novelty under Article 54(3) EPC even if the patent is entitled to the earliest priority date.

(14) D1 discloses a combination including a compounds disclosed therein with further pharmaceutical agents, including particular amounts of tenofovir alafenamide or salts thereof and emtricitabine (D1, paragraph 96):

tenofovir alafenamide and 200 mg emtricitabine. In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed.

(15) Thus, this single embodiment of D1 discloses:

- a "compound disclosed herein"
- 25 mg tenofovir alafenamide (as fumarate, hemifumarate or free compound); and
- 200 mg emtricitabine.

(16) The most preferred "compound disclosed herein" is bictegravir sodium (see claim 1 of D1). Therefore, no selection is required to choose this compound. The amounts of the compound are defined later in paragraph [0096] to be 50 mg to 500 mg, and for the purposes of the argument we will accept that choosing the lower limit of this range requires a (single) selection.

(17) The most preferred form of tenofovir alafenamide is the hemifumarate salt and the most preferred form of emtricitabine is the free compound (claim 19):

19. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide hemifumarate and emtricitabine.

(18) Moreover, the above passage refers to emtricitabine (i.e., the free compound), and two of the three options for tenofovir alafenamide are salts: the fumarate and the hemifumarate. A restriction of a list i.e., to remove the option that tenofovir alafenamide is the free compound is permissible without disclosing new subject-matter (see Case Law, II.E.1.6.3).

(19) Finally, the only claimed, and thus most preferred, dosage form for the compositions in D1 is a tablet:

18. The pharmaceutical composition of claim 12, further comprising tenofovir alafenamide and emtricitabine.

20. The pharmaceutical composition of any one of claims 12 to 18, wherein the pharmaceutical composition is in a unit dosage form.

21. The pharmaceutical composition of claim 20, wherein the unit dosage form is a tablet.

(20) Accordingly, the subject-matter of claim 1 is disclosed in D1 by making, at most, a single permissible selection by defining the dose of the bictegravir sodium to be 50 mg, and therefore claim 1 at least lacks novelty.

(21) The opposition division held that three selections were needed, namely to choose (i) a tablet, (ii) a salt of tenofovir alafenamide, and (iii) the dose of the bictegravir salt.

(22) We do not agree that any selection is required to choose a tablet. As discussed above, the tablet is the preferred form disclosed by D1. We note that, when considering added subject-matter, the opposition division agreed with the patentee that a tablet was preferred by the application as filed and therefore no selection was required to choose that form (fifth full paragraph on sheet 10 of the decision). The opposition division should also have held that no selection was required to define a tablet when considering D1 as prior art.

(23) The opposition division was also correct to hold that a selection must be made to choose "tenofovir alafenamide among the three possible tenofovir salts". In making this objection, the opposition appears to have misunderstood this compound. The claim relates to a salt of tenofovir alafenamide, not a salt which is tenofovir alafenamide. Tenofovir alafenamide is the free compound, not the salt: tenofovir alafenamide is a prodrug ester of tenofovir. As explained above, the three options in paragraph [0096] of D1 include two salts (the fumarate and hemifumarate) and the free compound, and this list can be permissibly restricted to the salts without making a selection -- and in any case the hemifumarate is shown to be preferred by the claims.

(24) For the purposes of the argument, we can accept that defining the dose of bictegravir sodium to be 50 mg requires a selection, but a single selection is permissible.

3.2 Lack of inventive step over D5 (Articles 100(a) and 56 EPC)

3.2.1 The closest prior art

(25) The patent relates to a triple combination of bictegravir (an integrase inhibitor), emtricitabine and tenofovir for the treatment of HIV (see paragraph [0001] of the patent).

(26) D5 relates to the combination of dolutegravir (another integrase inhibitor), emtricitabine and tenofovir (see title). These combinations were shown to be effective against HIV-1 NL4-3 and HIV-1 R263K, (see Tables 1 and 2 on pages 25 and 26).

(27) Therefore, as it also relates to triple combinations including an integrase inhibitor, emtricitabine, and tenofovir for treating HIV, D5 is a possible starting point for the assessment of inventive step.

(28) The closest embodiment in D5 is a pharmaceutical composition comprising 50 mg dolutegravir, 200 mg emtricitabine and 25 mg tenofovir alafenamide (page 19 to 20):

In an alternatively preferred embodiment the pharmaceutical composition of the present invention comprises
about 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir
(c), in particular tenofovir alafenamide, or

(29) By the oral proceedings, at least for the purposes of the argument, the patentee accepted that this embodiment of D5 could be taken as the starting point. However, in the written proceedings, the patentee argued that D5 should not be the closest prior art and, even if taken as the closest prior art, that the above embodiment would not be taken as the starting point within D5.

(30) In relation to the choice of document, the patentee argued that the closest prior art can only be a document disclosing the same three active ingredients (D37) and cannot be a document relating to a fixed-dose combination in which one of the active ingredients is different (D5).

(31) The premise of the patentee's argument – that a single closest document must be identified and that any attacks based on other documents can then be dismissed as not starting from the closest prior art – has been rejected many times by the boards (Case Law I.D.3.1; T261/19, r 2.5, citing T1742/12, r 6.3 and 6.6 and T967/97, r 3.2).

(32) There is of course therefore no rule that the closest prior art must be a document disclosing the same combination of compounds. In certain situations, the patentee's suggested test would mean that there was no possible closest prior art document and an assessment of inventive step could not take place. Indeed, D37 fails the patentee's (incorrect) test because this document does not disclose bicitgravir. Rather, this document refers to GS-9883, which was not known to be bicitgravir at the priority date.

(33) In relation to the starting point within D5, the patentee argues that the preferred compositions in D5 include a ratio of from 1:1 to 1:3 of dolutegravir to emtricitabine. Therefore, according to the patentee, because the above embodiment has a ratio of dolutegravir to emtricitabine of 1:4, the skilled person would be "guided" to other compositions which satisfy this ratio and would not select the above composition without hindsight.

(34) As an initial point, the case law is clear that the use of hindsight is permissible, and in fact essential, when determining the closest prior art (T 1443/16, r 4.3.2). This applies when selecting the most appropriate document as the starting point and when choosing the most appropriate embodiment within that document (T 72/18, r 3.9.2). The patentee's argument that the skilled person would be guided to other formulations is irrelevant. The above embodiment is feasible, and therefore can be taken as a starting point.

(35) Further, the ratio is not an essential feature of D5, which discloses compositions including active ingredient in particular ratios but also in particular amounts (page 1):

"The present invention concerns 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 treatment of viral infection/disease such as an HIV infection. Further, the present invention relates to a pharmaceutical composition comprising the pharmaceutical combination and optionally further pharmaceutical excipient(s)." (Emphasis added.)

(36) The preferred embodiment at page 19 is an example of a composition including "specific amounts" of the compounds, and therefore does not fall outside the teaching of D5.

(37) Moreover, even to the extent other embodiments in D5 are (even) more preferred, the state of the art includes all embodiments in the closest prior art, and not only those which are indicated to be preferred (T 72/18, r 3.9.3):

"3.9.3 Panobinostat is not just encompassed by the Markush formula (I) of D10. It is also disclosed as an individualised embodiment (compound 200, prepared according

to Example P3, one of three individually listed options in claim 38). Selecting panobinostat as the starting point would thus be the appropriate choice even if this embodiment were not, moreover, characterised in D10 as one of three 'important' (i.e. preferred) compounds of formula (I) (see point 3.4 above and D10: page 17, fourth paragraph)." (Emphasis added.)

(38) In summary, the decision was correct to take the starting point as the composition including 50 mg dolutegravir, 200 mg emtricitabine and 25 mg tenofovir alafenamide as the starting point.

3.2.2 The distinguishing features

(39) The most preferred pharmaceutical composition in D5 is a tablet, and therefore defining the composition to be a tablet does not involve selection (page 23):

The pharmaceutical composition of the present invention can be preferably a solid oral dosage form. It is further preferred that the dosage form of the invention is a capsule or a tablet, in particular a tablet.

(40) The distinguishing features of claim 1 are to use an integrase inhibitor which is a salt of bictegravir rather than an integrase inhibitor which is dolutegravir, and to use tenofovir alafenamide as a salt.

(41) The distinguishing features of claim 4 are to use an integrase inhibitor which is a salt of bictegravir rather than an integrase inhibitor which is dolutegravir, and to use a coated tablet.

(42) The decision refers only to the distinguishing feature which is the use of 50 mg dolutegravir rather than 50 mg bictegravir.

(43) We think that the opposition division took this approach because the patentee did not argue that the other distinguishing features – the coating and the use of salt forms of particular active ingredients – had any significance for the assessment of inventive step.

3.2.3 The objective technical problem

(44) The patentee referred to three technical effects at first instance: food effects, resistance profile, and improved forgiveness under conditions of sub-optimal adherence.

3.2.3.1 Food effects

(45) The decision held that the patent showed that a composition including 50 mg bictegravir has a reduced food effect relative to a composition including 75 mg bictegravir.

(46) However, the closest prior art is not a composition comprising 75 mg bictegravir. The objective technical problem is defined by identifying the technical effect of the distinguishing features (GL: G-VII. 5.2). There is no point in identifying the starting point and then the

distinguishing features if the objective technical problem is then defined based on features that distinguish a different embodiment not found in the closest prior art.

(47) Therefore, the decision was incorrect to take into account food effects when defining the objective technical problem.

3.2.3.2 Resistance profile

(48) Although this effect was not discussed by the opposition division in the decision, the patentee also relied upon post-published D41 which compares dolutegravir and bictegravir monotherapies and supposedly shows that bictegravir has an improved resistance profile.

(49) In our view the patentee cannot rely on post-published evidence because there is no evidence whatsoever to suggest that the claimed combinations have improved resistance profiles in the application as filed (e.g., T 1329/04). This effect is not encompassed by the technical teaching or embodied by the same originally disclosed invention (G 2/21).

(50) However, even if considered, D41 does not allow the objective technical problem to be defined ambitiously. D41 compares inter alia dolutegravir and bictegravir monotherapies. Comparative data are relevant only if the comparative example reflects the starting point in the prior art and the inventive example adequately represents the claimed subject-matter (T 712/13, r 3.8(a)). In the present case, the effects of the monotherapies do not reflect the specific triple combination therapy claimed or that disclosed in the closest prior art. The relative efficacy of two specific triple combinations cannot be inferred by comparing two of their constituent monotherapies.

3.2.3.3 Improved forgiveness under conditions of sub-optimal adherence

(51) Although this effect was also not discussed by the opposition division in the decision, the patentee also relied upon post-published D42 which compares the claimed triple combination including bictegravir with the triple combination including dolutegravir according to D5, and allegedly shows that the bictegravir triple combination has a higher barrier to resistance and less viral breakthrough.

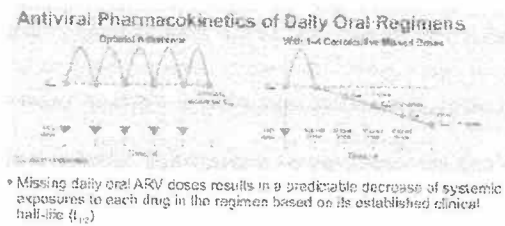
(52) Again, the effect supposedly demonstrated by D42 is not mentioned or supported by the application as filed, and therefore we do not believe that the patentee can rely on post-published evidence. However, again, we will provide detailed comments after the publication of G 2/21.

(53) Even if considered, D42 does not allow the objective technical problem to be defined ambitiously. D42 discloses in vitro tests which supposedly reflect in vivo conditions and show how viral breakthrough and development of resistance varies depending on the level of patient adherence to the required dosage regimen.

(54) In D42, MT-2 cells infected with HIV-1 IIIb cells are exposed to different fixed concentrations of inter alia tenofovir alafenamide, emtricitabine and bictegravir (supposedly reflecting the claim) or tenofovir alafenamide, emtricitabine and dolutegravir (supposedly

reflecting D5). After the exposure, CPE scoring every 3-4 days was used to measure viral breakthrough and sequencing was used to detect mutations (see Figure 1).

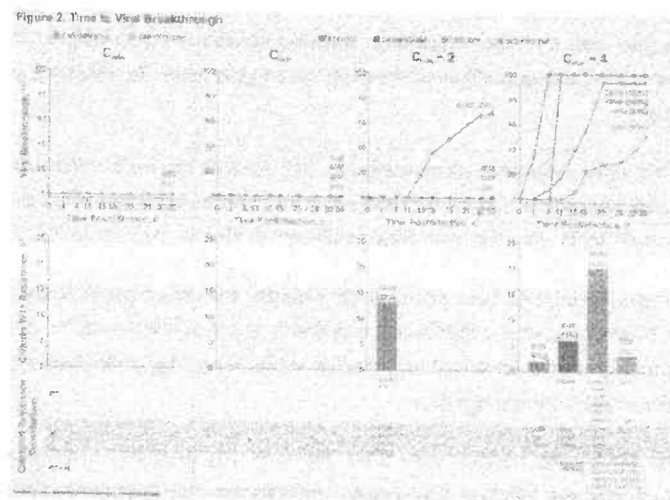
(55) The fixed in vitro concentrations are chosen to reflect the C_{min} (i) achieved by normal daily dosing (labelled " C_{min} ") (ii) present after two days of no dosing (labelled " $C_{min}-2$ "), and (iii) present after four days of no dosing (labelled " $C_{min}-4$ ").



(56) The appropriate in vitro concentrations were calculated by taking C_{min} from pharmacokinetic data, and then using modelling to estimate the levels to which this concentration would drop following no-dosing (see top of second column).

(57) The value of C_{min} when using 50 mg bictegravir was 133 nM, which drops to 19 nM (two days no dosing) and 2.7 nM (four days no dosing). The value of C_{min} when using 50 mg dolutegravir was 91 nM, which drops to 8.5 nM (two days no dosing) and 0.8 nM (four days no dosing).

(58) The comparison of the two relevant triple combinations (50 mg DTG, FTC and TAF with 50 mg BIC, FTC and TAF) is shown by Figure 2, where the results for these two triple combinations are shown with those for two double combinations which are not relevant for the claim and prior art:



(59) The results under " C_{min} " which utilise 133 nM bictegravir and 91 nM dolutegravir show that there is no difference in viral breakthrough (top graph) and neither triple combination resulted in any mutations (bottom two graphs).

(60) The results under " $C_{min} - 2$ " which utilise 19 nM bictegravir and 8.5 nM dolutegravir show that there is also no difference in viral breakthrough (top graph) and neither triple combination resulted in any mutations (bottom two graphs). One of the combinations studied using the " $C_{min} - 2$ " concentrations does show viral breakthrough and the emergence of some resistant mutations, but this is the double combination of dolutegravir and lamivudine (3TC).

(61) The results under " $C_{min} - 4$ ", which utilise 2.7 nM bictegravir and 0.8 nM dolutegravir, shows that the in vitro data intended to reflect the claimed bictegravir triple combination show that both combinations result in viral breakthrough and resistant mutations, and that these effects are somewhat more significant for the dolutegravir triple combination.

(62) Comparative data are relevant only if the comparative example reflects the starting point in the prior art and the inventive example adequately represents the claimed subject-matter (T 712/13, r 3.8(a)). Furthermore, the comparative data must credibly show an effect over the entire scope claimed (T 712/13, r 3.8(c)).

(63) In the present case, therefore, these data are irrelevant. First, because they do not reflect the CPA. D42 shows that there is no advantage using the C_{min} provided when the two combinations are administered once-daily, as recommended by the patent (see paragraph [0290]) and the closest prior art D5 (see page 17, lines 27 to 29). We note that the following the teaching of the prior art, in fact higher average plasma concentrations would result because a fixed C_{min} does not reflect repeated daily dosing (see the figure illustrating dosing regimens above).

(64) Secondly, because the data do not show an effect across the whole scope of the claim, which is not limited to any particular dosing regimen. D42 only shows an effect when the plasma concentration is that which would be achieved following four days of no dosing i.e., using 0.8 nM of dolutegravir rather than the C_{min} provided using the intended regimen which would be 91 nM, and even then only when the concentration is held at this extremely low level for weeks.

(65) However, the claim is not limited to any dosing regimen, and therefore an advantage shown by one (extreme) dosage regimen is not relevant across the full scope of the claim. Even if this represented one advantage of the product, an advantage associated with a particular dosing regime but not others (and in particular not that recommended by the closest prior art), is relevant only if the claim is limited to that dosage regimen. If the patentee wanted to rely upon this effect in the present case, i.e., a dosing regimen which occurs when patients do not take drug in the recommended way, then they need to limit the claim accordingly.

3.2.3.4 Summary

(66) The objective technical problem is the provision of an alternative composition for the treatment of HIV. The decision was incorrect to take into account food effects when defining the problem.

3.3 Obviousness of the solution

(67) The opposition division was correct to hold that the skilled person would be motivated to modify the integrase inhibitor, and that bictegravir would have been considered a good alternative integrase inhibitor based on D3.

(68) However, the opposition division held that the skilled person would not necessarily use 50 mg bictegravir based on the use of 50 mg dolutegravir in D5. We agree that the skilled person would need to undertake some routine tests to determine the appropriate dose, and could not merely assume that 50 mg was optimised based on the use of 50 mg of a different compound in D5. However, the boards have explained that such dose optimisation is routine (see T 237/15, r 4.6.1):

"The determination of the optimum dosage regimen required to achieve the therapeutic effect in the (human) patient is a matter of routine experimentation for the skilled person. Such routine tests do not require inventive skill and can consequently not establish an inventive step."

(69) Therefore, because the effect considered by the decision is not relevant, AR1 relates to a convention situation in which the claim relates to an obvious dose.

(70) For completeness, we note that the other distinguishing features of AR1 – the coating and the use of salt forms of particular active ingredients – are standard options that solve no problem and are routine to the skilled person. We note that neither the patentee nor the opposition division relied on these features.

Dr Richard Cooke
European Patent Attorney
Elkington and Fife LLP (ref R79369OP)
02 May 2023



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Gilead Sciences, Inc.	

Appeal number: T0355/23-3.3.07

Please find enclosed a copy of the statement setting out the grounds of Appeal filed by Opponent 01 (Teva Pharmaceutical Industries Ltd.), Opponent 02 (Dr. Richard Cooke) and Opponent 03 (Sandoz GmbH).

Any reply must be filed within **4 months** of this notification.

The Registry B. Atienza Vivancos
Tel.: 089 / 2399 - 3371

Annex(es):

- Letter of Opponent 01 dated 25.04.2023
- Letter of Opponent 02 dated 02.05.2023
- Letter of Opponent 03 dated 28.04.2023

Registered letter



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**Partner der Partnerschaft bis 2020
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Your reference
T0355/23-3.3.07

Our reference
ESP00476TEV

25 April 2023
MF

Re.: European Patent No. 3 346 995
European Patent Application No. 16798063.0
Patentee: Gilead Sciences, Inc.
Opponent: Teva Pharmaceutical Industries Ltd. (Opponent 1)

Further to the notice of appeal dated 23rd February 2023, the appellant files herewith the grounds of appeal.

1. Requests

The requests as per the notice of appeal, i.e.

- 1) to set aside the decision and to revoke European patent EP 3 346 995 in its entirety, and
- 2) to summon to oral proceedings as an auxiliary request

are maintained.

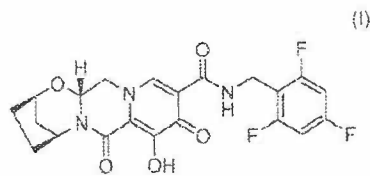
2. Cited documents

We will refer to documents D1 to D46 as cited during opposition proceedings.

3. The opposed patent

3.1 Technical field and background

3.1.1 According to paragraph [0001], the opposed patent relates to solid oral dosage forms for treating HIV comprising the compound of formula I, emtricitabine and tenofovir alafenamide. All three compounds are known anti-HIV agents (opposed patent, paragraphs [0006], [0043], [0045] and [0050]). The compound of formula I has the following chemical structure (see paragraph [0040]):



3.1.2 The sodium salt of the compound of formula I is a compound of formula II (see paragraph [0037]). The compound of formula I later received the international non-proprietary name of bictegravir (often abbreviated as BIC). This denomination is used in the appealed decision and will be used in this writ. Tenofovir alafenamide and emtricitabine are often abbreviated as TAF and FTC, respectively.

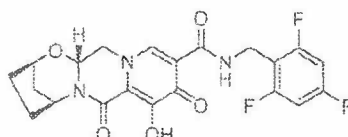
3.1.3 The opposed patent explains in the background art section that the goal of antiretroviral therapy is to achieve viral suppression in the HIV-infected patient. According to the treatment guidelines by the United States Department of Health and Human Services, this requires the use of combination therapies, i.e., several drugs from at least two or more drug classes (opposed patent, paragraph [0004]).

3.2 The claims

Claim 1 of the main request, upheld by the Opposition Division, relates to

1. A tablet comprising 50 mg of the compound of Formula I:

(I)



or a pharmaceutically acceptable salt thereof,

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

200 mg emtricitabine or a pharmaceutically acceptable salt thereof,

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.

3.3 The examples

3.3.1 The opposed patent contains 10 examples. Examples 1, 2, 2A, 3, 4, and 5 are reference examples.

3.3.2 Reference example 1 discloses the preparation of tablet F1, containing 75 mg bictegravir (as the sodium salt), microcrystalline cellulose, lactose, croscopovidone and sodium stearyl fumarate.

3.3.2 Reference example 2 discloses the preparation of bilayer tablet F2, containing 75 mg bictegravir (as the sodium salt), 200 mg emtricitabine, 25 mg tenofovir alafenamide (as the hemifumarate salt), microcrystalline cellulose, croscarmellose sodium and magnesium stearate (i.e., all 3 drugs formulated with excipients different from those of tablet F1 containing only bictegravir).

3.3.3 Reference example 2A discloses the preparation of tablet F3, containing 200 mg emtricitabine, 25 mg tenofovir alafenamide (as the hemifumarate salt), microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

3.3.4 Reference example 3 discloses a pharmacokinetic study on the bioavailability of 3 formulations:

- A) tablet F1 (with 75 mg bicittegravir as sodium salt) co-dosed with tablet F3 under fasted conditions;
- B) tablet F2 (with 75 mg bicittegravir as sodium salt) in fasted conditions;
- C) tablet F2 (with 75 mg bicittegravir as sodium salt) in fed conditions with a high-fat meal.

Tablet F2 exhibits a 30% higher exposure of bicittegravir (see paragraph [0320]), most likely due to the different excipients (croscarmellose sodium and magnesium stearate instead of crospovidone and sodium stearyl fumarate, see example 5). Moreover, tablet F2 exhibits a food effect.¹

Contrary to the statement in paragraph [0329], the food effect of tablet F1 is unknown. As a matter of fact, the bioavailability of tablet F1 in fed conditions was not studied. Paragraphs [0323-4] relate to the food effect of an unknown tablet containing a higher amount of bicittegravir (100 mg).² Therefore, it is not known whether the food effect is higher or lower in formulation F1 or F2.

3.3.5 Reference example 4 discloses the composition of reference tablet F3-A, containing 75 mg bicittegravir (as the sodium salt), microcrystalline cellulose, croscarmellose sodium and magnesium stearate. Moreover, it discloses in figure 1 the dissolution in non-sink conditions of tablet F1 co-dosed with tablet F3, tablet F3-A co-dosed with tablet F3 and tablet F2. Using only 250 mL of dissolution medium (instead of the standard 900 mL), tablet F2 exhibits a slightly better dissolution than the others.

3.3.6 Reference example 5 discloses the effects of the different excipients on the dissolution of bicittegravir in bilayer tablets F1, F2, F4, F5 and F6, all containing 75 mg bicittegravir as the sodium salt (opposed patent, paragraph [0333]). According to figure 3, the order of dissolution

¹ Bicittegravir is a weak acid. Therefore, its solubility at acidic pH is limited but increases with the pH and the consequent conversion of bicittegravir to its salt. The stomach has a higher pH in fed conditions than in fasted conditions because food acts as a buffer, partially neutralising the acid of the stomach. Due to the higher pH, an acidic compound is more soluble and thus generally more bioavailable in fed conditions. On the other hand, the dissolution of the same compound in fasted conditions is limited by its reduced solubility.

² The dose of the medicament influences the magnitude of the food effect. With a higher dose, a larger part of the medicament remains undissolved in the less favourable conditions (fasted conditions for bicittegravir), thus giving rise to a larger food effect. For these reasons, a meaningful comparison of the food effect of two formulations can only be made if they contain the same amount of active ingredient.

is $F2 > F4 > F5 > F6 > F1$. Croscarmellose sodium and magnesium stearate improve the dissolution of bictegravir compared to crospovidone and sodium stearyl fumarate (opposed patent, paragraph [0334]).

3.3.7 Example 6 discloses the composition of tablet F7, containing 50 mg bictegravir (as the sodium salt), 200 mg emtricitabine, 25 mg tenofovir alafenamide (as the hemifumarate salt), microcrystalline cellulose, croscarmellose sodium and magnesium stearate (i.e., having the same qualitative composition of tablet F2, but containing only 50 mg bictegravir).

3.3.8 Example 7 discloses the dissolution of tablet F7 in comparison with that of tablet F8, which contains 50 mg bictegravir (as the sodium salt), microcrystalline cellulose, lactose, crospovidone and sodium stearyl fumarate, i.e., the excipients that, according to example 5, limit the dissolution of bictegravir. According to figure 4 and in line with example 6, tablet F7 exhibits a better dissolution than tablet F8, thus confirming the role of the excipients on the dissolution of bictegravir already shown in example 5.

3.3.9 Example 8 discloses a generic manufacturing process.

3.3.10 Example 9 discloses the repetition of arm A and 3 further arms (D, E and F) of the pharmacokinetic study of example 3:

- A) tablet F1 (with 75 mg bictegravir as sodium salt) co-dosed with tablet F3 under fasted conditions;
- D) tablet F7 (with 50 mg bictegravir as sodium salt) under fasted conditions,
- E) tablet F7 (with 50 mg bictegravir as sodium salt) under fed conditions with a high-fat meal;
- F) tablet F7 (with 50 mg bictegravir as sodium salt) under fed conditions with a moderate-fat meal.

Comparing the table in paragraph [0351] with the one in paragraph [0319] of example 3, it can be seen that the bictegravir exposure of the same tablet F1 co-dosed with the same tablet F3 in fasted conditions is about 20% higher in example 9 than in example 3 ($AUC_{last} = 142,396.6$ vs $119,619.4$). This difference is not surprising, due to the high error of these measurements (the coefficients of variation³ are 30.5% and 26.6%, respectively). Tablet F7 exhibits a food effect slightly lower than that of tablet F2. This is expected due to the reduced dose.²

³ The coefficient of variation, also known as relative standard deviation, is defined as the ratio of the standard deviation to the mean and is often expressed as a percentage.

3.3.11 Example 10 discloses compression studies with various amounts of MCC, lactose, croscarmellose sodium and magnesium stearate. Formulation I on page 66 is the final prototype.

3.3.12 In conclusion, the examples of the opposed patent disclose the pharmaceutical development of the combination tablet containing bicittegravir, tenofovir alafenamide and emtricitabine. The examples show that the dissolution and bioavailability of bicittegravir depend on the excipients used, with croscarmellose sodium and magnesium stearate having a beneficial effect compared to crospovidone and sodium stearyl fumarate.

The tablet initially developed contained 75 mg bicittegravir as monotherapy, lactose monohydrate, crospovidone and sodium stearyl fumarate. These excipients were later substituted with croscarmellose sodium and magnesium stearate in the combination tablet. Due to the improved dissolution and bioavailability caused by the different excipients, it was necessary to reduce the bicittegravir dosage from 75 mg to 50 mg to make the combination tablet bioequivalent to the previously tested monotherapy.

The reported pharmacokinetic parameters have large errors (25-30%, depending on study and considered parameter).

4. Lack of novelty

4.1 Document D1 is a patent application filed before the priority date of the opposed patent and published after that date. D1 validly entered the European phase (see D1a). Therefore, D1 is prior art under Article 54(3) EPC for the claimed subject matter.

4.2 Claim 1 of D1 is directed to bicittegravir sodium specifically (a compound of formula II). Claim 12 is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of bicittegravir sodium. In claim 19 of D1, it is specified that the pharmaceutical composition of claim 12 comprises tenofovir alafenamide hemifumarate and emtricitabine.

4.3 Claim 21 of D1 specifies that the pharmaceutical composition is a tablet. The same teaching can be found in paragraph [0065]. Therefore, D1 directly and unambiguously discloses a tablet comprising bicittegravir sodium, tenofovir alafenamide hemifumarate and emtricitabine.

4.4 D1 further discloses the preferred dosages of the 3 ingredients (a compound of formula II being exclusively bicitegravir sodium):

"In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed."

(D1, paragraph [0096])

4.5 Therefore, D1 directly and unambiguously discloses a tablet comprising 50 mg of bicitegravir sodium, 25 mg tenofovir alafenamide fumarate or hemifumarate and 200 mg emtricitabine.

4.6 There is no need to select and combine multiple features to arrive at the claimed subject matter. The expression "a compound disclosed herein" refers exclusively to bicitegravir sodium and not to bicitegravir free acid, as incorrectly found by the Opposition Division. Indeed, claim 1, the title and the abstract of D1 only disclose the sodium salt of bicitegravir and not its free acid. Therefore, no selection of bicitegravir sodium is needed.

4.7 As far as tenofovir alafenamide is concerned, 2 of the 3 forms disclosed in said paragraph are salts (fumarate and hemifumarate). Limiting a list of 3 members to only 2 of them cannot be considered as involving a selection from a list of a certain length.

4.8 The dosages of the tenofovir alafenamide salts and emtricitabine are individualised in D1. The same is true for the endpoints 50-500 mg of the dosage range of bicitegravir sodium. Even if one were to select the dosage of 50 mg between the 2 endpoints, this would not amount to a selection from a list of a certain length. Moreover, D1 explicitly teaches to consider the dosages as if "each combination of dosages were specifically and individually listed". We must thus disagree with the Opposition Division that this statement is irrelevant (appealed decision, item 3).

4.9 Moreover, there cannot be doubts that a tablet is the most preferred pharmaceutical composition of D1. Therefore, a tablet does not need to be separately selected. The fact that paragraph [0096] does not refer to a tablet is immaterial.

4.10 In conclusion, D1 directly and unambiguously discloses a tablet comprising 50 mg of bictegravir sodium, 25 mg of a pharmaceutically acceptable salt of tenofovir alafenamide and 200 mg of emtricitabine, taking away the novelty of claim 1 of auxiliary request 1.

4.11 Hence, claim 1 of auxiliary request 1 does not meet the requirements of Article 54 EPC.

5. Lack of inventive step

5.1 The closest prior art

5.1.1 Document D5 is directed to a pharmaceutical combination comprising dolutegravir, emtricitabine and tenofovir or a prodrug thereof and its use for the treatment of HIV (D5, abstract). D5 is thus in the same technical field as the opposed patent and is directed to the same purpose, a combination therapy for the treatment of HIV.

5.1.2 In particular, D5 discloses a pharmaceutical composition comprising 50 mg dolutegravir, 200 mg emtricitabine and 25 mg tenofovir alafenamide:

"In an alternatively preferred embodiment the pharmaceutical composition of the present invention comprises about 50 mg dolutegravir, about 200 mg emtricitabine and about 25 mg tenofovir (c), in particular tenofovir alafenamide"
(D5, sentence bridging pages 19-20, emphasis added)

5.1.3 According to D5, the term "tenofovir alafenamide" encompasses its pharmaceutically acceptable salts, most preferably tenofovir alafenamide hemifumarate:

"In addition, the term "tenofovir alafenamide" comprises all the pharmaceutically acceptable salts, hydrates and/or solvates thereof"
(D5, page 13, lines 11-12)

"In a particularly preferred embodiment tenofovir alafenamide is present in form of its hemifumarate or fumarate, especially its hemifumarate."
(D5, page 13, lines 16-17)

5.1.4 The most preferred pharmaceutical composition of D5 is a tablet (page 23, lines 6-8; claim 14). Therefore, D5 directly and unambiguously discloses a tablet comprising 50 mg dolutegravir, 200 mg emtricitabine and 25 mg tenofovir alafenamide hemifumarate.

5.1.5 In conclusion, this embodiment of D5 is directed to the same purpose and has the most technical features in common with claim 1 of auxiliary request 1. Therefore, it constitutes the closest prior art. The Opposition Division correctly started the inventive step assessment from this embodiment.

5.1.6 The respondent contested in front of the Opposition Division the choice of the closest prior art. They substantially argued that the skilled person would not start from the embodiment bridging pages 19-20 of D5 because it is not in line with the claims of the same document which require a 1:1 to 1:3 ratio of dolutegravir and emtricitabine.

5.1.7 It is however uncontested that the selected embodiment has the most technical features in common with claim 1 of auxiliary request 1. Since what is claimed is essentially within the discretion of the applicant, the disclosure of a prior art document cannot be reduced to its claims.

5.1.8 Importantly, the skilled person would consider the chosen embodiment as a realistic starting point based on their common general knowledge represented by document D7, the British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy in 2015.

5.1.9 D7 shows on page 13 that the combination of tenofovir with emtricitabine is the preferred backbone of anti-HIV therapy. This backbone is combined with a third drug, such as dolutegravir. This triple combination was the gold standard of HIV therapy at the priority date.

5.1.10 As far as the doses of emtricitabine and dolutegravir are concerned, they also belonged to the common general knowledge, as evidenced by D8, the British national formulary. D8 shows on page 557 that the authorised dosage of dolutegravir is 50 mg and on page 566 that the authorised dosage of emtricitabine is 200 mg.

5.1.11 The skilled person, reading D5 in light of the common general knowledge, would have immediately recognised the dosages of dolutegravir and emtricitabine disclosed in the above-quoted embodiment as the standard dosages authorised and commercialised for the treatment

of HIV. The skilled person would have thus considered the dosages disclosed in the passage bridging pages 19-20 of D5 as a realistic starting point.

5.1.12 In conclusion, the Opposition Division correctly identified the embodiment bridging pages 19-20 of D5 as the right starting point for the inventive step assessment.

5.2 The objective technical problem

5.2.1 The distinguishing feature between the subject matter of claim 1 of auxiliary request 1 and D5 is the use of 50 mg bicitegravir as a pharmaceutically acceptable salt instead of 50 mg dolutegravir.

5.2.2 There are no data in the opposed patent comparing the claimed tablet with a tablet comprising 50 mg dolutegravir, 25 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine. Therefore, no technical effect can be associated with the distinguishing feature.

5.2.3 Hence, the objective technical problem must be formulated as the provision of an alternative combination tablet for treating HIV.

5.2.4 The respondent relied in front of the Opposition Division on the somewhat reduced food effect for tablet F7 of example 7 (containing 50 mg of bicitegravir) compared to tablet F2 of example 2 (containing 75 mg of bicitegravir). Based on this incorrect comparison, the Opposition Division erroneously acknowledged that *"the problem with respect to the teaching of D5 is to provide an alternative composition (to that of D5) with good food effects to treat HIV infection"* (appealed decision, page 14, item 4, second-last paragraph).

5.2.5 However, we need to remember that the comparison to be made for the purpose of the inventive step assessment is between the claimed subject matter and the closest prior art, which is a tablet comprising dolutegravir, tenofovir alafenamide and emtricitabine. As stressed in the first instance proceedings, there is no evidence that the claimed tablet exhibits a reduced food effect compared to the tablet of the closest prior art.

5.2.6 Moreover, the comparison between tablet F2 and tablet F7 is not appropriate because the two tablets include different excipients. As explained in section 3.3 above, the opposed patent shows that the different excipients influence the dissolution and the bioavailability of bicitegravir in a substantial manner.

5.2.7 Moreover, differences between the food effects of tablets F2 and F7 are small and plagued by large errors. Even if this difference were statistically significant, it would not be clinically significant, i.e., play any role in clinical practice. Only if a drug has a narrow therapeutic index, such a small food effect may be relevant. However, document D36 clearly shows that this is not the case for bictegravir, which exhibits comparable effects on HIV replication at doses of 25, 50 and 100 mg (D36, page 71, table 18. see p-values between 25 and 100 mg (0.097), 50 and 100 mg (0.15) and 25 and 50 mg (0.81), none of them being statistically significant).

5.2.8 Last, but not least, a slight reduction of the food effect is simply the expected consequence of the dose reduction. With a lower dose, less medicament remains undissolved in the less favourable conditions (fasted conditions for bictegravir), thus giving rise to a smaller food effect. Since the dose of the medicament influences the magnitude of the food effect, a meaningful comparison of the food effect of two formulations can only be made if they contain the same amount of active ingredient.

5.2.9 For these reasons, no reference to the food effect should be included in the formulation of the objective technical problem.

5.2.10 In a different line of arguments, the respondent relied in the first instance proceedings on post-published evidence D41 and D42. Based on D41, the respondent argued that bictegravir has an improved resistance profile compared to dolutegravir. Based on D42, they argued that the combination of bictegravir, emtricitabine and tenofovir alafenamide has a higher forgiveness and barrier to resistance than the analogous combination with dolutegravir.

5.2.11 The Opposition Division, correctly, did not rely on these documents for the assessment of inventive step, also considering that the outcome of decision G2/21 was not available on the day of the oral proceedings.

5.2.12 The skilled person, having the common general knowledge in mind, and based on the application as originally filed, would not have derived an improved resistance profile, a higher forgiveness and a higher barrier to resistance as being encompassed by the technical teaching and embodied by the same originally disclosed invention. Therefore, in line with G2/21, these effects cannot be taken into account for the reformulation of the technical problem.

5.2.13 Indeed, there is not even a single hint in the original application that bictegravir can exhibit improved properties compared to dolutegravir. This is not surprising, considering that it is a classical formulation patent application and not a medical use patent application. As a matter of fact, all examples are either formulation examples or bioequivalence studies in healthy volunteers. Thus, bictegravir was not administered to patients infected with HIV in any of the examples of the original application.

5.2.14 Moreover, neither D41 nor D42, if properly analysed, can support the formulation of a more ambitious technical problem. We shall expand.

5.2.15 Document D41 cannot show the superiority of the claimed combination for two reasons. First of all, this document compares bictegravir *per se* with dolutegravir *per se*, and not the two triple combinations with each other. Bictegravir was a known compound at the relevant date. Therefore, D41 can at most support the patentability of bictegravir as a compound and the grant of its product patent based on its application D3.

5.2.16 Secondly, it is not true that bictegravir has an improved resistance profile compared to dolutegravir, as the respondent alleges. In figure 2 on page 3 of D41, the *in vitro* activity of raltegravir, elvitegravir, dolutegravir and bictegravir against wild-type virus (WT) and 10 known mutants are compared. Each mutant is characterised by a mutation aimed at overcoming a particular drug: 3 are raltegravir mutants, 2 are elvitegravir mutants and 5 are dolutegravir mutants (see the legend on the right-hand side of the figure).

5.2.17 No bictegravir mutants were however studied in D41. This is not surprising, because bictegravir was first launched in 2018, the publication year of D41, while dolutegravir had been authorised 5 years earlier, in 2013. Therefore, until 2018 bictegravir had been tested only in clinical trials, which offer a controlled environment in which only selected patients are enrolled. Instead, mutations usually occur in patients with a severely compromised immune system and/or with poor adherence to therapy, i.e., once a drug is authorised and used in a variety of patients. Therefore, in 2018 there had not been enough chances for the virus to develop mutations to overcome the effect of bictegravir. Nevertheless, D41 warns that this will inevitably happen (D41, page 12, left-hand column, last paragraph).

5.2.18 By definition, the activity of a compound is reduced against its mutants. If D41 had investigated also bictegravir mutants, it would have shown the reduced activity of bictegravir against said mutants. Since dolutegravir mutants, but no bictegravir mutants were studied in D41, this document cannot support a superiority of bictegravir over dolutegravir. There is

indeed no evidence on file that bictegravir mutants are less likely to emerge than dolutegravir mutants.

5.2.19 If we also consider D43 and D44, which were published in 2020 and 2021, respectively, we note that bictegravir mutants emerged as expected (D43, title; D44, title). These mutations, together with poor adherence to the therapy, led to virological failure. As the use of bictegravir spreads, bictegravir mutants will inevitably become more and more common.

5.2.20 As far as D42 is concerned, this is a poster funded by the respondent. Its authors were all employees of Gilead Science at its publication date and thus not impartial. Moreover, D42 only relates to an *in vitro* study. Claim 1 of the main request is however directed to a tablet comprising bictegravir, tenofovir alafenamide and emtricitabine. D42, being concerned with *in vitro* data, cannot show the superiority of the claimed tablet, which must be used *in vivo* after oral administration.

5.2.21 Moreover, it is well-known that *in vitro* models have limitations. Indeed, a direct translation of simulated missed doses *in vitro* to *in vivo* missed doses is not possible. An *in vitro* system is more sensitive to missed doses than *in vivo*, where the immune system contributes to viral suppression and helps keep HIV-1 in a latent state. Furthermore, a major reason for poor adherence are side effects: although a drug combination may have high forgiveness or a high resistance barrier in an *in vitro* assay, the combination may have more side effects, which would lead to poorer clinical adherence. Hence, there is no evidence that the claimed combination allows for greater forgiveness than the one of D5 in human patients. Indeed, D42 explicitly warns against such a conclusion:

"controlled clinical trials assessing the impact of missed doses of these ARV combinations have not been conducted"
(D42, "Conclusions")

5.2.22 In conclusion, there is no evidence in the opposed patent of any technical effect of the claimed combination over the one of D5. The small difference in food effects of two tablets containing two doses of bictegravir and different excipients cannot show an improvement over the closest prior art. Moreover, this difference is not clinically significant. The post-published data filed by the respondent with D41 and D42 cannot cure the deficiency either. Therefore, the objective technical problem can only be the provision of an alternative combination tablet for treating HIV.

5.2.23 As a matter of fact, document D36 proves that this is the correct formulation of the objective technical problem. D36 shows that the claimed combination was authorised based on its mere non-inferiority compared to the standard of care, including the combination of D5.

5.2.24 D36 explains starting from page 73 that four phase 3 studies were performed with the claimed combination:

1. vs abacavir/dolutegravir/lamivudine in treatment naïve subjects
2. vs dolutegravir/emtricitabine/tenofovir alafenamide in treatment naïve adults (see page 74)
3. vs abacavir/dolutegravir/lamivudine in treatment-experienced subjects
4. vs boosted atazanavir or darunavir + emtricitabine/tenofovir or abacavir/lamivudine

5.2.25 As can be seen in the “Hypothesis” box of each of the tables relating to the four studies, the respondent planned all of them as non-inferiority studies. Therefore, the respondent was the first one not to believe in any superiority of the claimed combination.

5.2.26 If we then closely examine the subgroup analysis on figure 9 on page 77 of D36, we can see that the claimed combination is slightly worse than the one of D5 in all subgroups. Since the differences are not statistically significant, the claimed combination met the non-inferiority criteria and was eventually authorised by the regulatory authorities.

5.2.27 Summing up, D36 unequivocally shows that both the respondent (who planned non-inferiority studies) and the regulatory authorities concluded that the claimed combination is non-inferior to that of the closest prior art D5. This is far from being better, as the respondent alleges. It is therefore evident that a more ambitious formulation of the objective technical problem is not justified.

5.2.28 In order to present our complete case with our grounds of appeal, we will address in the following paragraphs the wrong allegations of the respondent on the effect of tenofovir alafenamide and emtricitabine on the dissolution and bioavailability of bictegravir. We presented the following arguments in great detail at the oral proceedings, the list in item 6.5.4 on page 5 of the minutes of the oral proceedings providing only a short summary of the discussion. We note that the Opposition Division was convinced by our explanation since it did not rely on this line of argument of the respondent in the appealed decision.

5.2.29 The opposed patent is a formulation patent, whose examples detail the pharmaceutical development of the claimed combination tablet. The respondent argued in their reply to the oppositions that the presence of tenofovir alafenamide and emtricitabine surprisingly led to an increase in the bioavailability of bictegravir and thus required a reduction of the dosage from 75 mg to 50 mg. Since this effect of the 2 further active ingredients was unexpected, the selection of the 50 mg dose of bictegravir would be inventive. However, the very examples of the patent and document D36 tell a different story, which contradicts the one made up by the respondent for the purpose of this opposition. We shall expand.

5.2.30 The respondent first prepared tablets containing only bictegravir as an active ingredient at various dosages (see example 1 of the patent for the 75 mg tablet, named F1) and tested its effect on HIV infected patients (D36, page 46, table 6, second row; page 70, last 3 paragraphs, "Dose selection"). They selected the 75 mg dosage for further development (D36, page 71, first paragraph).

5.2.31 The respondent then tested tablet F1 administered together with the backbone of antiretroviral therapy, the combination of emtricitabine and tenofovir, in a separate tablet (see example 2A, tablet F3), in a phase 2 study, as explained in D36, page 71, second paragraph.

5.2.32 The next logical step was then the combination of the 3 active ingredients in a single tablet (see example 2), also considering that most anti-HIV therapies were administered as a single tablet at the relevant date (see D9, D10, D11, D13 and D14). However, when doing so, the respondent changed the excipients with which bictegravir was formulated and substituted lactose monohydrate, crospovidone and sodium stearyl fumarate of tablet F1 of example 1 with croscarmellose sodium and magnesium stearate of tablet F2 of example 2. This change of excipients improved the dissolution and consequently increased the bioavailability of bictegravir (see example 3 of the patent and the explanation given in more detail in section 3.3 of this writ).

5.2.33 The respondent was then faced with the problem of having already conducted clinical studies with a tablet containing 75 mg of bictegravir as monotherapy and having then developed a combination tablet which was not bioequivalent to the one previously tested. In order not to have to repeat the earlier clinical studies, they reduced the dosage of bictegravir from 75 mg to 50 mg in the combination tablet:

"According to these results, the FDC [fixed dose combination] containing BIC 50 mg instead of BIC 75 mg was selected for further evaluation in Phase 3 studies, in order to achieve equivalent BIC exposure than with BIC 75 mg single component"

(D36, page 72, fourth paragraph)

5.2.34 This approach avoided the repetition with the combination tablet of the earlier studies in HIV-infected patients and relied instead on the simple bioequivalence study in healthy volunteers described in example 9 of the opposed patent. This course of action was necessary because of the choice of the specific formulation of examples 2 and 6, i.e., a bilayer tablet with magnesium stearate and croscarmellose sodium in the bictegrovir layer. As demonstrated in example 5, these excipients, and not the presence of the other 2 active ingredients in a separate layer as the respondent creatively argues,⁴ caused the increase in bioavailability and led to the need of reducing the dosage.

5.2.35 Figure 1 of the opposed patent confirms in its very title that the choice of the formulation determines the dissolution and thus the bioavailability of bictegrovir:⁵ *"Effect of bi-layer process on dissolution of the compound of formula II under non-sink condition (FaSSIF pH 6.5, 250 mL, paddle, 100 rpm)"* (opposed patent, figure 1, emphasis added). Therefore, the patent itself confirms that the bioavailability of bictegrovir depends on the choice of a bilayer tablet with specific excipients.

5.2.36 In conclusion, the respondent invented a specific formulation of bictegrovir (a bilayer tablet with magnesium stearate and croscarmellose sodium) but claims instead the dosage of bictegrovir. However, 50 mg is just an appropriate dosage of bictegrovir when using the specific excipients in the specific formulation of example 6.

5.2.37 Hence, no surprising technical effect is brought about by the claimed subject matter. The objective technical problem solved over document D5 must be formulated as the provision of an alternative combination tablet for treating HIV.

⁴ Bictegrovir is incorporated in one layer of formulations F2 and F7, while tenofovir alafenamide and emtricitabine are in a separate layer. It is thus evident for the pharmaceutical technologist that it is not plausible that tenofovir alafenamide and emtricitabine increase the bioavailability of bictegrovir. This increase is instead due to the other components (the excipients) of the bictegrovir layer.

⁵ This experiment was performed with a very small volume (250 mL) of dissolution medium, instead of the standard volume of 900 mL. These conditions do not allow the full dissolution of the active ingredients (non-sink conditions). The purpose of this choice is to highlight small differences in dissolution.

5.3 Obviousness

5.3.1 Starting from the combination of D5, the skilled person would have prepared an alternative tablet for the treatment of HIV using 3 drugs with the same mechanism of action as those of D5.

5.3.2 As explained in paragraphs 5.1.8-9 above, tenofovir and emtricitabine were already an established combination and the gold standard for the treatment of HIV at the priority date, constituting the preferred backbone of antiretroviral therapy. The third agent could instead vary and could be, e.g., an integrase inhibitor, such as dolutegravir or raltegravir.

5.3.3 Therefore, as correctly recognised by the Opposition Division, the most straightforward option for the skilled person looking for an alternative treatment of HIV was to retain the backbone of tenofovir alafenamide and emtricitabine and vary the HIV integrase inhibitor (appealed decision, item 4, page 15, third and fourth paragraphs).⁶

5.3.4 The skilled person would have thus consulted document D3, which discloses integrase inhibitors (see D3, page 3, lines 11-12). Compound 42 in example 42 on pages 99-101 of D3 is bictegravir. In table 1 in example 104 on pages 212-216 the antiviral activity of the compounds of D3 is disclosed. As can be seen on page 214, bictegravir is among the best compounds disclosed in D3, since it possesses one of the lowest inhibitory concentrations in both columns.⁷

5.3.5 Even more importantly, bictegravir is one of just 11 compounds tested in the pharmacokinetic study in beagle dogs in example 107 on pages 222-224. The skilled person understands that only the best compounds were tested in animals. Moreover, bictegravir is one of only 5 compounds for which oral bioavailability data (F) are provided in table 4, the other 6 compounds being apparently not bioavailable. The table also shows that bictegravir has the second-best bioavailability (28%).

5.3.6 Last, but not least, bictegravir (or salts thereof) is one of only 7 compounds claimed in claim 32 of D3. Therefore, as correctly recognised by the Opposition Division, the skilled

⁶ It is not contested that it belonged to the common general knowledge that dolutegravir is an HIV integrase inhibitor (D8, page 557). Indeed, the simple fact that its INN ends in -tegravir means that it is an HIV integrase inhibitor.

⁷ The EC50 is the concentration effective in producing 50% of the maximal response and is a convenient way of comparing drug potencies. CC50 is the concentration of the 50% cytotoxic effect.

person would have recognised bicitegravir as one of the most preferred compounds of D3 (appealed decision, item 4, page 15, fifth paragraph)

5.3.7 Hence, the skilled person would have selected bicitegravir as an alternative to dolutegravir with a reasonable expectation of solving the technical problem of providing an alternative tablet for the treatment of HIV.

5.3.8 Indeed, D3 explicitly confirms that the integrase inhibitors of the invention should be combined with one or more additional therapeutic agents, such as a nucleoside reverse transcriptase inhibitor and a nucleotide reverse transcriptase inhibitor (claim 36), with emtricitabine belonging to the first and tenofovir alafenamide fumarate to the second class (see D3, page 38, lines 13-16 and 18-20). The skilled person would have thus found confirmation in D3 of the suitability of bicitegravir as a substitute for dolutegravir disclosed in the closest prior art D5.

5.3.9 This consideration would have also been supported by the common general knowledge, evidenced by document D18, the list of international non-proprietary names (INN) of new drugs, and reporting on page 205 the INN and the structure of bicitegravir. Such INNs are given following specific rules (see D19): e.g., all HIV integrase inhibitors must end in -tegravir (elvi-tegravir, ral-tegravir, dolutegravir).

5.3.10 As the skilled person knows well, a pharmaceutical company does not apply for an INN for a new drug in an early development stage, but only at a later stage (usually in phase 2 or 3). Therefore, the skilled person was aware at the relevant date that a new HIV integrase inhibitor had reached such an advanced stage of development to receive the INN bicitegravir.

5.3.11 New active ingredients are developed only if they can be at least comparable with existing ingredients. In the present case, dolutegravir had been on the market for 2 years at the relevant date and enjoyed a high acceptance among doctors and patients. The skilled person would have been aware that a pharmaceutical company does not embark on advanced clinical trials if it does not consider the new drug to be at least comparable with the authorised standard therapy.

5.3.12 Therefore, based on the common general knowledge reflected in D18, the skilled person would have been aware that bicitegravir was a promising HIV integrase inhibitor at the relevant date. They would have thus replaced dolutegravir with bicitegravir in the tablet of D5

with the reasonable expectation of obtaining an alternative combination tablet for the treatment of HIV.

5.3.13 As far as the dosage of bicitgravir is concerned, D3 discloses on page 35 suitable amounts for a pharmaceutical composition: on line 22 the preferred amount of 50 mg is explicitly disclosed.

5.3.14 Importantly, the Boards of Appeal have consistently ruled that finding the optimum dosage is a matter of routine experimentation, which does not require inventive skill (T 1760/08, T 1409/06, T 237/15).

5.3.15 In case T 1409/06, the data in the patent showed that the best antiemetic effects were obtained by i.v. administration of 1 mg and 3 mg granisetron as compared to 0.1 mg disclosed in the prior art, where the effect was less accentuated. The Board of Appeal revoked the opposed European patent for the following reasons:

"The board is of the opinion that the mere determination of the dosage which yields the best effect does not involve an inventive step when, as in the present case, the effect as such is already known or obvious. The person skilled in the art is aware that the intensity of a pharmacological effect depends inter alia on the concentration of the active agent. Finding the optimum dosage is a matter of routine experimentation, which does not require inventive skill."

(T 1409/06, r. 3.2.1)

5.3.16 The same applies to the present case: D3 already teaches that bicitgravir is an integrase inhibitor useful for the treatment of HIV. In this case, the technical effect achieved by the claimed dosage is simply the treatment of HIV, which was however known at the relevant date.

5.3.17 Document D36, the assessment report of Biktarvy by the European Medicines Agency, demonstrates that bicitgravir exhibits comparable effects on HIV replication at doses of 25, 50 and 100 mg (D36, page 71, table 18, see also paragraph 5.2.7 above). Moreover, D36 shows that the respondent argued with the regulatory authority about the lack of relevance of differences of 30-40% in the bioavailability of bicitgravir:

"The dose of BIC was therefore reduced from 75 mg to 50 mg and a new B/F/TAF 50/200/25 mg FDC tablet was developed, showing lower BIC exposures (BIC AUC and C_{max} decreased by 0.78 fold as compared to the 75 mg BSIC+FTC/TAF) but within the confidence interval that was enlarged (70-143%) to take into account the different BIC doses. An enlarged CI could be accepted given the lack of lower boundary of BIC therapeutic window and the clinical efficacy results"

(D36, page 67, fifth paragraph)

5.3.18 The EMA accepted the enlarged confidence interval (70-143%) proposed by the respondent because differences of this magnitude are not clinically relevant. This also confirms that the difference in the food effects of tablet F2 (+54% in the AUC, see table in paragraph [0324]) and tablet F7 (+24% in the AUC, see table in paragraph [0354]) is not clinically relevant. This difference of 30% (even disregarding the high errors of the measurements) is fully within the bioequivalence interval indicated by the respondent to the regulatory authorities.

5.3.19 It is thus evident that the dosage of 50 mg of bictegravir in the claimed combination is not even the optimal dosage of this drug, but just a suitable dosage. No technical effect is achieved by the claimed dose that was not already known or obvious based on the prior art. Therefore, the established case law is fully applicable to the present case.

5.3.20 The Opposition Division came to a different conclusion only because they acknowledged the advantage of a reduced food effect for the claimed dosage and thus formulated a more ambitious technical problem. As explained in the previous section, this is not correct. If the objective technical problem is correctly formulated as the provision of a mere alternative combination tablet, no inventive step can be acknowledged.

5.3.21 In the following, we will address for completeness' sake further arguments of the respondent presented in the first instance proceedings. The respondent first argued that the skilled person would not have changed anything in the closest prior art. If this reasoning were accepted, all patents would be inventive.

5.3.22 The respondent further argued that the skilled person would not have replaced dolutegravir with an investigational integrase inhibitor, such as bictegravir, but rather with another one already on the market, such as raltegravir or elvitegravir. However, it belonged to the common general knowledge, evidenced by review D21b, that dolutegravir is better than

raltegravir and elvitegravir. Therefore, the skilled person would not have replaced dolutegravir with a compound that was notoriously inferior to dolutegravir.

5.3.23 Indeed, elvitegravir and raltegravir are first-generation integrase inhibitors. Raltegravir is dosed twice daily, a clear disadvantage. Elvitegravir necessitates the booster cobicistat, a potent CYP3A4 inhibitor that can lead to clinically significant drug-drug interactions. Both integrase inhibitors have a low genetic barrier to resistance and are associated with cross-resistance. Dolutegravir is instead a second-generation integrase inhibitor, which is administered once/day without a pharmacokinetic booster and which can be co-formulated in a single-tablet regimen (D21b, abstract). Therefore, dolutegravir was known to be better than elvitegravir and raltegravir. In any case, the fact that other fixed-dose combinations may have been obvious does not render the claimed combination inventive.

5.3.24 Indeed, not only bictegravir, but each of the preferred integrase inhibitors disclosed in D3 is an obvious solution to the technical problem of providing an alternative combination tablet for the treatment of HIV, not a very ambitious problem indeed. The selection of one from several obvious solutions cannot involve an inventive step.

5.3.25 If we then consider document D18 as a secondary document instead of D3 and not as evidence of the common general knowledge, we do not even need to select bictegravir among the handful of integrase inhibitors of D3, because D18 individualizes bictegravir.

5.3.26 In conclusion, claim 1 of auxiliary request 1 does not involve an inventive step over document D5 in combination with either D3 or D18 and thus does not meet the requirements of Article 56 EPC.

6. Auxiliary claim requests

6.1 In the first instance proceedings, the respondent requested to maintain the opposed patent as granted (main request) or according to auxiliary requests 1-10 filed on 26th August 2022.

6.2 Auxiliary request 2

6.2.1 In auxiliary request 2, granted claims 1 and 3 are combined, the claimed tablet being thus limited to 52 mg bictegravir sodium and 28 mg tenofovir alafenamide hemifumarate.

6.2.2 However, the reference to pharmaceutically acceptable salts of emtricitabine was not amended to exclude said salts, like in the main request. Therefore, auxiliary request 2 adds matter for the same reasons as the main request (appealed decision, page 9-10, item A.2).

6.2.3 As far as inventive step is concerned, D3 teaches that the integrase inhibitors disclosed therein can be in the form of a pharmaceutically acceptable salt (D3, claim 1) and identifies the sodium salt as a preferred example of such a salt (D3, page 14, line 20). The hemifumarate is disclosed in D5 as the most preferred salt of tenofovir alafenamide (D5, page 13, lines 16-18).

6.2.4 The amount of 52 mg of bictegravir sodium corresponds to 50 mg of bictegravir free acid and the amount of 28 mg of tenofovir alafenamide hemifumarate corresponds to 25 mg of tenofovir alafenamide free base. Therefore, the claimed dosages of these active ingredients are unchanged. Hence, the inventive step reasoning put forward for auxiliary request 1 fully applies to auxiliary request 2, which is not inventive.

6.3 Auxiliary request 3

6.3.1 In auxiliary request 3, granted claims 1 and 5 are combined, the claimed tablet being thus limited to a coated tablet.

6.3.2 However, the opposed patent does not disclose any technical effect related to the coating, which is thus arbitrary and to be ignored in the inventive step assessment. Coated tablets are standard dosage forms, which are commonplace in the art. Therefore, auxiliary request 3 is not inventive for the same reasons as auxiliary request 1.

6.4 Auxiliary request 4

6.4.1 Auxiliary request 4 specifies that bictegravir and tenofovir alafenamide are segregated in separate layers of a multilayer tablet of a total weight of less than 1 g.

6.4.2 However, handbook D15 and review D16 explain that multilayer tablets are standard dosage forms: *"Multilayer tablets are made primarily to separate incompatible drugs from each other, i.e. incompatible drugs can be incorporated into the same tablet"* (D16, page 412, left-hand column, fourth paragraph). The opposed patent does not disclose any technical effect connected with the use of a multilayer tablet, since it offers no comparison between a tablet in which bictegravir and tenofovir alafenamide are blended or granulated together and a

multilayer tablet in which bicitgravir and tenofovir alafenamide are segregated in separate layers.

6.4.3 As far as the total weight of the tablet is concerned, it depends on the weight of the 3 active ingredients, which are 50, 25 and 200 mg for a total of 275 mg, a relatively small amount. For comparison, a standard aspirin tablet contains 500 mg of acetylsalicylic acid. The skilled person is well aware of the need of preparing a tablet with a reasonable size and thus of using a moderate quantity of excipients. Certainly, it would not have been a challenge for the skilled person to prepare a tablet containing 275 mg of active ingredients and about 700 mg of excipients. Therefore, the same inventive step reasoning put forward for auxiliary request 1 fully applies to auxiliary request 4.

6.5 Auxiliary request 5

6.5.1 Auxiliary request 5 is limited to a multilayer tablet, whose first layer comprises 52 mg of bicitgravir sodium and is free of tenofovir alafenamide and emtricitabine or salts thereof, whose second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine free base and is free of bicitgravir or salts thereof.

6.5.2 As explained in connection with auxiliary request 4, there is no evidence in the opposed patent that the segregation of bicitgravir leads to any technical effect, let alone a surprising one. The specific amounts of the salts of the active ingredients are not inventive, as explained in connection with auxiliary request 2. Hence, auxiliary request 5 is obvious for the reasons explained in relation to auxiliary requests 1, 2 and 4.

6.6 Auxiliary request 6

6.6.1 Auxiliary request 6 is directed to a multilayer tablet comprising 52 mg of bicitgravir sodium, 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine free base

6.6.2 Unlike auxiliary request 5, this request does not specify how the 3 active ingredients are distributed in the layers of the tablet. Auxiliary request 6 is thus broader than auxiliary request 5 and must therefore fall for the same reasons.

6.7 Auxiliary request 7

6.7.1 Auxiliary request 7 is directed to a tablet comprising 52 mg bicittegravir sodium, 28 mg tenofovir alafenamide hemifumarate, 200 mg emtricitabine free base, 360 ± 30 mg microcrystalline cellulose, 50 ± 8 mg croscarmellose sodium and 10.5 ± 3 mg magnesium stearate.

6.7.2 The opposed patent shows that the selected excipients yield a higher dissolution of bicittegravir compared to lactose, crospovidone and sodium stearyl fumarate. However, this does not translate into improved efficacy or safety. Therefore, the inventive step assessment remains unchanged compared to auxiliary request 1. Auxiliary request 7 is thus not inventive.

6.8 Auxiliary request 8

6.8.1 Auxiliary request 8 is directed to a bilayer tablet comprising 50 mg dolutegravir or a pharmaceutically acceptable salt thereof, 260 ± 20 mg microcrystalline cellulose, 20 ± 5 mg croscarmellose sodium and 5 ± 1.5 mg magnesium stearate in a first layer and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine free base, 113 ± 9 mg microcrystalline cellulose, 30 ± 3 mg croscarmellose sodium and 4 ± 1.1 mg magnesium stearate in a second layer.

6.8.2 The respondent cited original paragraph [0229] as basis for amendments (reply to the oppositions, page 22). Error margins for all components of the tablet were indicated in this paragraph. However, the respondent deleted in auxiliary request 8 the error margins of the active ingredients and kept those of the excipients.

6.8.3 In original paragraph [0229], all components of the tablets are disclosed as having a certain error margin, i.e., a certain variability. Deleting some error margins, but not others conveys a different teaching: the skilled person understands from auxiliary request 8 that the amounts of the actives cannot vary, while those of the excipients can. This teaching is not directly and unambiguously derivable from the original application. Therefore, auxiliary request 8 adds matter.

6.8.4 As far as the inventive step assessment is concerned, the respondent admits that this request is not entitled to priority (letter of the respondent of 24th January 2022, page 11). Therefore, documents D1, D2, D11, D13, D31 and D32 belong to the state of the art according to Article 54(2) EPC.

6.8.5 In particular, D31 was published on 19th November 2015 and discloses the protocol of a phase 3 clinical trial in which the safety and efficacy of a fixed dose combination of GS-9883/emtricitabine/tenofovir alafenamide are compared to those of dolutegravir and emtricitabine/tenofovir alafenamide in the treatment of HIV (D31, sections A.3 and A.3.1). Therefore, document D31 qualifies as the closest prior art for subject matter not entitled to priority. The Opposition Division seemed to share this opinion (preliminary opinion, item 6.4.2).

6.8.6 The tested fixed dose combination is a film-coated tablet containing 50 mg GS-9883, 200 mg emtricitabine and 25 mg tenofovir alafenamide (D31, D.3.4, D.3.8, D.3.10.1 and D.3.10.3). D31 does not explicitly disclose that the lab-code GS-9883 corresponds to bicitegravir.

6.8.7 D32 was published on 24th February 2016, i.e., after the first priority date, but before the second priority date. D32 is a statement of the non-proprietary name bicitegravir adopted by the USAN Council⁸ and thus represents the general knowledge of the skilled person. In the same document, the lab code GS-9883 is also indicated.

6.8.8 The skilled person reading D31 in light of the common general knowledge immediately understands that the lab-code GS-9883 corresponds to bicitegravir. Therefore, D31 discloses a film-coated tablet comprising 50 mg of bicitegravir, 25 mg of tenofovir alafenamide and 200 mg of emtricitabine.

6.8.9 The difference between claim 1 of auxiliary request 8 and D31 is that D31 does not disclose the sodium salt of bicitegravir, the hemifumarate salt of tenofovir alafenamide and the specific excipients. As explained in connection with auxiliary requests 2 and 7, these differences are not connected with any technical effect, let alone a surprising one. The objective technical problem is thus the provision of an alternative tablet comprising bicitegravir, tenofovir alafenamide and emtricitabine, which is obvious. Moreover, similar considerations to those concerning higher ranking requests apply to auxiliary request 8. Therefore, auxiliary request 8 is not inventive over D31 in light of the common general knowledge evidenced by D32.

⁸ The USAN Council is responsible for selecting simple, informative and unique non-proprietary (generic) drug names.

6.9 Auxiliary request 9

6.9.1 Auxiliary request 9 is directed to a bilayer tablet comprising 50 mg dolutegravir or a pharmaceutically acceptable salt thereof, 246 ± 5 mg microcrystalline cellulose, 19 ± 1.75 mg croscarmellose sodium and 5 ± 0.5 mg magnesium stearate in a first layer and 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, 200 mg emtricitabine free base, 113 ± 4 mg microcrystalline cellulose, 30 ± 1.4 mg croscarmellose sodium and 4 ± 0.5 mg magnesium stearate in a second layer.

6.9.2 The respondent cited original paragraph [0234] as basis for amendments (reply to the oppositions, page 22). Error margins for all components of the tablet were indicated in this paragraph. However, like in auxiliary request 8, the respondent deleted in auxiliary request 9 the error margins of the active ingredients and kept those of the excipients. Therefore, auxiliary request 9 adds matter for the reasons explained in connection with auxiliary request 8.

6.9.3 Moreover, auxiliary request 9 is not entitled to priority and is thus not inventive for the same reasons as auxiliary request 8.

6.10 Auxiliary request 10

6.10.1 Auxiliary request 10 is directed to a bilayer tablet comprising 52.5 mg dolutegravir sodium, 246 mg microcrystalline cellulose, 19 mg croscarmellose sodium and 5 mg magnesium stearate in a first layer and 28 mg tenofovir alafenamide hemifumarate, 200 mg emtricitabine free base, 113 mg microcrystalline cellulose, 30 mg croscarmellose sodium and 4 mg magnesium stearate in a second layer.

6.10.2 Neither auxiliary request 10 is entitled to priority and is thus not inventive for the same reasons as auxiliary request 8.

7. Conclusion

It has been shown above that none of auxiliary requests 1 to 10 are in accordance with the requirements of Articles 54, 56 and 123(2) EPC, and that the Opposition Division erred in their decision. Therefore, the request to set aside said decision and to revoke EP 3 346 995 in its entirety is fully justified.

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Declarations under Rule 4.17:

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(54) Title: PHARMACEUTICAL FORMULATIONS

(57) Abstract: The invention provides a solid oral dosage form comprising rilpivirine or a pharmaceutically acceptable salt thereof,
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PHARMACEUTICAL FORMULATIONS

TECHNICAL FIELD

This invention provides pharmaceutical formulations suitable for treating viral infections such as HIV, and in particular solid oral dosage forms including rilpivirine, emtricitabine and tenofovir alafenamide

BACKGROUND

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

The success of potent and well-tolerated ART means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS associated comorbidities. Clinical attention has become more focused on optimizing tolerability, long-term safety, and adherence (Costagliola D. Demographics of HIV and aging *Curr. Opin. HIV AIDS*, 2014, 9(4), 294). There remains a significant medical need for safe and effective new therapies that take into consideration the aging patient population, non-HIV-related comorbidities, virologic resistance, and regimen simplification.

SUMMARY

All the compositions and oral dosage forms herein include rilpivirine or a pharmaceutically acceptable salt thereof.

The inventors have successfully formulated an oral dosage form containing rilpivirine, tenofovir alafenamide and emtricitabine. This oral dosage form is suitable for use in medicine, and in particular in treating viral infections such as HIV.

In one aspect, a solid oral dosage form comprising rilpivirine or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof is provided. For instance, in certain embodiments, the dosage form comprises 25 mg rilpivirine as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine. In certain embodiments, the dosage form comprises 27.5

mg rilpivirine hydrochloride, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine.

The inventors have found that it is possible to formulate solid oral dosage forms that are pharmaceutically acceptable (i.e. pharmacologically efficacious and physically acceptable) while reducing the total amount of excipients necessary to achieve stability. Accordingly, in one aspect the invention provides a solid oral dosage form comprising 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg (e.g. less than 800 mg or less than 700 mg).

The inventors have demonstrated that it is possible to formulate stable compositions containing tenofovir alafenamide and emtricitabine that exhibit acceptable stability. Accordingly, in another aspect the invention provides a composition comprising (a) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) emtricitabine or a pharmaceutically acceptable salt thereof, where the total quantity of degradation products derived from the tenofovir alafenamide or the pharmaceutically acceptable salt thereof is less than 3% after storage for one month at 40°C/75% RH in open conditions. Such compositions may further comprise rilpivirine or a pharmaceutically acceptable salt thereof.

In another aspect, a coated tablet comprising 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof is provided.

In another aspect, a tablet comprising 27.5 mg rilpivirine hydrochloride, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine is provided.

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

In another aspect, a tablet comprising from 2.5-4.5 % w/w rilpivirine or a pharmaceutically acceptable salt thereof, 2.5-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 27-33 % w/w emtricitabine or a pharmaceutically acceptable salt thereof is provided, where the weight percentages denote a proportion of the whole tablet. In some embodiments, (a) the rilpivirine is present as rilpivirine hydrochloride and/or (b) the tenofovir alafenamide is present as tenofovir alafenamide hemifumarate. Typically, the

rilpivirine will be present as rilpivirine hydrochloride and the tenofovir alafenamide will be present as tenofovir alafenamide hemifumarate.

The inventors have found that the use of multilayer tablets may assist in achieving appropriate pharmacokinetic parameters and/or adequate tablet stability. Accordingly, in another aspect a multilayer tablet comprising (a) rilpivirine or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided.

The inventors have also found that there is a relationship between the stability of tenofovir alafenamide and the concentration of tenofovir alafenamide within a given composition. Accordingly, in another aspect a solid composition comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof is provided wherein the proportion of tenofovir alafenamide or a pharmaceutically acceptable salt thereof in the composition is from about 4% to about 12% by weight. Another aspect provides a solid composition comprising from about 5% to about 15% by weight tenofovir alafenamide hemifumarate.

In another aspect, a dry granulated mixture of (a) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) emtricitabine or a pharmaceutically acceptable salt thereof is provided.

In another aspect, a kit comprising (a) a tablet comprising rilpivirine or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant (e.g. silica gel) is provided.

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

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

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows the percent of degradation of tenofovir alafenamide hemifumarate as a function of drug load.

Figure 2 is a flow diagram illustrating the preparation of a monolayer tablet formulation of emtricitabine, rilpivirine HCl and tenofovir alafenamide hemifumarate.

Figures 3A and B illustrate the impact on the stability of tenofovir alafenamide hemifumarate of the presence of (i) emtricitabine, and (ii) emtricitabine and rilpivirine HCl. Figure 3A shows the total degradation of tenofovir alafenamide hemifumarate at 40°C/75% RH under

open conditions, and Figure 3B shows the total degradation of tenofovir alafenamide hemifumarate at 60°C under closed conditions.

Figure 4 is a flow diagram illustrating the preparation of a bilayer tablet formulation of emtricitabine, rilpivirine HCl and tenofovir alafenamide hemifumarate.

Figure 5 shows the results of studies carried out on a bilayer tablet formulation of emtricitabine, rilpivirine HCl and tenofovir alafenamide hemifumarate and a monolayer formulation of emtricitabine, rilpivirine HCl and tenofovir alafenamide hemifumarate to assess the dissolution of rilpivirine, as compared to the dissolution of rilpivirine from COMPLERA® and EDURANT®.

Figures 6A, B and C show the results of studies carried out on a bilayer tablet formulation to assess the dissolution of rilpivirine HCl, emtricitabine and tenofovir alafenamide hemifumarate, respectively, as a function of tablet hardness (*i.e.* at a tablet hardness of 13, 16 and 19 kP).

Figure 7 shows the total tenofovir alafenamide hemifumarate degradation products of various tablets containing rilpivirine HCl, emtricitabine and tenofovir alafenamide hemifumarate, relative to the tenofovir alafenamide hemifumarate degradation products from a tablet containing only emtricitabine and tenofovir alafenamide hemifumarate as active pharmaceutical ingredients.

Figures 8A, B and C show the results of studies carried out on a bilayer tablet formulation to assess whether the dissolution of rilpivirine HCl, emtricitabine and tenofovir alafenamide hemifumarate, respectively, changes following storage of the tablet for 1 month, 3 months and 6 months under differing conditions.

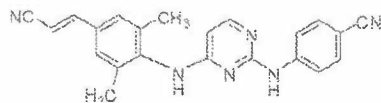
Figure 9 shows the tensile strength of the individual rilpivirine HCl and emtricitabine/tenofovir alafenamide hemifumarate powder blends as a function of upper punch pressure.

DETAILED DESCRIPTION

Typically, the oral dosage forms disclosed herein comprise three active pharmaceutical ingredients: rilpivirine (or a pharmaceutically acceptable salt thereof), tenofovir alafenamide (or a pharmaceutically acceptable salt thereof), and emtricitabine (or a pharmaceutically acceptable salt thereof).

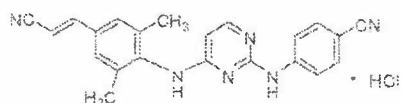
Rilpivirine

Rilpivirine (R or RPV), a diarylpyrimidine derivative, is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with *in vitro* activity against wild type HIV-1 and NNRTI-resistant mutants. It has the following formula (see WO2003/016306):



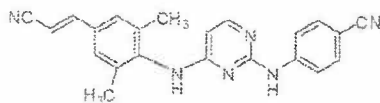
Its IUPAC name is 4-([4-([4-[(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl)amino]pyrimidin-2-yl)amino]benzonitrile. It is currently authorised as part of EDURANT[®] (rilpivirine HCl 27.5 mg, equivalent to 25 mg rilpivirine) and COMPLERA[®]/ EVIPLERA[®] (rilpivirine HCl 27.5 mg, tenofovir disoproxil fumarate 300 mg, 200 mg emtricitabine)

Solid oral dosage forms disclosed herein include rilpivirine, usually in the form of a pharmaceutically acceptable salt. Rilpivirine can be present within an oral dosage form in solvated or unsolvated form, and references to "rilpivirine" include both of these forms. Typically, rilpivirine is in the form of rilpivirine HCl, having the formula below:



In certain specific embodiments, solid oral dosage forms containing 25 mg of rilpivirine, e.g. as about 27.5 mg of rilpivirine HCl, are provided.

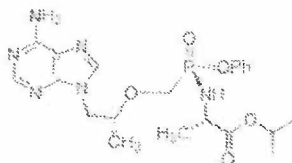
As used herein, and in the absence of a specific reference to a particular pharmaceutically acceptable salt and/or solvate of rilpivirine (e.g. rilpivirine *hydrochloride*), any dosages, whether expressed in e.g. milligrams or as a % by weight, should be taken as referring to the amount of rilpivirine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



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

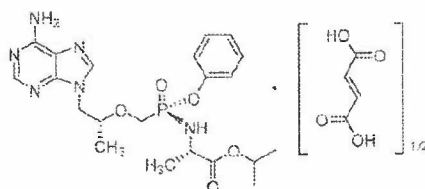
Tenofovir alafenamide

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

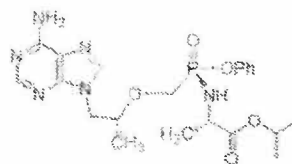


Its IUPAC name is (S)-isopropyl-2-((S)-((R)-1-(6-amino-9H-purin-9-yl)propan-2-yl)oxy)methyl(phenoxy)phosphorylamino)propanoate. It is also referred to as 19-[(R)-2-[(S)-[(S)-1-(isopropoxycarbonyl)ethyl] amino]phenoxyphosphinyl]-methoxy]propyl]adenine).

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



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



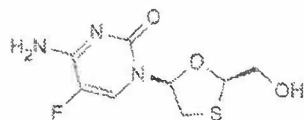
For example, therefore, a reference to "25 mg tenofovir alafenamide or a pharmaceutically acceptable salt and/or solvate thereof" means an amount of tenofovir alafenamide or a

pharmaceutically acceptable salt and/or solvate thereof which provides the same amount of tenofovir alafenamide as 25 mg of tenofovir alafenamide *free base*.

The amount of tenofovir alafenamide in a solid oral dosage form provided herein is generally between 10 mg and 30 mg, for instance within the range of 20 mg to 30 mg, and more typically between 24 mg and 28 mg. In certain embodiments, the solid oral dosage form contains 10 mg tenofovir alafenamide *e.g.* as about 11 mg of tenofovir alafenamide hemifumarate. In other certain specific embodiments, solid oral dosage forms containing 25 mg of tenofovir alafenamide *e.g.* as about 28 mg of tenofovir alafenamide hemifumarate, are provided.

Emtricitabine

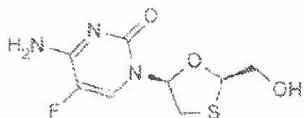
Emtricitabine (FTC) is a nucleoside reverse transcriptase inhibitor having the formula below



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

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

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



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

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

Solid oral dosage forms

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

In addition to the clinical benefits described above that are expected to result from the use of tenofovir alafenamide, the dosage forms of the present invention may afford further advantages. In particular, the inventors have determined that it is possible to formulate the three active ingredients into a solid oral dosage form which has a total weight of less than 1.0 g, for instance less than about 800 mg, or even less than about 700 mg. This is advantageous given that COMPLERA® has a total weight of about 1200 mg. The provision of a relatively small dosage form (in particular a tablet) represents a clinical advantage because it may be expected to increase patient convenience and thus compliance as compared to larger dosage forms which are more burdensome for patients to swallow. In specific 25 embodiments, the solid oral dosage form of the invention has a total weight of between 600 and 700 mg. By way of comparison, COMPLERA® contains over 650 mg of excipients, whereas the presently disclosed dosage forms may comprise less than 600 mg of excipients, such as less than 500 mg of excipients, or less than 400 mg of excipients. For example, solid oral dosage forms disclosed herein may comprise between 200 and 600 mg of excipients, or 30 between 250 mg and 550 mg of excipients, or between 300 mg and 500 mg of excipients. Most typically, solid oral dosage forms disclosed herein comprise between 350 mg and 450 mg of excipients. In such embodiments, the dosage forms will typically comprise as active ingredients (a) 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg 35 emtricitabine or a pharmaceutically acceptable salt thereof. In certain embodiments, the dosage forms will typically comprise as active ingredients (a) 27.5 mg rilpivirine

hydrochloride, (b) 28 mg tenofovir alafenamide hemifumarate, and (c) 200 mg emtricitabine.

The solid oral dosage forms described herein will typically be in the form of a tablet. In particular embodiments, they may be in the form of a multilayer tablet. This is because the
5 Inventors have found that the use of multilayer tablets may assist in optimizing the properties of the dosage form, particularly the stability (e.g. of tenofovir alafenamide). They have also discovered that the use of multilayer tablets may affect the dissolution profile of one or more of the active ingredients within the dosage form, and is therefore likely to have an impact on the *in vivo* pharmacokinetics of the dosage form. In particular, it has been observed that
10 the dissolution of rilpivirine varies depending on whether the tablet is a monolayer or multilayer tablet. The provision of a tablet with particular pharmacokinetic parameters, e.g. pharmacokinetic parameters that are bioequivalent with existing medicines (or medicines at an advanced stage of the regulatory procedure) is a particular advantage afforded by the present invention. Achieving bioequivalence may require the use of a multilayer tablet.

15 In one embodiment, a multilayer tablet comprising (a) rilpivirine or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof is provided. Typically, each layer contains at least one of (a), (b), and (c). For instance, the tablet may comprise (a) a first layer comprising rilpivirine or a pharmaceutically acceptable salt thereof,
20 (b) a second layer comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof. In such embodiments, typically (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof. In one
25 embodiment (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g. the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight rilpivirine or a pharmaceutically acceptable salt
30 thereof).

A particular embodiment provides a tablet, wherein the first layer comprises rilpivirine or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g. the first layer contains less than 1% by weight
35 tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of

rilpivirine or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight rilpivirine or a pharmaceutically acceptable salt thereof). In a particular embodiment, the invention provides a tablet, wherein (a) the first layer comprises 27.5 mg rilpivirine hydrochloride and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof (e.g. the first layer contains less than 1% by weight tenofovir alafenamide or a pharmaceutically acceptable salt thereof), and (b) the second layer comprises 28 mg tenofovir alafenamide hemifumarate and 200 mg emtricitabine and is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof (e.g. the second layer contains less than 1% by weight rilpivirine or a pharmaceutically acceptable salt thereof), wherein the first layer has a total weight of less than about 400 mg, such as about 300 mg, and the second layer has a total weight of less than about 450 mg, such as about 350 mg. In one embodiment, the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch.

The tablets disclosed herein are typically immediate release tablets. In one embodiment, the invention provides a tablet which releases at least 80% of (a) tenofovir alafenamide and/or (b) emtricitabine in 20 minutes, measured using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm. Typically, the tablets disclosed herein release at least 90% of (a) tenofovir alafenamide and/or (b) emtricitabine in 20 minutes, measured using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm. In some embodiments, a tablet that releases less than 50% of rilpivirine in 60 minutes is provided, measured using USP Apparatus II, in 1000 ml of pH 4.5 sodium acetate with 2% polysorbate 20 at 37 °C and paddle speed of 75 rpm.

Tablets disclosed herein will generally have a hardness within the range 13-19 kP, and, in certain specific embodiments, have a hardness of 16 kP. Hardness can conveniently be assessed by driving an anvil to compress a tablet at a constant loading rate until it fractures, operating in accordance with USP <1217> (using e.g. a TBH 220, ERWEKA GmbH, Heusenstamm Germany hardness tester).

Tablets of the invention will generally have a friability of <1% by weight. Friability can be assessed according to USP <1216>.

The core of a tablet provided herein may have a hardness of between 13-19 kP, and a friability of <1% by weight.

Tablets will typically include one or more excipients. Excipients should be compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof. Examples of suitable excipients are well known to the person skilled in the art of tablet formulation and may be found e.g. in *Handbook of Pharmaceutical Excipients* (eds.

Rowe, Sheskey & Quinn), 6th edition 2009. As used herein the term "excipients" is intended to refer to *inter alia* basifying agents, solubilisers, glidants, fillers, binders, lubricant, diluents, preservatives, surface active agents, dispensing agents and the like. The term also includes agents such as sweetening agents, flavoring agents, coloring agents and preserving agents. Such components will generally be present in admixture within the tablet.

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

Examples of lubricants, glidants and flow aids include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl behenate, sodium stearyl fumarate, colloidal silicon dioxide, and talc. The amount of lubricant in a tablet can generally be between about 0.5-5% by weight. In certain specific embodiments, tablets of the invention include magnesium stearate. In certain embodiments, the tablet includes less than about 20 mg magnesium stearate.

Examples of disintegrants include, but are not limited to, starches, celluloses, cross-linked PVP, sodium starch glycolate, croscarmellose sodium, *etc.*

Examples of fillers (also known as bulking agents or diluents) include, but are not limited to, starches, maltodextrins, polyols (such as lactose), and celluloses. Tablets provided herein may include lactose and/or microcrystalline cellulose. Lactose can be used in anhydrous or hydrated form (e.g. monohydrate), and is typically prepared by spray drying, fluid bed granulation, or roller drying. In certain embodiments, tablets provided herein include less than about 250 mg lactose, in particular less than about 200 mg lactose, and/or less than about 250 mg microcrystalline cellulose, in particular less than about 200 mg microcrystalline cellulose. Lactose monohydrate is preferred.

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

Tablets provided herein may be uncoated or coated (in which case they include a coating). Although uncoated tablets may be used, it is more usual to provide a coated tablet, in which case a conventional non-enteric coating may be used. Film coatings are known in the art and can be composed of hydrophilic polymer materials, but are not limited to, polysaccharide materials, such as hydroxypropylmethyl cellulose (HPMC), methylcellulose, hydroxyethyl

cellulose (HEC), hydroxypropyl cellulose (HPC), poly(vinylalcohol-co-ethylene glycol) and other water soluble polymers. Though the water soluble material included in the film coating of the present invention may include a single polymer material, it may also be formed using a mixture of more than one polymer. The coating may be white or coloured e.g. gray. Suitable coatings include, but are not limited to, polymeric film coatings such as those comprising polyvinyl alcohol e.g. 'Opadry® II' (which includes part-hydrolysed PVA, titanium dioxide, macrogol 3350 and talc, with optional colouring such as iron oxide or indigo carmine or iron oxide yellow or FD&C yellow #6). The amount of coating will generally be between about 2-4% of the core's weight, and in certain specific embodiments, about 3%. Unless specifically stated otherwise, where the dosage form is coated, it is to be understood that a reference to % weight of the tablet means that of the total tablet, i.e. including the coating.

Pharmacokinetics

The inventors have found that it is possible to formulate rilpivirine (in particular rilpivirine hydrochloride), emtricitabine and tenofovir alafenamide (in particular tenofovir alafenamide hemifumarate) in a solid oral dosage form which is capable of demonstrating bioequivalence, i.e. equivalent systemic exposure (AUC_{inf} , C_{max}), for each active ingredient compared to standard comparators. In particular, in some embodiments the tablets of the invention provide plasma concentrations (AUC_{inf} , C_{min}) of one or more of the three active pharmaceutical ingredients that are bioequivalent to the plasma concentrations produced by the administration of EDURANT® (rilpivirine HCl, 27.5 mg) and/or a fixed dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (E/C/F/TAF) (corresponding to 150/150/200/10 mg of free base), the latter of which is the subject of a New Drug Application filed in November 2014 with the U.S. Food and Drug Administration. Achieving bioequivalence of rilpivirine to the currently approved rilpivirine single agent formulation, EDURANT®, was initially a challenge because the dissolution of rilpivirine was found to vary depending on the properties of the dosage form in which the rilpivirine was presented. Based on the findings of the inventors and the present disclosure, the skilled person is able to provide dosage forms which provide such bioequivalence (see for instance the examples, below).

Accordingly, in one embodiment a solid oral dosage form (in particular a tablet) is provided as described herein, wherein the dosage form:

- (a) releases emtricitabine *in vivo* in fed human subjects to provide a plasma C_{max} of from about 1250 to about 2050 ng/mL and/or a AUC_{inf} of from about 7650 to about 12050 h•ng/mL, and/or

- (b) releases rilpivirine *in vivo* in fed human subjects to provide a plasma C_{max} of from about 90 to about 160 ng/mL and/or a AUC_{inf} of from about 3050 to about 4850 h•ng/mL, and/or
- (c) releases tenofovir alafenamide *in vivo* in fed human subjects to provide a plasma C_{max} of from about 150 to about 260 ng/mL and/or a AUC_{inf} of from about 200 and 340 h•ng/mL.

In some embodiments, the solid oral dosage form will exhibit properties (a) and (b). In other embodiments, the solid oral dosage form will exhibit properties (a) and (c). In some embodiments, the solid oral dosage form will exhibit properties (b) and (c). Typically, the solid oral dosage form will exhibit properties (a), (b) and (c).

In some embodiments, a solid oral dosage form (in particular a tablet) as described herein is provided, for which:

- (a) the 90% confidence interval of log-transformed C_{max} and log-transformed AUC_{inf} for rilpivirine in fed human subjects fall completely within the range 80-125% of the log-transformed C_{max} and log-transformed AUC_{inf} , respectively, of a reference tablet, wherein the reference tablet has (i) a core consisting of 27.5 mg rilpivirine hydrochloride, lactose monohydrate, croscarmellose sodium, polyvinylpyrrolidone, polysorbate 20, silicified microcrystalline cellulose and magnesium stearate, and (ii) a film coating consisting of a mixture of lactose monohydrate, hypromellose 2910, titanium dioxide E171, polyethylene glycol (macrogol 3000) and triacetin, and/or
- (b) the 90% confidence interval of log-transformed C_{max} and log-transformed AUC_{inf} for emtricitabine in fed human subjects fall completely within the range 80-125% of the log-transformed C_{max} and log-transformed AUC_{inf} , respectively, of a reference tablet, wherein the reference tablet has (i) a core consisting of 150 mg elvitegravir, 60.8 mg lactose monohydrate, 241.5 mg microcrystalline cellulose, 7.5 mg hydroxypropyl cellulose, 11.3 mg sodium lauryl sulfate, 65.8 mg croscarmellose sodium, 200 mg emtricitabine, 11.2 mg tenofovir alafenamide hemifumarate, 288.5 mg cobicistat on silicon dioxide (corresponding to 150 mg of cobicistat), 13.5 mg magnesium stearate, and (ii) a film coating consisting of 31.5 mg of a mixture of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine and iron oxide (such as Opadry® II Green), and/or
- (c) the 90% confidence interval of log-transformed C_{max} and log-transformed AUC_{inf} for tenofovir alafenamide in fed human subjects fall completely within the range 80-125% of the log-transformed C_{max} and log-transformed AUC_{inf} , respectively, of a reference tablet, wherein the reference tablet has (i) a core consisting of 150 mg elvitegravir, 60.8 mg lactose monohydrate, 241.5 mg microcrystalline cellulose, 7.5

mg hydroxypropyl cellulose, 11.3 mg sodium lauryl sulfate, 65.8 mg croscarmellose sodium, 200 mg emtricitabine, 11.2 mg tenofovir alafenamide hemifumarate, 288.5 mg cobicistat on silicon dioxide (corresponding to 150 mg of cobicistat), 13.5 mg magnesium stearate, and (ii) a film coating consisting of 31.5 mg of a mixture of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine and iron oxide (such as Opadry® II Green)

In some embodiments, the solid oral dosage form will exhibit properties (a) and (b). In other embodiments, the solid oral dosage form will exhibit properties (a) and (c). In some embodiments, the solid oral dosage form will exhibit properties (b) and (c). Typically, the solid oral dosage form will exhibit properties (a), (b) and (c).

C_{max}

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

In particular embodiments, solid oral dosage forms of the invention provide a plasma C_{max} of rilpivirine in fed patients of from about 90 to about 160 ng/mL, e.g. about 120 ng/mL.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma C_{max} of emtricitabine in fed patients of from about 1250 to about 2050 ng/mL, e.g. about 1600 ng/mL.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma C_{max} of tenofovir alafenamide in fed patients of from about 150 to about 260 ng/mL, e.g. about 200 ng/mL.

AUC_{inf}

AUC_{inf} is the area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-12h} + (C_{12h}/k_e)$.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma AUC_{inf} of rilpivirine in fed patients of from about 3050 to about 4850 h•ng/mL, e.g. about 3850 h•ng/mL.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma AUC_{inf} of emtricitabine in fed patients of from about 7650 to about 12050 h•ng/mL, e.g. about 9600 h•ng/mL.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma AUC_{inf} of tenofovir alafenamide in fed patients of from about 200 and 340 h•ng/mL, e.g. about 260 h•ng/mL.

AUC_{last}

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

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma AUC_{last} of rilpivirine in fed patients of from about 2950 to about 4650 h•ng/mL, e.g. about 3700 h•ng/mL.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma AUC_{last} of emtricitabine in fed patients of from about 7500 to about 12600 h•ng/mL, e.g. about 9400 h•ng/mL.

In certain specific embodiments, solid oral dosage forms of the invention provide a plasma AUC_{last} of tenofovir alafenamide in fed patients of from about 200 and 315 h•ng/mL, e.g. about 250 h•ng/mL.

C_{last}

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

C_{max}, C_{last}, AUC_{inf}, and AUC_{last} are standard pharmacokinetic parameters that can be estimated manually or by using modelling software well known in the art, such as the Pharsight WinNonlin package using a non-compartmental model. The general basis for calculation of these quantities is well-known (e.g. see Rowland & Tozer (2010) *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications* ISBN 978-0781750097, or Jambhekar & Breen (2012) *Basic Pharmacokinetics* ISBN 978-0853699804). Typically the parameters will be assessed as the average (e.g. geometric or arithmetic mean) from within a group of at least 12 (and normally between 24 and 36) healthy human adults. Parameters should be measured in accordance with standards and practices which would be acceptable to a pharmaceutical regulatory agency such as FDA, EMA, MHLW, or WHO. The values may be based on measurements taken at appropriate intervals following the time of tablet ingestion, such as every hour, or at increasingly sparse sampling intervals, such as 1, 3, 5, 7, 9, 11, 13, 15, 20, and 24 hours after ingestion. They can be assessed either following a single-dose of drug or at steady state, but will typically be assessed following a single-dose.

It is well known in the bioavailability and bioequivalence arts how to determine whether any particular tablet meets regulatory requirements for equivalent bioavailability and pharmacokinetic bioequivalence e.g. see: Niazi (2014) *Handbook of Bioequivalence Testing*, 2nd Edition, ISBN 978-1482226379; *Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*

FDA March 2003; and *Guideline On The Investigation Of Bioequivalence*, EMEA 2010 CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. To ensure statistical power a study to measure the C_{max} , AUC_{last} and AUC_{inf} values will be performed in multiple subjects e.g. in a group of at least 12 (and normally between 24 and 36) healthy human adults.

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

Stability

As mentioned above and as explained in more detail in the examples below, the stability of tenofovir alafenamide deteriorates in the presence of emtricitabine. The degradation of
15 tenofovir alafenamide is further accelerated in the presence of rilpivirine. Known degradation products of tenofovir alafenamide include PMPA and PMPA anhydride. Similarly, the stability of emtricitabine in the presence of tenofovir alafenamide and rilpivirine HCl is a challenge in formulating a composition comprising these three active ingredients. Known degradation products of emtricitabine include cyclic-FTU-I and FTU

20 The inventors have found that solid oral dosage forms of the invention are stable, i.e. they have acceptable shelf-life, despite the dosage forms containing rilpivirine, tenofovir alafenamide and emtricitabine. Accordingly, solid oral dosage forms that do not comprise a pharmaceutically unacceptable amount of a tenofovir alafenamide degradation product are provided. Also provided is a composition comprising (a) tenofovir alafenamide or a
25 pharmaceutically acceptable salt thereof, and (b) emtricitabine or a pharmaceutically acceptable salt thereof, where the total quantity of degradation products derived from the tenofovir alafenamide or the pharmaceutically acceptable salt thereof is less than 3% (such as less than 2%) after storage for one month at 40°C/75% RH in open conditions. Optionally, the composition further comprises rilpivirine or a pharmaceutically acceptable salt thereof.

30 The inventors have conducted drug load studies and have realized that the chemical stability of tenofovir alafenamide varies depending on the proportion of tenofovir alafenamide within a given composition. Accordingly, in some embodiments, a solid composition comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof is provided, wherein the proportion of tenofovir alafenamide or a pharmaceutically acceptable salt thereof in the
35 composition is from about 4% to about 12% by weight. In some embodiments, a solid composition is provided which comprises from about 5% to about 15% by weight tenofovir

alafenamide hemifumarate, e.g. about 7% to about 9% by weight tenofovir alafenamide hemifumarate, in particular about 8% by weight tenofovir alafenamide hemifumarate. In another embodiment, a solid composition comprising from about 2-4% by weight tenofovir alafenamide hemifumarate is provided, e.g. 2.5% by weight tenofovir alafenamide hemifumarate. The composition may take various forms. It may, for example, be in the form of a powder. In other embodiments, the composition is a compressed dosage form, such as a tablet.

In addition, tenofovir alafenamide undergoes solid-state hydrolysis and accordingly the inclusion of desiccant may assist in facilitating an acceptable shelf-life. Thus, a kit is provided which comprises (a) a tablet comprising rilpivirine or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant. The inventors have observed that the stability of tenofovir alafenamide in certain formulations is dependent on desiccant level. In certain embodiments, therefore, the kit includes silica gel as a desiccant. In certain specific embodiments, the kit includes 3 g silica gel as a desiccant. The kit may optionally further include polyester coil packing material. In certain embodiments of the kit, the total quantity of degradation products derived from the tenofovir alafenamide or the pharmaceutically acceptable salt thereof in the tablet is less than 2% (such as less than 1%) after storage for six months at 50°C/75% RH.

The use of multilayer tablets of the type described above may also assist in optimizing the stability of the dosage forms. For instance, a tablet is provided which comprises (a) 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g. Multilayer tablets are described in further detail above and in the examples below.

The invention provides a multilayer tablet comprising (a) rilpivirine or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.

In an embodiment, the multilayer tablet disclosed herein comprises (a) a first layer comprising rilpivirine or a pharmaceutically acceptable salt thereof, (b) a second layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof.

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

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

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

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

In one embodiment, the multilayer tablet disclosed herein comprises 27.5 ± 3 mg of rilpivirine HCl. In one embodiment, the multilayer tablet disclosed herein comprises 200 ± 20 mg of emtricitabine. In one embodiment, the multilayer tablet disclosed herein comprises 28 ± 3 mg of tenofovir alafenamide hemifumarate.

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

In one embodiment, the first layer of the multilayer tablet comprises a basifying agent. In one embodiment, the basifying agent is selected from croscarmellose sodium, calcium carbonate, sodium hydroxide, aluminum oxide, alkali metal hydroxides (e.g. such as sodium hydroxide, potassium hydroxide and lithium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide, and magnesium hydroxide), aluminum hydroxide, dihydroaluminum, sodium carbonate, aluminum magnesium hydroxide sulfate, aluminum hydroxide magnesium carbonate, ammonium hydroxides, magnesium carbonate, magnesium stearate, piperazine, sodium acetate, sodium citrate, sodium tartrate, sodium maleate, and sodium succinate and mixtures thereof.

In one embodiment, the first layer of the multilayer tablet of the invention comprises croscarmellose sodium and polysorbate 20. In one embodiment, the first layer of the multilayer tablet of the invention comprises lactose monohydrate, povidone, croscarmellose sodium, polysorbate 20, microcrystalline cellulose, and magnesium stearate.

In one embodiment a tablet is provided wherein less than about 15 weight percent of the first layer is rilpivirine hydrochloride. In one embodiment a tablet is provided wherein less than about 12.2 weight percent of the first layer is rilpivirine hydrochloride. In one embodiment a tablet is provided wherein less than about 12 weight percent of the first layer is rilpivirine hydrochloride.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 230 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 240 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 250 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 260 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 270 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 280 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 290 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 300 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 330 mg and is less than about 325 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 300 mg and is less than about 325 mg.

In one embodiment a tablet is provided wherein the first layer comprises 27.5 ± 1.4 mg of rilpivirine hydrochloride and wherein the total weight of the first layer is at least about 290 mg and is less than about 310 mg.

In one embodiment, the first layer of the multilayer tablet of the invention has a total weight of 300 ± 75 mg, or 300 ± 25 mg, or 300 ± 10 mg, or 300 mg.

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

Ingredient	Mass (mg)
Rilpivirine or a salt thereof	20-35
Microcrystalline cellulose	40-100
Croscarmellose sodium	1-30
Lactose	150-250
Povidone	1-10
Polysorbate 20	0.1-5
Magnesium stearate	1-10

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

Ingredient	Mass (mg)
Rilpivirine HCl	24-31
Microcrystalline cellulose	50-80
Croscarmellose sodium	2-20
Lactose	130-230
Povidone	2-5
Polysorbate 20	0.1-2
Magnesium stearate	2-6

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

Ingredient	Mass (mg)
Rilpivirine HCl	27.5 ± 3
Microcrystalline cellulose	60.0 ± 12
Croscarmellose sodium	15 ± 3
Lactose monohydrate	189 ± 40

Povidone	3.3 ± 1
Polysorbate 20	0.4 ± 0.1
Magnesium stearate	3.0 ± 1

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

Ingredient	Mass (mg)
Rilpivirine HCl	27.5 ± 2.8
Microcrystalline cellulose	60.0 ± 6.0
Croscarmellose sodium	16.1 ± 1.6
Lactose	189.8 ± 19.0
Povidone	3.3 ± 0.3
Polysorbate 20	0.4 ± 0.04
Magnesium stearate	3.0 ± 0.3

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

Ingredient	Mass (mg)
Rilpivirine HCl	27.5 ± 1.4
Microcrystalline cellulose	60.0 ± 3.0
Croscarmellose sodium	16.1 ± 0.8
Lactose	189.8 ± 9.5
Povidone	3.3 ± 0.17
Polysorbate 20	0.4 ± 0.02
Magnesium stearate	3.0 ± 0.15

8 In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
Rilpivirine HCl	27.5
Microcrystalline cellulose	60.00
Croscarmellose sodium	16.10
Lactose	189.8
Povidone	3.25
Polysorbate 20	0.35

Magnesium stearate	3.00
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In one embodiment, the first layer of the multilayer tablet consists of:

Ingredient	Mass (mg)
<i>Intragranular</i>	
Rilpivirine HCl	27.5
Lactose monohydrate	55.10
Polysorbate 20	0.35
Povidone K29/32	3.25
Croscarmellose sodium	1.10
<i>Extragranular</i>	
Lactose Monohydrate	134.70
Croscarmellose sodium	15.00
Microcrystalline sodium	60.00
Magnesium stearate	3.00
<i>Total layer weight</i>	<i>300</i>

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

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

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

In one embodiment, the second layer of the multilayer tablet comprises 20-30 mg of croscarmellose sodium. In one embodiment, the second layer of the multilayer tablet comprises 80-90 mg of microcrystalline sodium. In one embodiment, the second layer of the multilayer tablet comprises 1-7 mg of magnesium stearate.

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

In one embodiment, second layer of the multilayer tablet consists of emtricitabine, tenofovir alafenamide hemifumarate, croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

5 In one embodiment, the second layer of the multilayer tablet has a total weight of less than 600 mg, or less than 500 mg, or less than 400 mg, or less than 375 mg. In one embodiment, the second layer of the multilayer tablet has a total weight of 350 mg $\pm$ 50 mg or 350 mg $\pm$ 25 mg, or 350 mg $\pm$ 5 mg, or 350 mg.

10 In one embodiment, over 40 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 50 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment of the invention, over 60 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 64 % by weight of the second layer of the multilayer tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment of the invention, over 65 % by weight of the second layer of the multilayer tablet is emtricitabine and tenofovir alafenamide hemifumarate.

15 In one embodiment, the second layer of the multilayer tablet contains less than 250 mg of excipients, for example less than 200 mg, or less than 150 mg, or less than 130 mg, or less than 120 mg of excipients.

20 In one embodiment, at least 50% by weight of the second layer of the multilayer tablet is emtricitabine. In one embodiment of the invention, at least 55% by weight of the second layer of the multilayer tablet is emtricitabine.

25 In one embodiment, at least 5% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 7% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 8% by weight of the second layer of the multilayer tablet is tenofovir alafenamide hemifumarate.

30 In one embodiment, less than 20% by weight of the second layer of the multilayer tablet is croscarmellose sodium. In one embodiment, less than 10% by weight of the second layer of the multilayer tablet is croscarmellose sodium. The use of croscarmellose sodium may provide particular advantages in terms of stabilizing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof. For instance, the inventors have found that the use of about 7 to 9% (e.g. about 8%) croscarmellose sodium by weight of the second layer may

provide enhanced stability relative to other amounts of croscarmellose sodium (e.g. 6% by weight) and/or other disintegrants e.g. polyvinylpyrrolidone.

In one embodiment, less than 40% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 30% by weight of the second layer of the multilayer tablet is microcrystalline cellulose. In one embodiment, less than 25% by weight of the second layer of the multilayer tablet is microcrystalline cellulose.

In one embodiment, the total weight of the second layer is less than 200% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 150% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 130% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 120% of the total weight of the first layer. In one embodiment, the total weight of the second layer is less than 117% of the total weight of the first layer.

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

Ingredient	Mass (mg)
Emtricitabine or a salt thereof	150-250
Tenofovir alafenamide or a salt thereof	20-35
Croscarmellose sodium	20-35
Microcrystalline cellulose	70-100
Magnesium stearate	1-7

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

Ingredient	Mass (mg)
Emtricitabine	170-230
Tenofovir alafenamide hemifumarate	22-32
Croscarmellose sodium	20-35
Microcrystalline cellulose	70-100
Magnesium stearate	1-7

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

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Croscarmellose sodium	28 ± 3

Microcrystalline cellulose	89 ± 9
Magnesium stearate	5.2 ± 1.1

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

Ingredient	Mass (mg)
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28 ± 1.4
Croscarmellose sodium	28 ± 1.4
Microcrystalline cellulose	89 ± 4
Magnesium stearate	5.2 ± 0.5

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

Ingredient	Mass (mg)
Emtricitabine	199.99
Tenofovir alafenamide hemifumarate	28.04
Croscarmellose sodium	28.00
Microcrystalline cellulose	88.69
Magnesium stearate	5.20

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

Ingredient	Mass (mg)
<i>Intragranular</i>	
Emtricitabine	199.99
Tenofovir alafenamide hemifumarate	28.04
Croscarmellose sodium	28.00
Microcrystalline cellulose	88.69
Magnesium stearate	2.60
<i>Extragranular</i>	
Magnesium stearate	2.60
<i>Total layer weight</i>	350

5

In one embodiment of the multilayer tablet of the invention, the first layer is in contact with the second layer.

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

- 5 In one embodiment, the multilayer tablet further comprises a film coating. In one embodiment the film coating comprises polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and black iron oxide. In one embodiment the film coating consists of 19.5 ± 10 mg of Opadry II 85F17636 Gray.

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

Ingredient	Mass (mg)
Rilpivirine HCl	27.5 ± 3
Microcrystalline cellulose	60.0 ± 12
Croscarmellose sodium	16 ± 3
Lactose monohydrate	189 ± 40
Povidone	3.3 ± 1
Polysorbate 20	0.4 ± 0.1
Magnesium stearate	3.0 ± 1

- 10 and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 20
Tenofovir alafenamide hemifumarate	28 ± 3
Croscarmellose sodium	28 ± 3
Microcrystalline cellulose	89 ± 9
Magnesium stearate	5.2 ± 1.1

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

Ingredient	Mass (mg)
Rilpivirine HCl	27.5 ± 1.4
Microcrystalline cellulose	60.0 ± 3.0
Croscarmellose sodium	16.1 ± 0.8
Lactose	189.8 ± 9.5
Povidone	3.3 ± 0.17

Polysorbate 20	0.4 ± 0.02
Magnesium stearate	3.0 ± 0.15

and a second layer consisting of:

Ingredient	Mass (mg)
Emtricitabine	200 ± 10
Tenofovir alafenamide hemifumarate	28 ± 1.4
Croscarmellose sodium	28 ± 1.4
Microcrystalline cellulose	89 ± 4
Magnesium stearate	5.2 ± 0.5

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

	Weight (mg)	% w/w (in layer)
<i>Intragranular</i>		
Rilpivirine HCl	27.50	9.2
Lactose Monohydrate	55.10	18.4
Polysorbate 20	0.35	0.12
Povidone K29/32	3.25	1.1
Croscarmellose sodium	1.10	0.37
<i>Extragranular</i>		
Lactose Monohydrate	134.70	44.9
Croscarmellose sodium	15.00	5.0
Microcrystalline cellulose	60.00	20.0
Magnesium stearate	3.00	1.0

and a second layer consisting of:

	Weight (mg)	% w/w (in layer)
<i>Intragranular</i>		
Emtricitabine	199.99	57.1
Tenofovir alafenamide hemifumarate	28.04	8.01
Croscarmellose sodium	28.00	8.0
Microcrystalline cellulose	88.69	25.3
Magnesium stearate	2.60	0.75

<i>Extragranular</i>		
Magnesium stearate	2.60	0.75

and optionally a film coating

In one embodiment, a tablet is provided consisting of a first layer consisting of:

	Weight (mg)	% w/w (in layer)
<i>Intragranular</i>		
Rilpivirine HCl	27.50	5.2
Lactose Monohydrate	55.10	18.4
Polysorbate 20	0.35	0.12
Povidone K29/32	3.25	1.1
Croscarmellose sodium	1.10	0.37
<i>Extragranular</i>		
Lactose Monohydrate	134.70	44.9
Croscarmellose sodium	15.00	5.0
Microcrystalline cellulose	60.00	20.0
Magnesium stearate	3.00	1.0

and a second layer consisting of:

	Weight (mg)	% w/w (in layer)
<i>Intragranular</i>		
Emtricitabine	199.99	57.1
Tenofovir alafenamide hemifumarate	28.04	8.01
Croscarmellose sodium	28.00	8.0
Microcrystalline cellulose	88.69	25.3
Magnesium stearate	2.60	0.75
<i>Extragranular</i>		
Magnesium stearate	2.60	0.75

and a film coating consisting of 19.5 mg of Opadry II 85F17636 Gray (a combination of polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide and iron oxide black).

Another aspect of the invention provides a solid oral dosage form comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof. In one embodiment, this solid oral dosage form is a tablet.

In one embodiment, the tablet comprises microcrystalline cellulose and croscarmellose sodium.

In one embodiment, the tablet comprises microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

5 In one embodiment, the tablet comprises 20-30 mg of croscarmellose sodium. In one embodiment, the tablet comprises 80-90 mg of microcrystalline sodium. In one embodiment, the tablet comprises 2-7 mg of magnesium stearate.

In one embodiment, the tablet does not comprise lactose. In one embodiment, the tablet does not comprise starch. In one embodiment, the tablet comprises neither lactose nor starch.

10 In one embodiment, the tablet has a total weight of less than 600 mg, or less than 500 mg, or less than 400 mg, or less than 375 mg. In one embodiment, the tablet has a total weight of 350 mg $\pm$ 50 mg or 350 mg $\pm$ 25 mg, or 350 mg $\pm$ 5 mg, or 350 mg.

In one embodiment, over 40 % by weight of the tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 50 % by weight of the tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 60 % by weight of the tablet of the invention is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment, over 64 % by weight of the tablet is emtricitabine or a salt thereof and tenofovir alafenamide or a salt thereof. In one embodiment of the invention, over 65 % by weight of the tablet is emtricitabine and tenofovir alafenamide hemifumarate.

20 In one embodiment of the invention, the tablet contains less than 250 mg of excipients, for example less than 200 mg, or less than 150 mg, or less than 130 mg, or less than 120 mg of excipients.

In one embodiment of the invention, at least 50% by weight of the tablet is emtricitabine. In one embodiment of the invention, at least 55% by weight of the tablet is emtricitabine.

In one embodiment, at least 5% by weight of the tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 7% by weight of the tablet is tenofovir alafenamide hemifumarate. In one embodiment, at least 8% by weight of the tablet is tenofovir alafenamide hemifumarate.

30 In one embodiment of the invention, less than 20% by weight of the tablet is croscarmellose sodium. In one embodiment of the invention, less than 10% by weight of the tablet is croscarmellose sodium.

In one embodiment of the invention, less than 40% by weight of the tablet is microcrystalline cellulose. In one embodiment of the invention, less than 30% by weight of the tablet is

microcrystalline cellulose. In one embodiment of the invention, less than 26% by weight of the tablet is microcrystalline cellulose.

In one embodiment of the invention, the tablet comprises:

Ingredient	Mass (mg)
Emtricitabine or a salt thereof	150-250
Tenofovir alafenamide or a salt thereof	20-35
Croscarmellose sodium	20-35
Microcrystalline cellulose	70-100
Magnesium stearate	1-7

In one embodiment of the invention, the tablet of the invention comprises:

Ingredient	Mass (mg)
Emtricitabine	170-230
Tenofovir alafenamide hemifumarate	22-32
Croscarmellose sodium	20-35
Microcrystalline cellulose	70-100
Magnesium stearate	1-7

5 In one embodiment of the invention, the tablet of the invention consists of:

Ingredient	Mass (mg)
Emtricitabine	200 $\pm$ 20
Tenofovir alafenamide hemifumarate	28 $\pm$ 3
Croscarmellose sodium	28 $\pm$ 3
Microcrystalline cellulose	89 $\pm$ 9
Magnesium stearate	5.2 $\pm$ 1.1

and optionally a film coating.

In one embodiment of the invention, the tablet of the invention consists of:

Ingredient	Mass (mg)
Emtricitabine	200 $\pm$ 10
Tenofovir alafenamide hemifumarate	28 $\pm$ 1.4
Croscarmellose sodium	28 $\pm$ 1.4
Microcrystalline cellulose	89 $\pm$ 4

Magnesium stearate	5.2 ± 0.5
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and optionally a film coating.

In one embodiment of the invention, the tablet of the invention consists of:

Ingredient	Mass (mg)
Emtricitabine	200.00
Tenofovir alafenamide hemifumarate	28.00
Croscarmellose sodium	28.00
Microcrystalline cellulose	88.70
Magnesium stearate	5.25

and optionally a film coating, for example a film coating comprising Opadry II Blue 85F105057 (a combination of Polyvinyl alcohol, polyethylene glycol (PEG), talc, titanium dioxide, FD&C blue #2).

In one embodiment of the invention, the tablet of the invention consists of:

Ingredient	Mass (mg)
<i>Intragranular</i>	
Emtricitabine	200.00
Tenofovir alafenamide hemifumarate	28.00
Croscarmellose sodium	28.00
Microcrystalline cellulose	88.70
Magnesium stearate	2.625
<i>Extragranular</i>	
Magnesium stearate	2.625
<i>Total core weight</i>	<i>350</i>

and a film coating consisting of Opadry II Blue 85F105057 (which contains 40.0% w/w Polyvinyl Alcohol-part hydrolyzed, 23.32% w/w Titanium Dioxide, 20.2% w/w Macrogol/PEG 3350, 14.8% w/w Talc, and 1.68% w/w FD&C Blue #2/Indigo Carmine Aluminum Lake).

Manufacturing methods

Methods for producing the compositions and dosage forms (in particular tablets) described herein are also provided. In some embodiments, the method comprises (a) compressing the emtricitabine or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a

pharmaceutically acceptable salt thereof as a second layer. The first layer and second layer may be compressed separately and subsequently combined. However, more typically, the first layer is formed by compression and subsequently the second layer is compressed onto the first layer. The inventors have discovered that the choice of layer order in the tableting of multilayer tablets may have an impact on the properties of the tablets (*e.g.* the adhesion of the layers within the tablet). Accordingly, compressing rilpivirine or a pharmaceutically acceptable salt thereof as a first layer *e.g.* to a first layer weight of about 300 mg., and then compressing tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer *e.g.* to a second layer weight of about 350 mg., is advantageous, because of the enhanced compressibility and flow of the first layer. This is contrary to the process used to produce Complera®/Eviplera® commercially, in which the rilpivirine-containing layer is compressed as the second layer.

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

Typically, the methods will include a step of coating the tablet cores after compression, *e.g.* with a film coating as described above.

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

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

Therapeutic methods

The solid oral dosage forms (in particular tablets) disclosed herein may be used to treat HIV (*e.g.* HIV-1).

Accordingly, methods for treating a subject having HIV are provided, comprising administering a solid oral dosage form of the invention (in particular a tablet) to the subject.

Similarly, a solid oral dosage form of the invention (in particular a tablet) is provided for use

in such treatment methods. The invention also provides the use of rilpivirine or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form of the invention (in particular a tablet) for treating HIV.

5 In some embodiments, the invention provides the use of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof, in the manufacture of an oral dosage form of the invention (in particular a tablet) for treating HIV.

10 In certain embodiments, a method of treating an HIV infection in a human having or at risk of having the infection is provided, wherein the method includes administering to the human the solid oral dosage forms disclosed herein.

In another embodiment, a use of the solid oral dosage forms disclosed herein for the treatment of an HIV infection in a human having or at risk of having the infection is provided.

15 In another embodiment, a method of using a solid oral dosage form disclosed herein in therapy is provided. In particular, a method of treating the proliferation of the HIV virus, treating AIDS, or delaying the onset of AIDS or ARC symptoms in a mammal (e.g., a human) is provided, comprising administering to the mammal a solid oral dosage form disclosed herein.

20 In a particular embodiment, the solid oral dosage forms disclosed herein are provided for use to prevent HIV infection from taking hold if the individual is exposed to the virus and/or to keep the virus from establishing a permanent infection and/or to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood. Accordingly, in certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1) are provided. For example, methods for reducing the risk of acquiring HIV (e.g., HIV-1) comprise administration of the solid dosage forms disclosed herein. In certain specific embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1) comprise administration of a solid oral dosage form disclosed herein in combination with safer sex practices. In certain embodiments, methods for reducing the risk of acquiring HIV (e.g., HIV-1) comprise administration of the solid dosage forms disclosed herein to an individual at risk of acquiring HIV. Examples of individuals at high risk for acquiring HIV include, without limitation, an individual who has partner(s) known to be HIV-1 infected, or who engages in sexual activity within an area or social network of high prevalence of HIV infection and one or more of the following: engages in sexual activity with inconsistent or no condom use, diagnosis of sexually transmitted infections, exchange of sex for commodities (such as

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money, food, shelter, or drugs), use of illicit drugs or alcohol dependence, incarceration, and partner(s) of unknown HIV-1 status with any of the factors listed above.

In certain embodiments, the reduction in risk of acquiring HIV is at least about 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In certain embodiments, the reduction in risk of acquiring HIV is at least about 75%.

In another embodiment, the use of a solid oral dosage form disclosed herein for the manufacture of a medicament for the treatment of an HIV infection in a human having or at risk of having the infection is disclosed.

In another embodiment, an article of manufacture comprising a solid oral dosage form disclosed herein, and packaging material comprising a label which indicates that the solid oral dosage form can be used to treat infection by HIV is disclosed.

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

In certain embodiments, the methods disclosed herein involve repeated administrations at intervals less than once daily. For example, in certain embodiments, the methods disclosed herein involve administration of the oral dosage forms disclosed herein every other day, five times per week, four times per week, three times per week, two times per week, or one time per week.

In certain embodiments, the methods disclosed herein involve administration prior to and/or after an event that would expose the individual to HIV or that would otherwise increase the individual's risk of acquiring HIV, i.e., as pre-exposure prophylaxis (PrEP). Examples of events that could increase an individual's risk of acquiring HIV include, without limitation, no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter or drugs for anal sex; sex with male partner and diagnosis of sexually transmitted infection; and no consistent use of condoms with sex partner known to be HIV-1 positive.

In certain embodiments, e.g., when administered as PrEP, the solid oral dosage forms disclosed herein are administered 2 to 72 hours, 2 to 48 hours, 2 to 24 hours, or 2 to 12 hours prior to an event that would increase the individual's risk of acquiring HIV (e.g., prior to sex). In some embodiments, the solid oral dosage forms disclosed herein are administered within 72 hours, 60 hours, 48 hours, 24 hours, 12 hours, 9 hours, 6 hours, 4 hours, 3 hours, 2 hours or 1 hour prior to an event that would increase the individual's risk of acquiring HIV.

(e.g., prior to sex). In certain embodiments, when the solid oral dosage forms disclosed herein are administered prior to an event that would increase the individual's risk of acquiring HIV, they are administered daily prior to the event. In certain embodiments, when the solid oral dosage forms disclosed herein are administered prior to an event that would increase the individual's risk of acquiring HIV, they are administered one to three times prior to the event.

In certain embodiments, e.g., when administered as PrEP, the solid oral dosage forms disclosed herein are administered 2 to 48 hours, 2 to 36 hours, 2 to 24 hours, or 2 to 12 hours following an event that would increase the individual's risk of acquiring HIV (e.g., following sex). In certain embodiments, the solid oral dosage forms disclosed herein are administered less than 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 12 hours, 18 hours, 24 hours, 36 hours, or 48 hours following an event that would increase the individual's risk of acquiring HIV (e.g., following sex). In certain other embodiments, the solid oral dosage forms disclosed herein are administered for 1 day, 2 days, 3 days, 4 days, or 5 days following an event that would increase the individual's risk of acquiring HIV (e.g., following sex). In certain embodiments, when the solid oral dosage forms disclosed herein are administered following an event that would increase the individual's risk of acquiring HIV, they are administered daily following the event. In certain embodiments, when the solid oral dosage forms disclosed herein are administered following an event that would increase the individual's risk of acquiring HIV, they are administered one to three times following the event. In certain embodiments, when the solid oral dosage forms disclosed herein are administered following an event that would increase the individual's risk of acquiring HIV, they are administered once following the event.

In certain embodiments, e.g., when administered as PrEP, the solid oral dosage forms disclosed herein are administered administered 2 to 72 hours, 2 to 48 hours, 2 to 24 hours, or 2 to 12 hours prior to an event that would increase the individual's risk of acquiring HIV (e.g., prior to sex) and 2 to 48 hours, 2 to 36 hours, 2 to 24 hours, or 2 to 12 hours following the event. For example, in some embodiments, one or more (e.g., one, two, or three) solid oral dosage forms disclosed herein are administered one to three days prior to an event that would increase the individual's risk of acquiring HIV (e.g., prior to sex) and once per day for a period of one to five days following the event. In some embodiments, one or more (e.g., one, two, or three) solid oral dosage forms disclosed herein are administered 2 to 24 hours prior to an event that would increase the individual's risk of acquiring HIV (e.g., prior to sex) and one or more times (e.g., one, two, or three times) 2 to 48 hours following the event. In some embodiments, the solid oral dosage forms disclosed herein are administered once per week, twice per week, three times per week, four times per week, or five times per week and one or more times (e.g., one, two, or three times) 2 to 48 hours following an event that would

increase the individual's risk of acquiring HIV (e.g., prior to sex). In one embodiment, the oral solid dosage forms disclosed herein are administered twice per week (one composition (i.e., tablet) per day) prior to an event and once (one composition) following an event that increases the individual's risk of acquiring HIV (e.g., one tablet within 24 hours of exposure, such as following sex).

General

The term "fed" in relation to administration of a solid oral dosage form to a human subject means administration of the dosage form orally under fed conditions (moderate fat meal) e.g. administration within about 30 minutes of the human consuming a standardized meal of about 200 to 600 calories and about 10 to about 15 grams of fat.

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.

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

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

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

The term "about" in relation to a numerical value x is optional and means, for example, $x \pm 10\%$, $x \pm 5\%$, or $x \pm 1\%$.

"% w/w" means the weight of a component as a percentage of the total weight of e.g. a layer or dosage form in which the component is present. For example, a composition comprising

"5% w/w X" refers to a composition in which the weight of component X is 5% of the total weight of the composition.

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

The term "pharmaceutically acceptable" with respect to a substance refers to that substance which is generally regarded as safe and suitable for use without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., *J. Pharma Sci.*, 66(1), 1-19 (1977), and Remington: *The Science and Practice of Pharmacy*, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

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

The term "solvate" means a molecular complex comprising a compound and one or more pharmaceutically acceptable solvent molecules. Examples of solvent molecules include water and C₁₋₆ alcohols, *e.g.* ethanol. When the solvate is water, the term "hydrate" may be used.

"Treating" and "treatment" of a disease include the following:

- 5 (1) preventing or reducing the risk of developing the disease, *i.e.* causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, *i.e.* arresting or reducing the development of the disease or its clinical symptoms, and
- 10 (3) relieving the disease, *i.e.* causing regression of the disease or its clinical symptoms.

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

EXAMPLES

The invention will now be illustrated by the following non-limiting examples.

Example 1 — Emtricitabine/tenofovir alafenamide hemifumarate tablets

20 The emtricitabine/tenofovir alafenamide hemifumarate formulation was initially developed to a target emtricitabine dose of 200 mg per tablet and target tenofovir alafenamide doses of 25 mg and 40 mg per tablet. Antiviral activity was measured by change in baseline in HIV-1 RNA and DAVG11. Statistically greater reductions in HIV-1 RNA and DAVG11 were observed for the 25 mg tenofovir alafenamide single-agent tablet and the 40 mg tenofovir
25 alafenamide single agent tablet as compared to the tenofovir disoproxil fumarate single-agent tablet, supporting further clinical investigation of 25 mg and 40 mg tenofovir alafenamide.

Emtricitabine/tenofovir alafenamide 200/25 mg and emtricitabine/ tenofovir alafenamide 200/40 mg fixed-dose combination tablet formulations containing 200 mg emtricitabine and 25 mg (tablet A) or 40 mg emtricitabine/tenofovir alafenamide (tablet B) as
30 emtricitabine/tenofovir alafenamide were developed and manufactured for a Phase I clinical study. The composition of emtricitabine/tenofovir alafenamide 200/25 mg and 200/40 mg fixed-dose combination tablet formulations evaluated were:

Component	Tablet A Emtricitabine/tenofovir alafenamide 200/25 mg (mg/tablet)	Tablet B Emtricitabine/tenofovir alafenamide 200/40 mg (mg/tablet)
Intragranular		
Emtricitabine	200.0	200.0
Tenofovir Alafenamide hemifumarate	28.0	44.9
Microcrystalline Cellulose	179.2	162.36
Croscarmellose Sodium	27.0	27.0
Magnesium Stearate	3.375	3.375
Extragranular		
Croscarmellose Sodium	9.0	9.0
Magnesium Stearate	3.375	3.375
Total Tablet Core Weight	450	450
Film-Coating		
Opadry II White 85F18422	13.5	13.5

Emtricitabine/tenofovir alafenamide 200/25 mg (tablet A) and 200/40 mg (tablet B) tablets evaluated were manufactured using a dry granulation / tablet compression / film-coating process train. Dry granulation by roller compaction was selected as the means of combining emtricitabine and tenofovir alafenamide in order to minimize exposure of tenofovir alafenamide to moisture during the granulation process. The overall manufacturing process consisted of co-blending and lubricating emtricitabine and tenofovir alafenamide with intragranular excipients, followed by roller compaction and milling. The resulting emtricitabine/tenofovir alafenamide granules were then blended and lubricated with extragranular excipients to produce the emtricitabine/tenofovir alafenamide final powder blend, which was compressed into 450 mg core tablets that were subsequently film-coated with Opadry II White 85F18422.

Example 2 – stability of emtricitabine/tenofovir alafenamide hemifumarate tablets

The stability of tablets A and B from Example 1 was evaluated at the long-term storage condition of 25 °C/60%RH for 24 months and at the accelerated condition of 40 °C/75%RH for 6 months. Stability results for emtricitabine and tenofovir alafenamide hemifumarate indicated that limited degradation of emtricitabine occurred for either emtricitabine/tenofovir alafenamide hemifumarate tablet strength at any storage condition. After 6 months at 40

°C/75% RH. 4.2% of total tenofovir alafenamide hemifumarate impurities products were observed for tablet A and 3.0% total tenofovir alafenamide hemifumarate impurities products were observed for tablet B.

5 Dissolution of emtricitabine and tenofovir alafenamide hemifumarate from these tablets did not change. Tablets stored at all conditions exhibited $\geq 98\%$ release of both active agents at all storage times (monitored using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm). Moisture contents of these tablets ranged from 1.5 to 2.5% over the course of the stability study. Overall, these stability data demonstrate that tablet A and tablet B packaged in HDPE bottles with 2 g of desiccant remain physically and
10 chemically stable under accelerated conditions (40 °C/75% RH) for 6 months and under long-term storage (25 °C/60% RH) for up to 24 months.

Example 3 – excipient ranging studies

Formulation development studies were performed by designing, manufacturing, and testing eleven prototype monolayer co-dry granulation emtricitabine/tenofovir alafenamide
15 hemifumarate tablet formulations. These formulations were evaluated for influence of excipient identity and relative composition on tenofovir alafenamide hemifumarate chemical stability. Compositions of the eleven formulations are summarized in the following table:

Lot Number	A	B	C	D	E	F	G	H	I	J	K
Formulation Composition (% w/w)											
Emtricitabine	44.4 4	44.4 4	44.4 4	44.4 4	44.4 4	44.4 4	44.4 4	44.4 4	44.4 4	57.1 4	57.1 4
Tenofovir alafenamide hemifumarate	2.49	2.49	2.49	2.49	2.49	2.49	2.49	6.25	6.25	3.20	8.91
Microcrystalline Cellulose	43.5 7	21.7 9	4.37	23.5 7	23.5 7	45.5 7	43.5 6	39.8 3	47.8 3	30.1 6	25.3 5
Dibasic Calcium Phosphate, Anhydrous	-	21.7 9	39.2 0	-	-	-	-	-	-	-	-
Lactose Monohydrate	-	-	-	20.0 0	-	-	-	-	-	-	-
Mannitol	-	-	-	-	20.0 0	-	-	-	-	-	-
Croscarmellose Sodium	8.00	8.00	8.00	8.00	8.00	6.00	-	8.00	-	8.00	8.00
Crospovidone	-	-	-	-	-	-	8.00	-	-	-	-
Magnesium Stearate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Total Tablet Core Weight (mg)	450	450	450	450	450	450	450	450	450	350	350
Opadry II Gray 85F97517	-	-	-	-	-	-	-	3	3	-	3
Opadry II Blue 85F105057	3	3	3	3	3	3	3	-	-	3	-

30 tablets were packaged in 60 mL HDPE bottles with 2 g of desiccant and polyester coil.
Bottles were induction-sealed with a PP cap.

"-" excipient not included in the composition

The following formulation attributes were examined:

- Filler type and excipient matrix composition: microcrystalline cellulose, microcrystalline cellulose and lactose monohydrate, microcrystalline cellulose and mannitol, or microcrystalline cellulose and dibasic calcium phosphate anhydrous.
- Disintegrant type and level: croscarmellose sodium or crospovidone.
- Tenofovir alafenamide hemifumarate drug load: tenofovir alafenamide hemifumarate concentrations of 2.49% and 3.20% w/w in emtricitabine/tenofovir alafenamide hemifumarate 200/10 mg tablets and tenofovir alafenamide hemifumarate concentrations of 6.23% and 8.01% w/w in emtricitabine/tenofovir alafenamide 200/25 mg tablets.

All film-coated tablets were packaged as a 30 count configuration in 60 mL HDPE bottle with 2 grams of silica gel desiccant and a polyester coil. HDPE bottles were induction-sealed using a polypropylene (PP) cap with an aluminum-faced liner. Chemical stability was monitored over 3 months at 40 °C/75% RH. For the 5 formulations tested (batches A-E), the total tenofovir alafenamide hemifumarate degradation products (compared to initial) increased by 0.7 to 1.7% after 1 month and by 2.3 to 2.7% after 3 months. Overall, the filler system did not significantly influence tenofovir alafenamide hemifumarate degradation after 3 months at the accelerated conditions.

Example 4 – effect of tenofovir alafenamide hemifumarate loading on stability in emtricitabine/tenofovir alafenamide hemifumarate tablets

The impact of tenofovir alafenamide hemifumarate drug load on tenofovir alafenamide hemifumarate stability in emtricitabine/tenofovir alafenamide 200/10 mg and 200/25 mg tablets was evaluated using a range of tenofovir alafenamide hemifumarate drug loads from 2.49% to 8.01% with concomitant adjustment in microcrystalline cellulose content. Emtricitabine/tenofovir alafenamide 200/10 mg tablet formulations contained 2.49% w/w tenofovir alafenamide hemifumarate or 3.20% w/w tenofovir alafenamide hemifumarate, while emtricitabine/tenofovir alafenamide 200/25 mg tablet formulations contained 6.23% w/w tenofovir alafenamide hemifumarate or 8.01% w/w tenofovir alafenamide hemifumarate. Higher drug loads were achieved by reducing the total tablet weight from 450 mg to 350 mg.

Tenofovir alafenamide hemifumarate chemical stability as a function of drug load is summarized in the table below:

Tenofovir alafenamide hemifumarate concentration (% w/w)	Tenofovir alafenamide hemifumarate 2.49%			Tenofovir alafenamide hemifumarate 3.20%				Tenofovir alafenamide hemifumarate 6.23%			Tenofovir alafenamide hemifumarate 8.01%			
Lot Number	A			J				H			K			
Condition: 40°C/75% RH	Time Point (months)			Time Point (months)				Time Point (months)			Time Point (months)			
	0	1	3	0	1	3	6	0	1	3	0	1	3	6
Tenofovir alafenamide hemifumarate Degradation Products (%)														
PMPA	0.2 2	0.6 0	1.3 2	0.2 6	0.4 9	0.8 2	2.0 4	0.2 3	0.4 9	1.0 0	0.2 1	0.4 8	0.7 7	1.3 3
PMPA Anhydride	0.2 9	0.4 3	1.2 1	0.2 9	0.3 7	0.7 6	1.9 7	0.2 8	0.3 7	0.8 5	0.2 7	0.3 7	0.6 7	1.2 4
Monophenyl PMPA	nd 6	0.0 6	0.0 7	0.0 5	0.0 5	0.0 4	0.1 3	0.0 6	0.0 5	0.0 7	nd 6	0.0 6	0.0 7	0.1 0
PMPA Monoamide	0.0 8	0.1 1	0.1 4	0.1 0	0.1 1	0.1 3	0.1 8	0.0 6	0.0 8	0.1 1	0.0 7	0.1 4	0.1 6	0.0 9
Phenol	nd 7	nd 7	0.0 7	nd 7	nd 7	nd 7	0.0 8	nd 7	nd 7	0.0 7	0.0 9	nd 7	0.0 5	0.0 7
Unspecified ^b	nd 1	0.1 1	0.1 6	nd 6	nd 6	0.1 2	0.2 2	nd 5	0.0 5	0.0 7	nd 6	0.0 6	nd 6	0.1 1
Total tenofovir alafenamide hemifumarate Deg. (%)	0.6 0.6	1.3 1.3	3.0 3.0	0.7 0.7	1.0 1.0	1.8 1.8	4.6 4.6	0.6 0.6	1.0 1.0	2.2 2.2	0.6 0.6	1.1 1.1	1.7 1.7	2.9 2.9

nd: not detected (< 0.025%) tr: trace (0.025% < impurity < 0.15%)

a 30 tablets were packaged in 60 mL HDPE bottles with 2 g of desiccant and polyester coil. Bottles were induction-sealed with a PP cap.

b represents sum of all unspecified degradation products/impurities

Emtricitabine/tenofovir alafenamide 200/10 mg tablets containing 2.49% w/w tenofovir alafenamide hemifumarate exhibited increases in total tenofovir alafenamide hemifumarate degradation products of 0.7% and 2.4% after 1 and 3 months, respectively. Emtricitabine/tenofovir alafenamide 200/10 mg tablets containing 3.20% w/w tenofovir alafenamide hemifumarate exhibited increases in total tenofovir alafenamide hemifumarate degradation products of 0.3% and 1.1% after 1 and 3 months, respectively. Increasing the tenofovir alafenamide hemifumarate drug load from 2.49% w/w to 3.20% w/w tenofovir alafenamide hemifumarate resulted in a 50% reduction in total tenofovir alafenamide hemifumarate degradation products after 3 months under accelerated conditions.

Emtricitabine/tenofovir alafenamide 200/25 mg tablets containing 8.01% w/w tenofovir alafenamide hemifumarate demonstrated better tenofovir alafenamide hemifumarate chemical stability than tablets containing 6.23% w/w tenofovir alafenamide hemifumarate. After 3 months, total tenofovir alafenamide hemifumarate degradation products in emtricitabine/tenofovir alafenamide 200/25 mg tablets increased by 1.5% for the 6.23% w/w tenofovir alafenamide hemifumarate formulation and 1.1% for the 8.01% w/w tenofovir alafenamide hemifumarate formulation. Based on the results of the tenofovir alafenamide hemifumarate drug load study, tenofovir alafenamide hemifumarate contents of 3.20% w/w and 8.01% w/w were selected for the emtricitabine/tenofovir alafenamide 200/10 mg and 200/25 mg fixed dose combination tablets, respectively.

Figure 1 shows a plot of the increase in tenofovir alafenamide hemifumarate-related degradation products as a function of tenofovir alafenamide hemifumarate loading at 1 month and 3 months (at 40 °C/75% RH).

Example 5

As a result of the excipient and drug load evaluations, two formulations (emtricitabine/tenofovir alafenamide 200/10 mg, tablet C; and emtricitabine/tenofovir alafenamide 200/25 mg, tablet D) were developed for use in further studies. The compositions of these formulations are shown in the following table:

Component	Tablet C Emtricitabine/tenofovir alafenamide 200/10 mg (mg/tablet)	Tablet D Emtricitabine/tenofovir alafenamide 200/25 mg (mg/tablet)
Intragranular		
Emtricitabine	200.00	200.00
Tenofovir Alafenamide Hemifumarate	11.20	28.00

Microcrystalline Cellulose	105.56	88.70
Croscarmellose Sodium	28.00	28.00
Magnesium Stearate	2.625	2.625
Extragranular		
Magnesium Stearate	2.625	2.625
Total Tablet Core Weight	350	350
Film-Coating		
Opadry II Gray 85F97517	10.5	--
Opadry II Blue 85F105057	--	10.5

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

Example 6

Tenofovir alafenamide hemifumarate undergoes solid-state hydrolysis and therefore the inclusion of desiccant in the primary package is included to control the level of moisture in emtricitabine/tenofovir alafenamide hemifumarate tablets. Packaging development was performed on tablets C and D to evaluate the impact of desiccant amount on the chemical stability of tenofovir alafenamide hemifumarate in emtricitabine/tenofovir alafenamide hemifumarate tablets during storage.

Tablets C and D were packaged at 30 count in 60 mL HDPE bottles with either 2 or 3 grams of desiccant and a polyester coil, and sealed with an induction seal. Chemical stability was monitored for up to 6 months at 40 °C/75% RH.

Tenofovir alafenamide hemifumarate-related total degradation products in tablet C after 6 months under accelerated conditions were 3.9% and 3.3% for bottles packaged with 2 g and 3 g of desiccant, respectively. In comparison, tenofovir alafenamide hemifumarate-related total degradation products in tablet D were 2.3% and 2.4% for bottles containing 2 g and 3 g desiccant, respectively.

Example 7 – Emtricitabine/tenofovir alafenamide hemifumarate bioequivalence studies

Tablets C and D were evaluated in three bioequivalence studies establishing equivalence of:

1. tablet C co-administered with both (a) cobicistat 150 mg and (b) elvitegravir 150 mg, and elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) 150/150/200/10 mg fixed dose combination tablets.
2. tablet D and elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/F/TAF) 150/150/200/10 mg fixed dose combination tablets, and
3. tablet D and EMTRIVA® capsule co-administered with tenofovir alafenamide 25 mg single-agent tablet.

Example 8 – Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate monolayer tablets

A mono-layer formulation (tablet F4) of emtricitabine, rilpivirine HCl and tenofovir alafenamide hemifumarate was prepared by co-dry granulation. Figure 2 is a flow diagram illustrating the preparation of this formulation. The composition of the co-granulated formulation is shown in the table below:

Component	Mass (mg/tablet)
Emtricitabine	200.0
Rilpivirine HCl	27.5
Tenofovir alafenamide hemifumarate	28.0
Microcrystalline cellulose	69.9
Croscarmellose sodium	25.5
Lactose	69.9
Magnesium Stearate	4.2
Total Core Weight	425

Example 9 – Tenofovir alafenamide hemifumarate stability studies

Studies were conducted to assess the stability of tenofovir alafenamide hemifumarate in the presence of (a) emtricitabine, and (b) emtricitabine and rilpivirine HCl. These data are presented in Figures 3A and B. Figure 3A shows the total degradation of tenofovir alafenamide hemifumarate at 40°C/75% RH in open conditions (i.e., unsealed containers with no desiccant present). Figure 3B shows the total degradation of tenofovir alafenamide hemifumarate at 60°C in closed conditions. These data show that the rate of degradation of tenofovir alafenamide hemifumarate is increased in the presence of emtricitabine, and is further increased in the presence of both emtricitabine and rilpivirine HCl.

Example 10 – Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate bilayer tablets

A bilayer formulation (tablet F1) of emtricitabine, rilpivirine HCl and tenofovir alafenamide hemifumarate was prepared using the method described in Example 15. Figure 4 is a flow diagram illustrating the preparation of bilayer tablets. The composition of the formulation is summarized in the table below.

Ingredient	Bilayer tablet F1 (mg/tablet)	
	Rilpivirine HCl Layer	Emtricitabine/ tenofovir alafenamide hemifumarate Layer
Emtricitabine		200.0
Rilpivirine HCl	27.5	
Tenofovir alafenamide hemifumarate		28.0
MCC	60.0	88.7
CCS	16.1	28.0
Lactose	189.8	
Povidone	3.25	
Starch		
Polysorbate 20	0.35	
Magnesium Stearate	3	5.2
Layer Weight	300	250
Tablet Core Weight	650	

Example 11 – dissolution studies

Studies were carried out to assess the dissolution profiles of tablets F1 and F4 and to compare these with the dissolution profiles of COMPLERA® and EDURANT®. Dissolution of rilpivirine HCl was measured using USP Apparatus II, in 1000 ml of pH 4.5 sodium acetate with 2% polysorbate 20, at 37 °C and paddle speed of 75 rpm. The results are shown in Figure 5. These data show that while the bilayer formulation (tablet F1) had comparable rilpivirine HCl dissolution to COMPLERA® and EDURANT®, the monolayer formulation (tablet F4) exhibited enhanced rilpivirine HCl dissolution.

Figures 6A, B and C shows the results of studies carried out on a bilayer formulation (F1) to assess how the tablet hardness affects the dissolution of rilpivirine HCl, emtricitabine and tenofovir alafenamide hemifumarate, respectively (i.e. at 13, 16 and 19 kP). Dissolution of rilpivirine HCl in these experiments was measured using USP Apparatus II, in 1000 ml of 0.01N HCl with 0.5% polysorbate 20, at 37 °C and paddle speed of 75 rpm. Dissolution of emtricitabine and tenofovir alafenamide hemifumarate was monitored using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm. These data show that all tablets exhibited acceptable dissolution across the selected tablet hardness range (13-19 kP).

Example 12 – Emtricitabine/rilpivirine/tenofovir alafenamide tablet formulation

The following tablet (tablet E) was selected for use in bioequivalence studies

Rilpivirine HCl Layer	Weight (mg/tablet)	% w/w (in layer)
Intragranular		
Rilpivirine HCl	27.50	9.2
Lactose Monohydrate	55.10	18.4
Polysorbate 20	0.35	0.12
Povidone K29/32	3.25	1.1
Croscarmellose sodium	1.10	0.37
Extragranular		
Lactose Monohydrate	134.70	44.9
Croscarmellose sodium	15.00	5.0
Microcrystalline cellulose	60.00	20.0
Magnesium stearate	3.00	1.0
Total Rilpivirine Layer Weight (mg)	300	100

Emtricitabine/tenofovir alafenamide hemifumarate Layer	Weight (mg)	% w/w (in layer)
Intragranular		
Emtricitabine	199.99	57.1
Tenofovir alafenamide hemifumarate	28.04	8.01
Croscarmellose sodium	28.00	8.0
Microcrystalline cellulose	88.69	25.3
Magnesium stearate	2.60	0.75
Extragranular		
Magnesium stearate	2.60	0.75
Total Emtricitabine/tenofovir alafenamide hemifumarate Layer Weight	350	100
Total Core Tablet Weight	650	
Opadry II 85F17636 Gray	19.5	3%

Example 13 – stability studies

Three batches of tablet E were tested. The results meet release and stability criteria and are shown in the table below and in Figure 7:

Analytical Test	Criteria	Batch 1	Batch 2	Batch 3
Assay	95-110%	FTC: 101.8% TAF: 100.9% RPV: 100.5%	FTC: 100.2% TAF: 99.4% RPV: 99.1%	FTC: 99.1% TAF: 98.9% RPV: 98.8%
Content Uniformity (RSD, AV)	USP <905>	FTC: 1.4%, 3.7 TAF: 1.5%, 3.6 RPV: 0.7%, 1.7	FTC: 1.5%, 3.6 TAF: 1.5%, 3.6 RPV: 1.3%, 3.1	FTC: 1.0%, 2.3 TAF: 1.4%, 3.3 RPV: 2.1%, 5.0
Water Content	Record	2.9%	2.7%	2.8%
Emtricitabine Degradation	NMT 0.5%	0.0%	0.0%	0.0%
Tenofovir alafenamide hemifumarate Degradation				

PMPA	NMT 2.50%	0.26%	0.19%	0.27%
PMPA Anhydride	NMT 1.00%	Trace	Trace	0.11%
Monophenyl PMPA	NMT 1.50%	ND	ND	ND
PMPA Monoamidate	NMT 1.00%	ND	ND	ND
Phenol	NMT 1.00%	Trace	Trace	Trace
Unspecified TAF Related	NMT 0.50%	ND	ND	ND
Total TAF Related	NMT 3.5%	0.3%	0.2%	0.4%
Rilpivirine HCl Degradation	NMT 1.0%	0.0%	0.0%	0.0%

Trace = <0.10%, ND = Not Detected (< 0.05%)

The stability of Batches 1, 2 and 3 (table above) (assessed in terms of total tenofovir alafenamide degradation products) of rilpivirine HCl/emtricitabine/ tenofovir alafenamide hemifumarate tablets is shown relative to that of emtricitabine 200 mg/ tenofovir alafenamide hemifumarate 25 mg tablets (assessed at 40 °C/75% RH) in Figure 7.

It was also observed that the dissolution of rilpivirine HCl, emtricitabine and tenofovir alafenamide hemifumarate from tablet E did not change following storage of the tablet for 1, 3 and 6 months under varying temperature and humidity conditions (see Figures 8A-C). Dissolution of rilpivirine HCl in these studies was monitored using USP Apparatus II, in 1000 ml of 0.01N HCl with 0.5% polysorbate 20, at 37 °C and paddle speed of 75 rpm. Dissolution of emtricitabine and tenofovir alafenamide hemifumarate was monitored using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm.

However, the stability of tenofovir alafenamide hemifumarate is sensitive to the water content of the tablet, as shown in the following table, which shows the total degradation of tenofovir alafenamide hemifumarate (Tablet E formulation) at 40°C/75% RH at time zero, 1 month, 3 months and 6 months as a function of the initial water content of the tablet:

Study Lot Number	Time (months)	Water Content by KF (%)	Total tenofovir alafenamide (TAF) hemifumarate Degradation Products (%)						Total entricitabine Degradation Products (%)	Total ribavirine HCl Degradation Products (%)
			PMMPA	PMMPA Anhydride	Monophenyl PMMPA	PMMPA Mononitrate	Phenol	Total (TAF) hemifumarate Deg. Products (%)		
AAA	0	2.9	0.24	trace	trace	trace	0.24	0.5	0.0	0.0
	1	2.3	0.35	0.13	trace	trace	0.21	0.7	0.0	0.0
	3	2.3	0.57	0.28	trace	trace	0.23	1.1	0.0	0.0
	6	2.4	0.81	0.47	trace	ND	0.41	1.7	0.0	0.0
BBB	0	3.5	0.25	trace	trace	trace	0.23	0.5	0.0	0.0
	1	2.6	0.46	0.16	trace	trace	0.26	0.9	0.0	0.0
	3	2.5	0.80	0.42	trace	trace	0.34	1.6	0.0	0.0
	6	2.6	1.12	0.67	trace	ND	0.53	2.3	0.0	0.0
CCC	0	4.0	0.26	trace	trace	trace	0.25	0.5	0.0	0.0
	1	2.7	0.55	0.21	trace	trace	0.29	1.1	0.0	0.0
	3	2.6	0.96	0.58	trace	trace	0.41	1.9	0.0	0.0
	6	2.7	1.47	0.93	0.10	ND	0.63	3.1	0.0	0.0
DDD	0	4.6	0.26	trace	trace	trace	0.24	0.5	0.0	0.0
	1	2.7	0.68	0.26	trace	trace	0.34	1.3	0.0	0.0
	3	2.8	1.28	0.78	trace	trace	0.52	2.6	0.0	0.0
	6	2.8	2.06	1.28	0.14	ND	0.79	4.3	0.0	0.0

As for the emtricitabine and tenofovir alafenamide hemifumarate tablets described above, the stability of tenofovir alafenamide hemifumarate in batches of tablet E packaged with varying levels of desiccant was also investigated. The data are shown in the table below.

	Tablet E				
		Batch X		Batch Y	
Condition: 40 °C/75 % RH	Timepoint (months)				
	0	1	3	1	3
Desiccant amount	N/A	1 g		3 g	
Water Content (%)	2.6	2.4	2.4	2.2	2.1
Tenofovir alafenamide hemifumarate Label Strength (%)	100.4	100.9	99.2	101.2	99.5
Tenofovir alafenamide hemifumarate Degradation Products (%)					
PMPA	0.27	0.49	0.88	0.37	0.56
PMPA anhydride	trace	0.18	0.42	0.14	0.26
Monophenyl PMPA	ND	ND	trace	ND	trace
PMPA Monoamidate	ND	trace	trace	trace	trace
Phenol	ND	0.17	ND	0.10	ND
Unspecified	ND	ND	0.12	ND	trace
Total tenofovir alafenamide hemifumarate Degradation Content (%)	0.3	0.8	1.4	0.6	0.8

Example 14 -- Rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate bioequivalence studies

A randomized, open-label, single-dose, 3-way, 6-sequence, crossover study was performed to determine the bioequivalence of emtricitabine and tenofovir alafenamide hemifumarate, administered as elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (E/C/F/TAF) fixed-dose combination tablet or as rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate fixed-dose combination tablet (tablet E), and the bioequivalence of

rilpivirine HCl administered as rilpivirine HCl single tablet or as rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate fixed-dose combination tablet (tablet E).

Duration of Treatment

Three single doses of (a) emtricitabine/rilpivirine/tenofovir alafenamide fixed-dose combination tablet (200/25/25 mg) – tablet E, (b) EDURANT[®] (rilpivirine, 25 mg, present as 27.5 mg rilpivirine HCl in the tablet) or (c) elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (E/C/R/TAF) (150/150/200/10 mg, wherein the tenofovir alafenamide is present as 11.2 mg tenofovir alafenamide hemifumarate in the tablet) fixed-dose combination tablet were administered orally under fed conditions during up to 53 days total study duration.

Criteria for Evaluation

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

Statistical Methods

Pharmacokinetics: Plasma concentrations and PK parameters were listed and summarized by analyte and treatment group using descriptive statistics. In addition, a parametric analysis of variance using a mixed-effects model appropriate for a crossover design was fitted to the natural logarithmic transformation of the PK parameters (AUC_{inf} , AUC_{last} , and C_{max}). Two-sided 90% confidence intervals (CIs) were constructed for the ratio of geometric least-squares means (GLSMs) of each PK parameter for emtricitabine, rilpivirine HCl, and tenofovir alafenamide hemifumarate. Bioequivalence of emtricitabine, rilpivirine HCl, and tenofovir alafenamide hemifumarate in the rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate fixed-dose combination (tablet E) to the emtricitabine, rilpivirine HCl, and tenofovir alafenamide hemifumarate components in rilpivirine HCl or elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate fixed-dose combination was concluded if the 90% CI of the GLSM (geometric least-squares mean) ratio of the pharmacokinetic parameters for each analyte between formulations fell within the prespecified bioequivalence boundary of 80% to 125%.

Results

Subject Disposition and Demographics

A total of 96 subjects were randomized and received at least 1 dose of study drug.

Pharmacokinetics Results: Statistical comparisons of the plasma rilpivirine HCl, emtricitabine and tenofovir alafenamide hemifumarate PK parameters AUC_{last} , AUC_{inf} , and C_{max} are presented below:

Emtricitabine PK Parameter	N	Tablet E Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
Emtricitabine/Rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) (Test) vs elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (150/150/200/10 mg by weight free base) (Reference)						
AUC _{last} (h•ng/mL)	95	9381.9 (21.7)	96	10139.4 (21.5)	92.24	90.84, 93.67
AUC _{inf} (h•ng/mL)	95	9603.2 (21.6)	96	10387.1 (21.5)	92.37	90.93, 93.83
C _{max} (ng/mL)	95	1608.6 (26.5)	96	1583.8 (23.8)	100.81	97.52, 104.21
Rilpivirine HCl PK Parameter	N	Tablet E Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
Emtricitabine/Rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) (Test) vs Rilpivirine HCl (25 mg by weight free base) (Reference)						
AUC _{last} (h•ng/mL)	95	3698.6 (34.9)	95	3373.4 (40.0)	111.70	106.31, 117.38
AUC _{inf} (h•ng/mL)	95	3843.1 (36.2)	95	3540.7 (43.0)	110.51	105.82, 115.42
C _{max} (ng/mL)	95	121.4 (26.1)	95	108.0 (28.7)	113.52	108.40, 118.89
Tenofovir alafenamide hemifumarate PK Parameter	N	Tablet E Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) (Test) vs elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (150/150/200/10 mg by weight free base) (Reference)						
AUC _{last} (h•ng/mL)	95	250.0 (43.4)	96	238.4 (36.5)	102.85	98.18, 107.75
AUC _{inf} (h•ng/mL)	82	263.6 (42.0)	85	247.4 (36.1)	103.85	98.27, 109.74
C _{max} (ng/mL)	95	198.0 (57.7)	96	191.5 (48.2)	100.78	91.63, 110.85

The GLSM ratios and corresponding 90% CIs of AUC_{last} , AUC_{inf} , and C_{max} for emtricitabine, rilpivirine, and tenofovir alafenamide were contained within the 80% to 125% boundary criteria specified for bioequivalence.

These values were calculated based on the data presented below for each active.

5 Emtricitabine

The following table shows the summary statistics of the emtricitabine pharmacokinetic parameters.

Emtricitabine PK Parameter ^a	Tablet E Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (Treatment A) (N = 95)	Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (Treatment C) (N = 96)
AUC_{last} (h•ng/mL)	9381.9 (21.7)	10159.4 (21.5)
AUC_{inf} (h•ng/mL)	9603.2 (21.6)	10387.1 (21.5)
C_{max} (ng/mL)	1608.6 (26.5)	1583.8 (23.8)
T_{max} (h)	2.00 (1.50, 3.00)	2.00 (2.00, 3.00)
$t_{1/2}$ (h)	18.71 (15.05, 25.27)	18.90 (15.89, 26.43)
CL/F (L/h)	21.7 (19.8)	20.1 (19.6)
Vz/F (L)	659.0 (43.5)	622.9 (43.5)

^a Data are mean (%CV), except T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3).

- 10 The following table shows statistical comparisons of emtricitabine pharmacokinetic parameters of AUC_{last} , AUC_{inf} , and C_{max} (when administered as emtricitabine/rilpivirine HCl/ tenofovir alafenamide hemifumarate (tablet E) or elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate E/C/F/TAF):

Emtricitabine PK Parameter	N	Tablet E Test GLSM	N	Reference GLSM	GLSM Ratio (Test/Reference) (%)	90% CI (%)
Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) (Test) vs elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (150/150/200/10 mg by weight free base) (Reference)						
AUC_{last} (h•ng/mL)	95	9112.91	96	9879.18	92.24	90.84, 93.67
AUC_{inf} (h•ng/mL)	95	9316.60	96	10085.96	92.37	90.93, 93.83
C_{max} (ng/mL)	95	1534.56	96	1522.22	100.81	97.52, 104.21

Rilpivirine HCl

The following table provides a summary of the rilpivirine HCl pharmacokinetic parameters following administration of Rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate (tablet E) or rilpivirine HCl:

Rilpivirine HCl PK Parameter ^a	Tablet E Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (Treatment A) (N = 95)	Rilpivirine HCl (Treatment B) (N = 95)
AUC _{last} (h•ng/mL)	3698.6 (34.9)	3373.4 (40.0)
AUC _{inf} (h•ng/mL)	3843.1 (36.2)	3540.7 (43.0)
C _{max} (ng/mL)	121.4 (26.1)	108.0 (28.7)
T _{max} (h)	4.00 (4.00, 5.00)	4.00 (4.00, 5.00)
t _{1/2} (h)	51.65 (36.83, 66.88)	52.51 (39.29, 66.79)
CL/F (L/h)	7.2 (30.9)	8.1 (36.6)
V _{Z/F} (L)	546.1 (40.5)	600.4 (33.6)

^a Data are mean (%CV), except T_{max} and t_{1/2}, which are reported as median (Q1, Q3).

The following table shows statistical comparisons of rilpivirine HCl pharmacokinetic parameters of AUC_{last}, AUC_{inf}, and C_{max} (when administered as rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate (tablet E) or rilpivirine HCl)

Rilpivirine HCl PK Parameter	N	Tablet E Test GLSM	N	Reference GLSM	GLSM Ratio (Test/Reference) (%)	90% CI (%)
Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) (Test) vs rilpivirine HCl (25 mg by weight free base) (Reference)						
AUC _{last} (h•ng/mL)	95	3510.57	95	3142.72	111.70	106.31, 117.38
AUC _{inf} (h•ng/mL)	95	3637.96	95	3291.86	110.51	105.82, 115.42
C _{max} (ng/mL)	95	117.48	95	103.48	113.52	108.40, 118.89

Tenofovir alafenamide hemifumarate

The following table shows the summary statistics of the tenofovir alafenamide hemifumarate pharmacokinetic parameters:

Tenofovir alafenamide hemifumarate PK Parameter ^a	Tablet E Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (Treatment A) (N = 95)	Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (Treatment C) (N = 96)
AUC _{last} (h•ng/mL)	250.0 (43.4)	238.4 (36.5)
AUC _{inf} (h•ng/mL)	263.6 (42.0)	247.4 (36.1)
C _{max} (ng/mL)	198.0 (57.7)	191.5 (48.2)
T _{max} (h)	1.50 (1.00, 2.00)	1.50 (1.00, 2.00)
t _{1/2} (h)	0.42 (0.39, 0.49)	0.41 (0.37, 0.48)
CL/F (L/h)	109.4 (35.9)	45.8 (36.2)
Vz/F (L)	72.0 (45.0)	28.7 (43.6)

^a Data are mean (%CV), except T_{max} and t_{1/2}, which are reported as median (Q1, Q3).

For AUC_{last}, t_{1/2}, CL/F, and Vz/F: n = 82 for Treatment A and n = 85 for Treatment C.

The following table shows statistical comparisons of tenofovir alafenamide pharmacokinetic parameters of AUC_{last}, AUC_{inf}, and C_{max} (when administered as emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (tablet E) or elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate).

Tenofovir alafenamide hemifumarate PK Parameter	N	Tablet E Test GLSM	N	Reference GLSM	GLSM Ratio (Test/Reference) (%)	90% CI (%)
Emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) (Test) vs elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (150/150/200/10 mg by weight free base) (Reference)						
AUC _{last} (h•ng/mL)	95	228.27	96	221.94	102.85	98.18, 107.75
AUC _{inf} (h•ng/mL)	82	234.87	85	226.18	103.85	98.27, 109.74
C _{max} (ng/mL)	95	177.98	96	176.60	100.78	91.63, 110.85

These studies demonstrate that:

1. The emtricitabine and tenofovir alafenamide hemifumarate components of the emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) fixed-dose combination (tablet E) are bioequivalent to the elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide hemifumarate (150/150/200/10 mg by weight free base) fixed-dose combination;

2. The rilpivirine HCl component of the emtricitabine/rilpivirine HCl/tenofovir alafenamide hemifumarate (200/25/25 mg by weight free base) fixed-dose combination (tablet E) is bioequivalent to rilpivirine HCl 25 mg (by weight free base) tablet (EDURANT®).

Example 15 – manufacturing process

- 5 The manufacturing/packaging procedure for rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate tablets is divided into five unit processes:
 - 1 mixing of rilpivirine HCl drug substance with intragranular excipients, fluid-bed granulation, milling, and blending with extragranular excipients to yield the rilpivirine HCl final powder blend;
 - 10 2. mixing of emtricitabine and tenofovir alafenamide hemifumarate drug substances with intragranular excipients, dry granulation, milling, and blending with extragranular excipients to yield emtricitabine/tenofovir alafenamide hemifumarate final powder blend;
 3. tablet compression to yield bilayer tablet cores;
 4. tablet film-coating to yield film-coated tablets; and
 - 15 5. packaging.

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

Rilpivirine HCl Final Powder Blend (Dispensing, Blending, Wet Granulation, Milling, Final Blending)

1. Weigh rilpivirine HCl and the excipients (lactose monohydrate and croscarmellose sodium). Correct the weight of rilpivirine HCl based on the drug content factor (DCF), with a concomitant reduction in the weight of lactose monohydrate.
2. Weigh purified water, polysorbate 20, and polyvinyl pyrrolidone. Mix to form the granulation binder fluid until fully dissolved.
- 25 3. Add rilpivirine HCl, lactose monohydrate, and croscarmellose sodium to the fluid-bed granulator/dryer and fluidize to pre-mix the components
4. Spray the entire volume of binder solution while maintaining powder bed fluidization.
5. Dry the granules.
6. Mill the granules using a rotating impeller screening mill
7. Add the dried, milled granules as well as extragranular lactose monohydrate, microcrystalline cellulose, and croscarmellose sodium and blend in a blender.
- 30 8. Add extragranular magnesium stearate and blend.

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

9. Weigh emtricitabine and tenofovir alafenamide hemifumarate drug substances and excipients (microcrystalline cellulose and croscarmellose sodium). Adjust the weight of emtricitabine and tenofovir alafenamide hemifumarate drug substances based on their corresponding DCF, with a concomitant adjustment to the weight of microcrystalline cellulose.
10. Blend in emtricitabine and tenofovir alafenamide hemifumarate drug substance, microcrystalline cellulose, and croscarmellose sodium to a tumble blender and blend
11. Blend in intragranular portion of magnesium stearate to the tumble blender and blend.
12. Dry granulate the resulting blend using a roller compactor
13. Blend in the extragranular portion of magnesium stearate.

Tableting

14. Compress the rilpivirine HCl final powder blend as the first layer and the emtricitabine/tenofovir alafenamide hemifumarate final powder blend as the second layer to a target rilpivirine HCl layer weight of 300 mg using a target total tablet weight of 650 mg with an appropriate main compression force to achieve a target hardness of 16 kP (range: 13 to 19 kP).

Film-coating

15. Prepare a suspension of Opadry® II Gray 85F17636. Film-coat the tablet cores to achieve the target tablet weight gain of 3% (range 2-4%). Dry film-coated tablets prior to cooling and discharge.

It was observed that the layer order in tableting has an impact on compressibility and flow, hence why rilpivirine HCl was selected as layer 1. Figure 9 shows the tensile strength of the tablet as a function of upper punch pressure in the final blends of rilpivirine HCl and emtricitabine/tenofovir alafenamide hemifumarate.

A hardness range of 13-19 kP with target of 16 kP selected to optimize friability, based on studies carried out to assess the impact of tablet hardness on friability reported in the following table:

Tamp Force (N)	Main Compression Force (kN)	Hardness (kP)*	Observations During Hardness Testing	Friability (%)	Observations During Friability Testing
800	11.3	10.8	None	0.0	Edge wear

800	12.7	11.7	None	0.0	Slight edge wear
800	15.0	14.4	None	0.0	None
800	20.0	20.3	None	0.0	None
800	21.7	20.5	None	0.0	None
800	25.0	20.9	Capping on layer 1 observed for 5 of 9 tablets	0.08	Capping on layer 1 observed for 1 of 10 tablets

a Average value of five to nine tablets

Example 16 – Long Term Stability Studies

The long term stability of Tablet E was measured over the course of 12 months at (30°C/75% RH). The results of those studies are provided in the following table:

	Tablet E		
Condition: 30/75 % RH	Timepoint (months)		
	0	6	12
Desiccant amount	3 g		
Water Content (%)	2.8	2.1	2.1
Tenofovir alafenamide hemifumarate Label Strength (%)	98.9	99.4	98.0
Tenofovir alafenamide hemifumarate Degradation Products (%)			
PMPA	0.27	0.41	0.56
PMPA anhydride	0.11	0.18	0.30
Monophenyl PMPA	-	-	trace
PMPA Monoamidate	-	trace	trace
Phenol	trace	0.11	0.19
Total tenofovir alafenamide hemifumarate Degradation Content (%)	0.4	0.7	1.1

These results demonstrate that TAF in the rilpivirine HCl/emtricitabine/tenofovir alafenamide hemifumarate tablets (packaged in an induction sealed, 100 mL HDPE bottles (30 tablets/bottle) with 3 g of desiccant) is stable under long term storage conditions (30°C/75% RH)

The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention

CLAIMS

1. A solid oral dosage form comprising rilpivirine or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and emtricitabine or a pharmaceutically acceptable salt thereof.
2. The solid oral dosage form of claim 1, wherein the dosage form comprises 25 mg rilpivirine as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.
3. The solid oral dosage form of claim 1 or 2, wherein the dosage form comprises 27.5 mg rilpivirine hydrochloride and 28 mg tenofovir alafenamide hemifumarate.
4. The solid oral dosage form of any one of claims 1-3, wherein the dosage form:
 - (a) releases emtricitabine *in vivo* in fed human subjects to provide a plasma C_{max} of from about 1250 to about 2050 ng/mL and/or a AUC_{inf} of from about 7650 to about 12050 h•ng/mL, and/or
 - (b) releases rilpivirine *in vivo* in fed human subjects to provide a plasma C_{max} of from about 90 to about 160 ng/mL and/or a AUC_{inf} of from about 3050 to about 4850 h•ng/mL, and/or
 - (c) releases tenofovir alafenamide *in vivo* in fed human subjects to provide a plasma C_{max} of from about 150 to about 260 ng/mL and/or a AUC_{inf} of from about 200 and 340 h•ng/mL.
5. The solid oral dosage form of claim 4, wherein the dosage form exhibits properties (a), (b) and (c).
6. The solid oral dosage form of any one of claims 1-5, for which:
 - (a) the 90% confidence interval of log-transformed C_{max} and log-transformed AUC_{inf} for rilpivirine in fed human subjects fall completely within the range 80-125% of the log-transformed C_{max} and log-transformed AUC_{inf} , respectively, of a reference tablet, wherein the reference tablet has (i) a core consisting of 27.5 mg rilpivirine hydrochloride, lactose monohydrate, croscarmellose sodium, polyvinylpyrrolidone, polysorbate 20, silicified microcrystalline cellulose and magnesium stearate, and (ii) a film coating consisting of a mixture of lactose monohydrate, hypromellose 2910, titanium dioxide E171, polyethylene glycol (macrogol 3000) and triacetin,
 - (b) the 90% confidence interval of log-transformed C_{max} and log-transformed AUC_{inf} for emtricitabine in fed human subjects fall completely within the range 80-125% of the

- log-transformed C_{max} and log-transformed AUC_{inf} , respectively, of a reference tablet, wherein the reference tablet has (i) a core consisting of 150 mg elvitegravir, 60.8 mg lactose monohydrate, 241.5 mg microcrystalline cellulose, 7.5 mg hydroxypropyl cellulose, 11.3 mg sodium lauryl sulfate, 65.8 mg croscarmellose sodium, 200 mg emtricitabine, 11.2 mg tenofovir alafenamide hemifumarate, 288.5 mg cobicistat on silicon dioxide (corresponding to 150 mg of cobicistat), 13.5 mg magnesium stearate, and (ii) a film coating consisting of 31.5 mg of a mixture of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine and iron oxide (such as Opadry® II Green), and/or
- (c) the 90% confidence interval of log-transformed C_{max} and log-transformed AUC_{inf} for tenofovir alafenamide in fed human subjects fall completely within the range 80-125% of the log-transformed C_{max} and log-transformed AUC_{inf} , respectively, of a reference tablet, wherein the reference tablet has (i) a core consisting of 150 mg elvitegravir, 60.8 mg lactose monohydrate, 241.5 mg microcrystalline cellulose, 7.5 mg hydroxypropyl cellulose, 11.3 mg sodium lauryl sulfate, 65.8 mg croscarmellose sodium, 200 mg emtricitabine, 11.2 mg tenofovir alafenamide hemifumarate, 288.5 mg cobicistat on silicon dioxide (corresponding to 150 mg of cobicistat), 13.5 mg magnesium stearate, and (ii) a film coating consisting of 31.5 mg of a mixture of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, indigo carmine and iron oxide (such as Opadry® II Green).
7. The solid oral dosage form of claim 6, wherein the dosage form exhibits properties (a), (b) and (c).
 8. The solid oral dosage form of any preceding claim, wherein the dosage form comprises 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein the dosage form has a total weight of less than 850 mg.
 9. The solid oral dosage form of claim 8, wherein the dosage form has a total weight of less than 800 mg.
 10. The solid oral dosage form of claim 8 or 9, wherein the active pharmaceutical ingredients in the dosage form consist of 25 mg rilpivirine 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.

11. A composition comprising (a) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) emtricitabine or a pharmaceutically acceptable salt thereof, where the total quantity of degradation products derived from the tenofovir alafenamide or the pharmaceutically acceptable salt thereof is less than 3% after storage for one month at 40°C/75% RH in open conditions, wherein the composition further comprises rilpivirine or a pharmaceutically acceptable salt thereof.
12. The solid oral dosage form of any one of the preceding claims, wherein the dosage form is a tablet.
13. A coated tablet comprising 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof and a coating.
14. A tablet comprising 27.5 mg rilpivirine hydrochloride, 28 mg tenofovir alafenamide hemifumarate, and 200 mg emtricitabine or a pharmaceutically acceptable salt thereof.
15. A tablet comprising (a) 25 mg rilpivirine or a pharmaceutically acceptable salt thereof, (b) 25 mg tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) 200 mg emtricitabine or a pharmaceutically acceptable salt thereof, wherein (a) and (b) are segregated, and wherein the tablet has a total weight of less than about 1.5 g.
16. The tablet of claim 15, wherein (a) and (b) are within separate layers in a multilayer tablet.
17. A tablet comprising from 2.5-4.5 % w/w rilpivirine or a pharmaceutically acceptable salt thereof, 2.5-4.5 % w/w tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and 27-33 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.
18. A tablet comprising from 2.5-4.5 % w/w rilpivirine, 2.5-4.5 % w/w tenofovir alafenamide, and 27-33 % w/w emtricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.
19. A multilayer tablet comprising (a) rilpivirine or a pharmaceutically acceptable salt thereof, (b) tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) emtricitabine or a pharmaceutically acceptable salt thereof.
20. The multilayer tablet of claim 19, wherein each layer contains at least one of (a), (b) and (c).
21. The tablet of claim 19 or 20, wherein the tablet comprises (a) a first layer comprising rilpivirine or a pharmaceutically acceptable salt thereof, (b) a second layer comprising

- tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (c) further comprises emtricitabine or a pharmaceutically acceptable salt thereof
22. The tablet of claim 21, wherein (a) the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and/or (b) the second layer is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof.
23. The tablet of claim 21 or 22, wherein (a) the first layer comprises rilpivirine or a pharmaceutically acceptable salt thereof and is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and (b) the second layer comprises tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof and is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof
24. The tablet of any one of claims 19-23, wherein the layer containing tenofovir alafenamide or a pharmaceutically acceptable salt thereof does not contain lactose and/or starch.
25. The tablet of any one of the preceding claims, wherein the tablet releases at least 80% of (a) tenofovir alafenamide and (b) emtricitabine in 20 minutes, measured using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm.
26. The tablet of claim 25, wherein the tablet releases at least 90% of (a) tenofovir alafenamide and (b) emtricitabine in 20 minutes, measured using USP apparatus II, in 500 ml of 50 mM sodium citrate pH 5.5, at 37 °C and paddle speed of 75 rpm.
27. The tablet of any one of the preceding claims, wherein the tablet releases less than 50% of rilpivirine in 60 minutes, measured using USP Apparatus II, in 1000 ml of pH 4.5 sodium acetate with 2% polysorbate 20 at 37 °C and paddle speed of 75 rpm.
28. A method of producing a tablet of any one of any one of the preceding claims, wherein the method comprises (a) compressing the rilpivirine or a pharmaceutically acceptable salt thereof as a first layer, and (b) compressing the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and emtricitabine or a pharmaceutically acceptable salt thereof as a second layer.
29. The method of claim 28, wherein the first layer and second layer are compressed separately and subsequently combined.
30. The method of claim 28, wherein the first layer is formed by compression and subsequently the second layer is compressed onto the first layer
31. The first layer obtainable by the method of claim 28.

32. The second layer obtainable by the method of claim 28.
33. A kit comprising (a) a tablet comprising rilpivirine or a pharmaceutically acceptable salt thereof, tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and entricitabine or a pharmaceutically acceptable salt thereof, and (b) a desiccant.
34. The kit of claim 33, wherein the desiccant is silica gel.
35. A solid oral dosage form or tablet according to any one of the preceding claims for use in the therapeutic treatment of an HIV infection.
36. A method of therapeutic treatment of an HIV infection comprising administering to a subject a solid oral dosage form or tablet according to any one of the preceding claims.
37. A tablet comprising from 2.5-4.5 % w/w rilpivirine hydrochloride, 2.5-4.5 % w/w tenofovir alafenamide benifumarate, and 27-33 % w/w entricitabine or a pharmaceutically acceptable salt thereof, where the weight percentages denote a proportion of the whole tablet.
38. A multilayer tablet, comprising:
- (a) a first layer comprising rilpivirine or a pharmaceutically acceptable salt thereof and a first pharmaceutically acceptable excipient; and
 - (b) a second layer comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof, entricitabine or a pharmaceutically acceptable salt thereof, and a second pharmaceutically acceptable excipient,
- wherein the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and the second layer is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof,
- wherein the multilayer tablet is manufactured by a method comprising:
- mixing the rilpivirine or a pharmaceutically acceptable salt thereof and the first pharmaceutically acceptable excipient to obtain a first powder blend;
 - mixing the entricitabine or a pharmaceutically acceptable salt thereof, the tenofovir alafenamide or a pharmaceutically acceptable salt thereof and the second excipient to obtain a second powder blend;
 - compressing the first powder blend, thereby obtaining the first layer; and
 - compressing the second powder blend, thereby obtaining the second layer.
39. A multilayer tablet, comprising:

(a) a first layer comprising rilpivirine or a pharmaceutically acceptable salt thereof and a first pharmaceutically acceptable excipient; and

(b) a second layer comprising tenofovir alafenamide or a pharmaceutically acceptable salt thereof, emtricitabine or a pharmaceutically acceptable salt thereof, and a second pharmaceutically acceptable excipient,

wherein the first layer is substantially free of tenofovir alafenamide or a pharmaceutically acceptable salt thereof, and the second layer is substantially free of rilpivirine or a pharmaceutically acceptable salt thereof.

40. The multilayer tablet of claim 38 or 39, wherein the first layer and the second layer are compressed separately and subsequently combined.
41. The multilayer tablet of claim 38 or 39, wherein the first layer is formed by compression and subsequently the second layer is compressed onto the first layer.
42. The multilayer tablet of any one of claims 38 to 41, comprising 25 mg rilpivirine as a pharmaceutically acceptable salt thereof, 25 mg tenofovir alafenamide as a pharmaceutically acceptable salt thereof, and 200 mg emtricitabine.
43. The multilayer tablet of claim 42, comprising 27.5 mg rilpivirine hydrochloride and 28 mg tenofovir alafenamide hemifumarate.
44. The multilayer tablet of any one of claim 38 to 43, wherein the first pharmaceutical excipient comprises microcrystalline cellulose and lactose.
45. The multilayer tablet of claim 44, wherein the first pharmaceutical excipient further comprises croscarmellose sodium.
46. The multilayer tablet of any one of claims 38 to 45, wherein the second pharmaceutical excipient comprises microcrystalline cellulose.
47. The multilayer tablet of claim 46, wherein the second pharmaceutical excipient further comprises croscarmellose sodium.
48. The multilayer tablet of any one of claims 38 to 47, wherein the second layer does not contain lactose and/or starch.

FIGURE 1

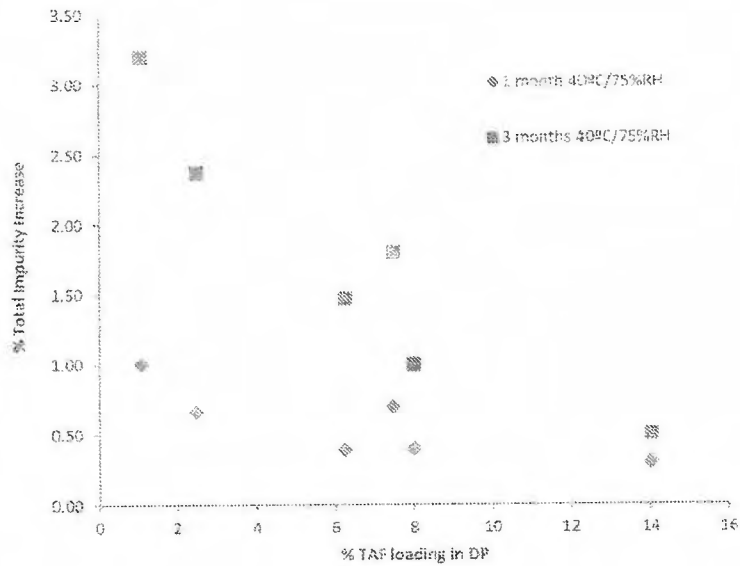


FIGURE 2

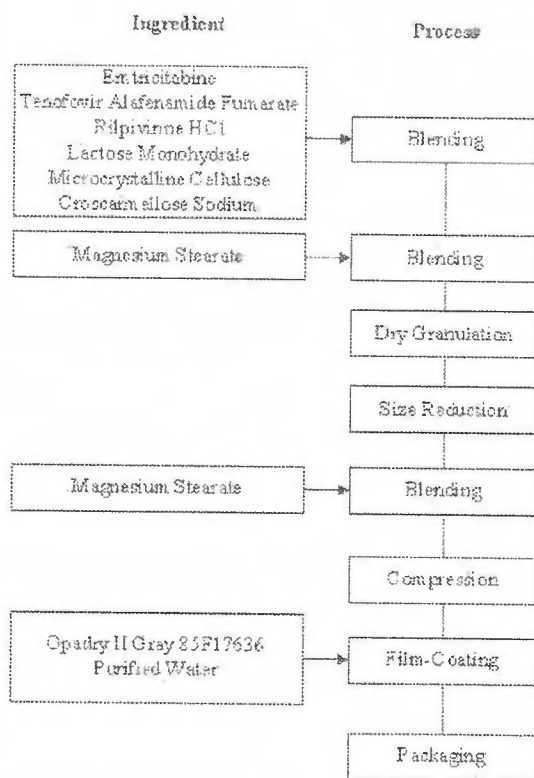


FIGURE 3A

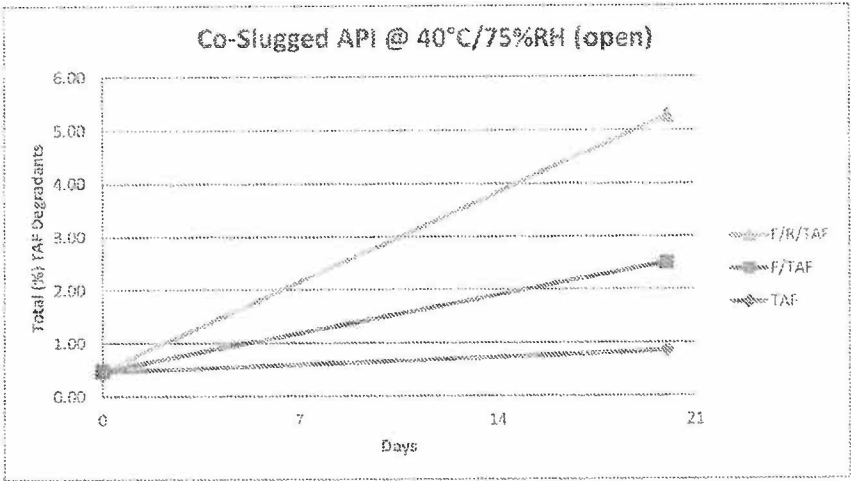


FIGURE 3b

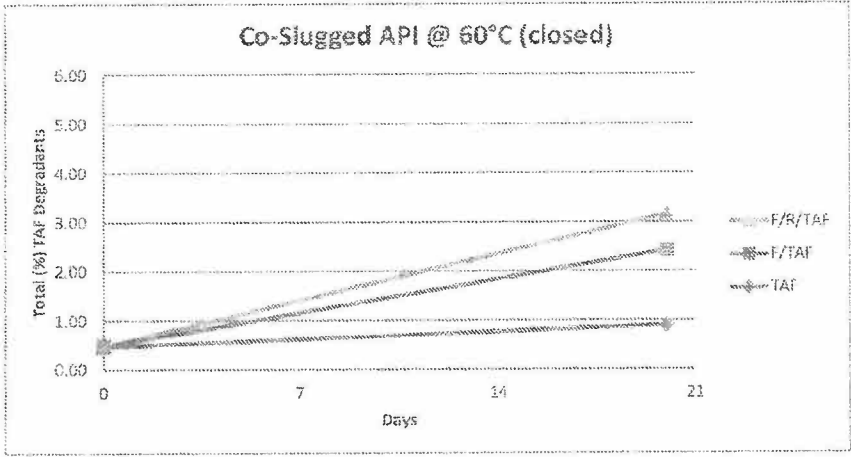


FIGURE 4

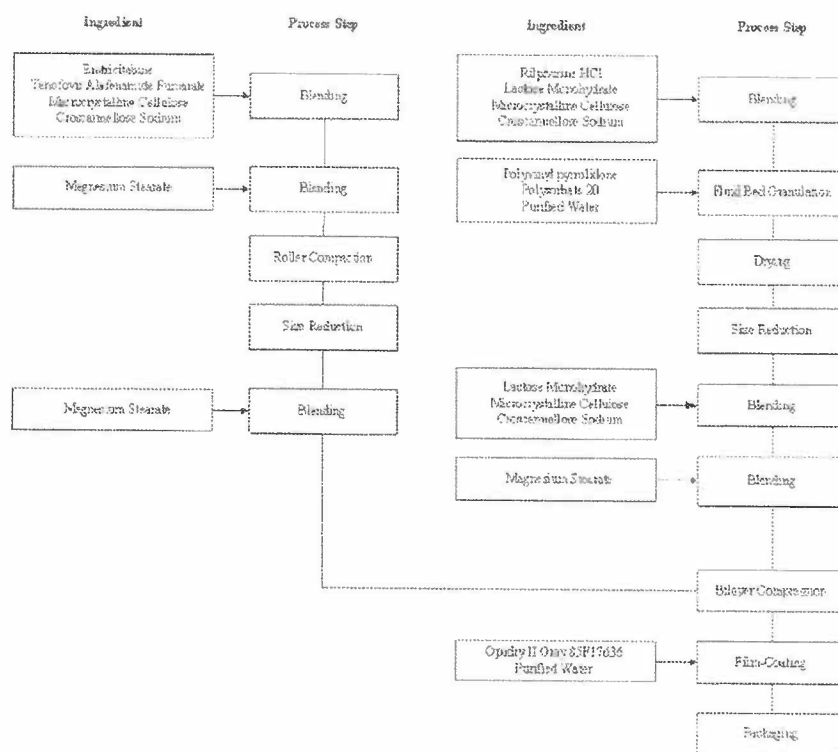


FIGURE 5

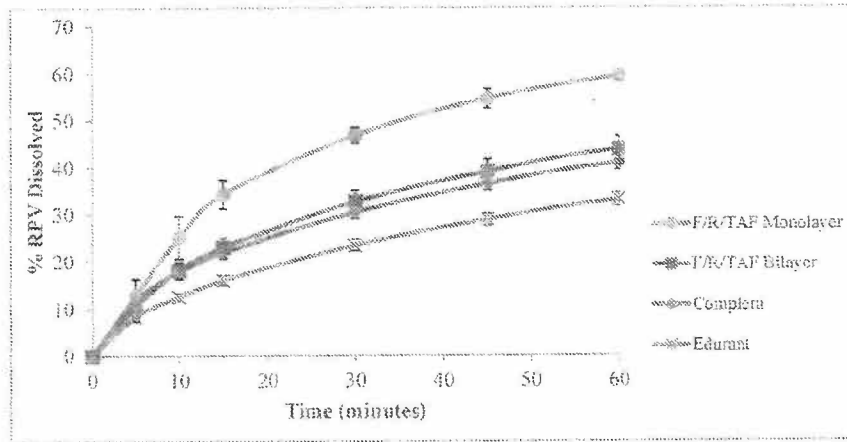


FIGURE 6a

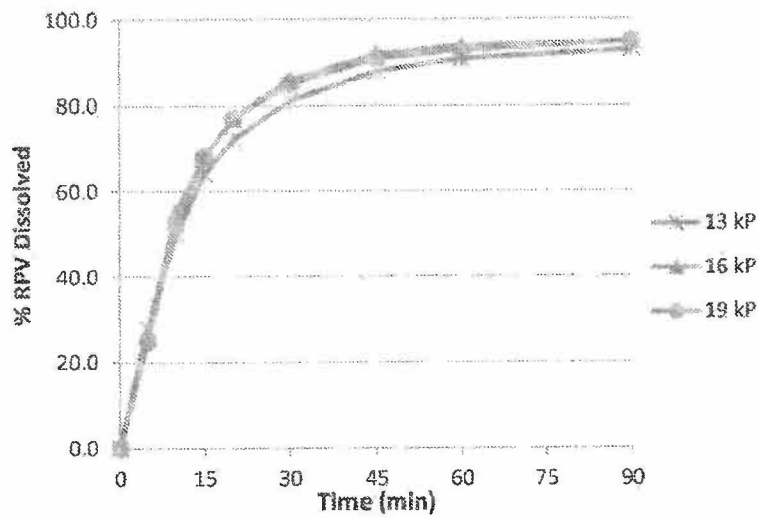


FIGURE 6b

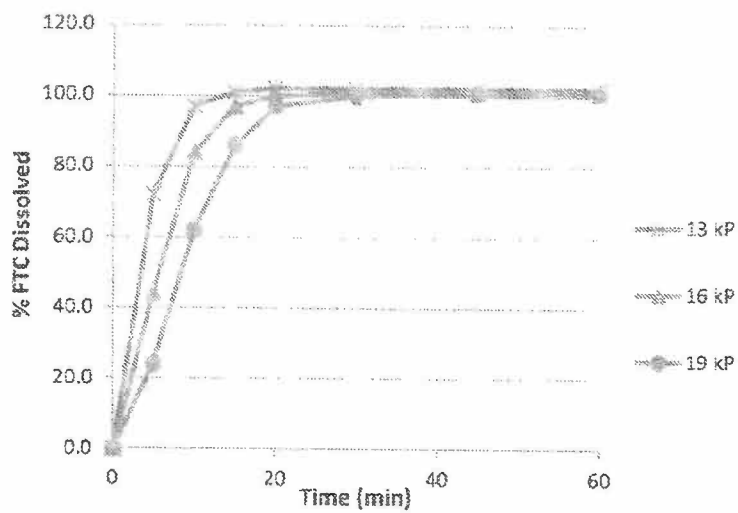


FIGURE 6c

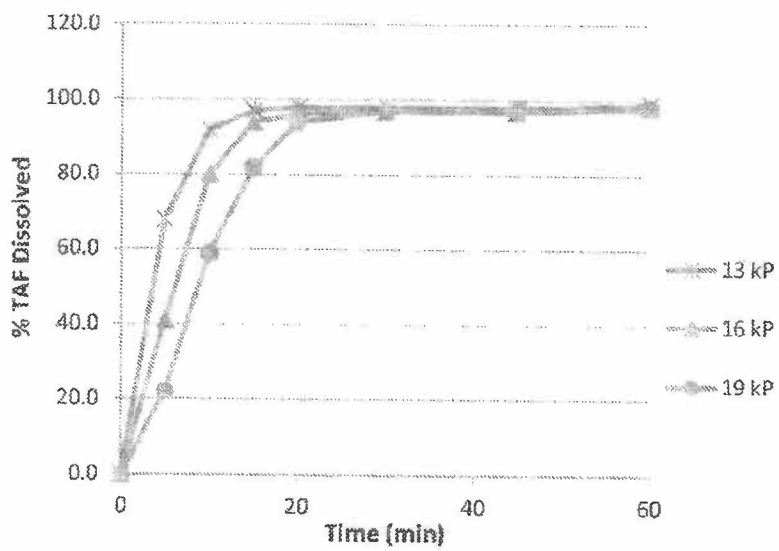


FIGURE 7

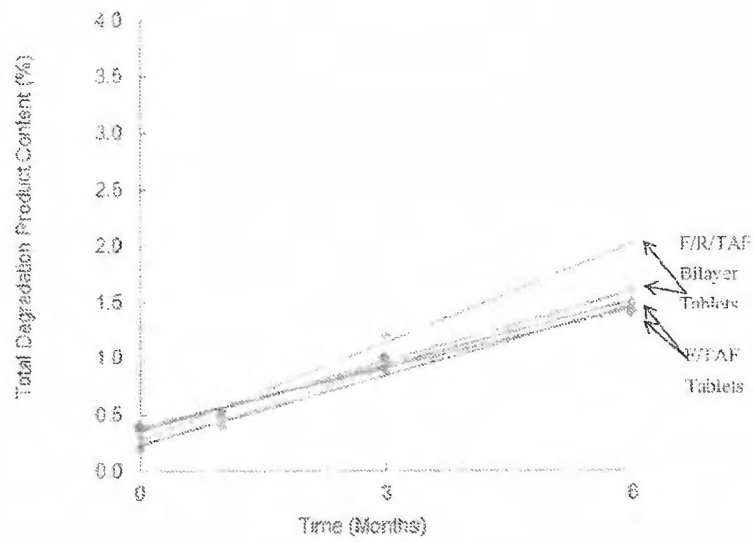


FIGURE 8A

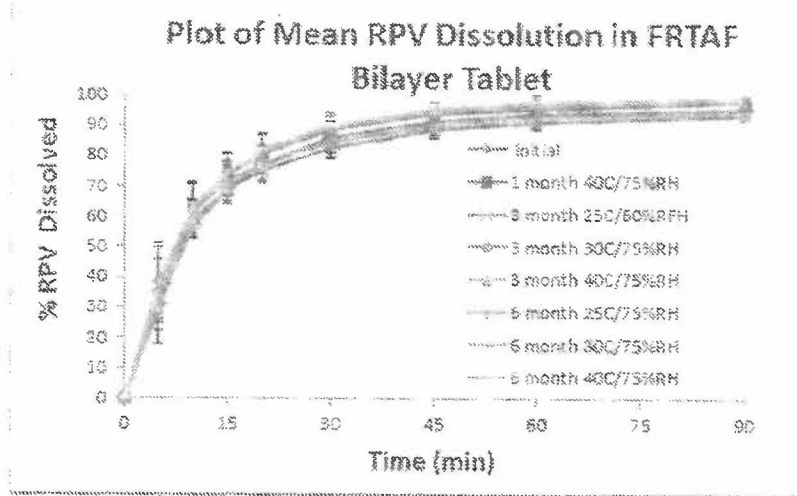


FIGURE 8B

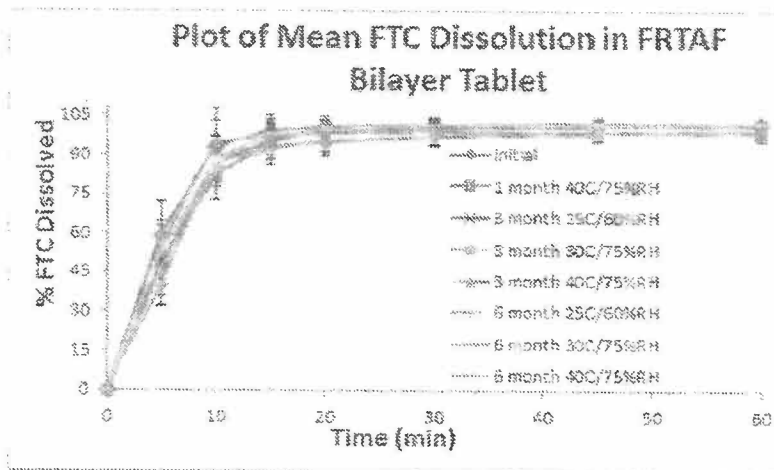


FIGURE 8C

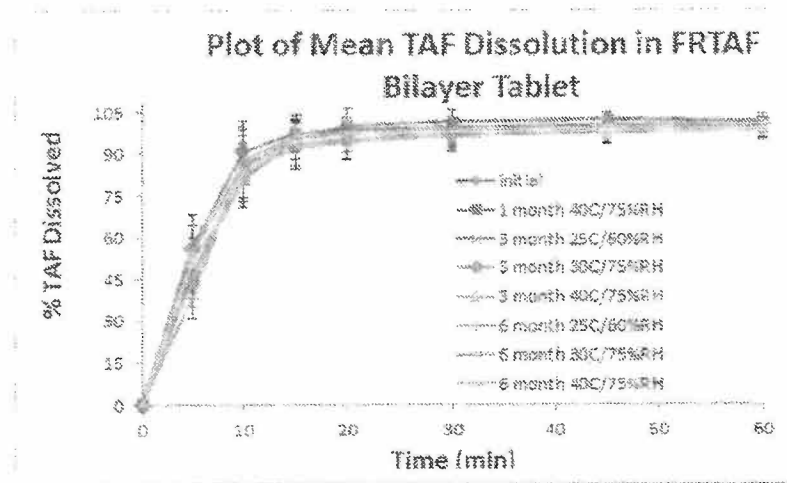
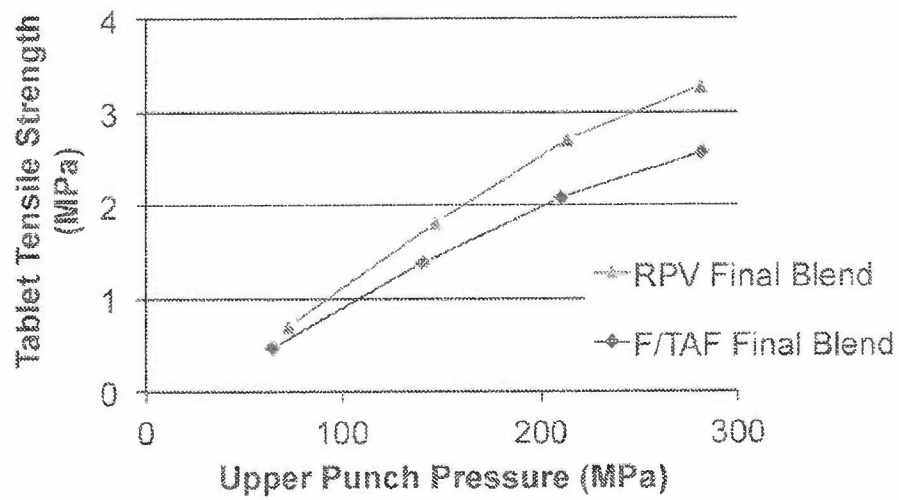


FIGURE 9





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Boards of Appeal
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Datum/Date
26.05.23

Zeichen/Reference/Référence	
O308281EP:CJH/PAK/HEB / APPR	
Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°	16798063.0 / 3346995
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire	
Gilead Sciences, Inc.	

Appeal number: T0355/23-3.3.07

Please find enclosed a copy of

- ☐ a letter of the patent proprietor dated
- ☒ a letter of the opponent 02 dated 22.05.23



for your information.

The Registry B. Aienza Vivancos
Tel.: 089 / 2399 - 3371
Annex(es):

Registered letter

EPO Form 3345

01/11





Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed document(s) pertaining to the following application:

Application number:

16795063.0

Applicant's or representative's reference:

RSC/R79369OP

	Description of document	Original file name	Assigned file name
1	Letter relating to the Appeal procedure	2023-05-18 EP 3 346 985 Reply to appeal.pdf.pdf	APPEAL-LETT-1.pdf
2	Letter relating to the Appeal procedure	2023-05-22-R79369OP-EPO Opposition Letter.pdf	APPEAL-LETT-2.pdf

	Payment	
1	Method of payment	Not specified

Signatures

Place: GB
Date: 23 May 2023
Signed by: Richard Cooke 10750
Association: Elkington and Fife LLP
Representative name: Richard COOKE
Capacity: (Representative)

RSC/R79369OP

ELKINGTON + FIFE

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Our ref RSC/YZZ/R79369OP

22 May 2023

ONLINE FILING

Re: European Patent No. 3346995 (Application No. 16798063.0)
Gilead Sciences, Inc.
Opponent: Dr Richard Cooke
T0355/23-3.3.07

We enclose our reply to the patentee's appeal.

Yours faithfully
Elkington and Fife LLP

[Signed Electronically]

Richard Cooke

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European patent no. 3 346 995

(application no. 16798063.0)

Gilead Sciences, Inc.

Opponent: Dr Richard Cooke

Reply to patentee's appeal

1. Requests

(01) The opposition division decided that the patent should be maintained in amended form in accordance with AR1 filed on 26.08.2022 and all parties i.e., the two opponents and the patentee, have appealed.

(02) The patentee's appeal is against the decision of the opposition division that the main request lacked compliance with Article 123(2) EPC.

(03) For completeness, please note that we maintain our requests that the decision be set aside and the patent be revoked in its entirety, and for oral proceedings.

2. Main request: added subject-matter (Articles 123(2) and 100(a) EPC)

(04) Claim 1 of the main request relates to a tablet comprising:

- 50 mg bictegravir or a salt thereof;
- 25 mg tenofovir alafenamide or a salt thereof; and
- 200 mg entricitabine or a salt thereof.

(05) The patentee discusses two possible derivations. First starting from claim 7 as filed, and secondly starting from paragraph [0008] of the application as filed.

2.1 Starting from claim 7

(06) As the patentee explains, claim 7 differs from the main request in that it describes an embodiment in which the tablet is coated.

(07) The patentee argues that a generalisation of claim 7, to delete the coating, is permissible because (i) the coating is not inextricably linked to the other features of the coating and (ii) the overall disclosure justifies the generalisation.

(08) As explained in our grounds of appeal, the test proposed by the patentee is taken from a section of the Guidelines for Examination (H-V, 3.2.1) which relates to the permissibility of isolating a feature from an embodiment in the application.

(09) However, the present case relates to the permissibility of deleting a feature from an embodiment, which is discussed in a different part of the Guidelines for Examination (H-V, 3.1). The current settled case law of the Boards of Appeal in these circumstances is that the three-part test (T 331/87) is necessary but not sufficient for compliance with Article 123(2) EPC, and therefore added subject-matter should be assessed only by reference to the gold standard (Case Law, II.E 1.4.4)

(10) The gold standard is not satisfied because claim 7 as filed does not directly and unambiguously disclose a tablet including the components of claim 1 as granted that is not coated. On the contrary, claim 7 as filed states that the tablet must be coated.

(11) The other parts of the application cited by the patentee are not relevant.

(12) Claim 6 as filed discloses a tablet without reference to a coating. However, when dependent on the earlier claims, claim 6 as filed discloses a tablet when the 50 mg bicitegravir must be present as a salt, the 25 mg tenofovir alafenamide must be present as a salt, and the 200 mg emtricitabine is defined without reference to salts (see claim 2 as filed). Therefore, claim 6 as filed does not provide basis for claim 1.

(13) Claim 9 as filed discloses a tablet which is not coated. However, in this embodiment, the bicitegravir and tenofovir alafenamide must be segregated and the tablet weight must be less than 1 g. Therefore, claim 9 as filed does not provide basis for claim 1.

(14) The patentee also refers to the statement of the description which states that in certain embodiments the tablets are coated and in other embodiments the tablets are not coated (paragraph 71). However, this does not assist the patentee, because the embodiment described by claim 7 is one in which the tablet is coated.

(15) We agree that it would be obvious to modify the embodiment of claim 7 as filed by removing the requirement for a coating in view of these other aspects of the application, and even based on the common general knowledge alone. However, the assessment of what is obvious has no relevance to Article 123(2) EPC (Case Law, II.E.1.3.4(a)).

2.2 Starting from paragraph {0006}

(16) As the patentee notes, the disclosure in this passage of the description relates to a tablet in which the 200 mg emtricitabine is defined without disclosing salts.

(17) The patentee refers to numerous other aspects of the description in which emtricitabine is defined with reference to salts. However, this argument is flawed for the same reasons as that starting from claim 7 as filed. There may be other compositions defined in the application in which the emtricitabine is said to be present as a salt. The description may also include general statements regarding the presence of salts. However, there is no disclosure of a composition

including 200 mg entricitabine or a salt thereof including the other features of claim 1 of the patent.

(18) The pateritee notes that there are numerous disclosures of compositions in which the entricitabine is present as a salt, and because no single additional feature was required in all such cases that the skilled person would understand that the feature had general applicability. However, the common teaching is that some other feature(s) must be present, when the entricitabine is defined more broadly such that it can also be present as a salt.

2.3 Summary

(19) There is no direct and unambiguous disclosure of the features of claim 1 as granted in the application as filed.

(20) Starting from claim 7 as filed, claim 1 as granted discloses new technical information by deleting the requirement for a coating.

(21) Starting from paragraph [0008] of the application as filed, claim 1 as granted discloses new technical information by disclosing that the 200 mg entricitabine can be present as a salt.

Dr Richard Cooke
European Patent Attorney
Elkington and Fife LLP (ref R79369OP)
22 May 2023

Effect of Food on the Pharmacokinetics of the Integrase Inhibitor Dolutegravir

lvy Song,^a Julie Borland,^a Shuguang Chen,^a Parul Patel,^a Toshihiro Wajima,^b Amanda Peppercorn,^a and Stephen C. Piscitelli^a
^aGlaxoSmithKline, Research Triangle Park, North Carolina, USA; and ^bSchering-Plough, Kenilworth, New Jersey, USA

Healthy subjects received dolutegravir at 50 mg in a single-dose crossover study while they were in the fasted state or with low-, moderate-, or high-fat meals. Food increased dolutegravir exposure and reduced the rate of absorption. The area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$) increased by 33%, 41%, and 66% when administered with low-, moderate-, or high-fat meals, respectively, compared with fasting. This increase in dolutegravir exposure is not anticipated to impact clinical safety, and therefore dolutegravir can be taken with or without food and without regard to fat content.

Dolutegravir (DTG; S/GSK1349572) is an integrase inhibitor for the treatment of HIV infection, does not require boosting with ritonavir, and possesses activity against raltegravir-resistant strains (3, 4). DTG is currently in phase III clinical development at a dose of 50 mg once daily in treatment-naïve and integrase-naïve treatment-experienced subjects and at 50 mg twice daily in subjects with resistance to raltegravir or elvitegravir. The pharmacokinetic (PK) profile of DTG is characterized by achievement of high plasma drug exposures, a half-life of approximately 15 h, low to moderate intersubject variability, and a well-described PK/pharmacodynamic relationship (5, 6). The ability to administer antiretroviral medications with or without food is an important aspect of dosing convenience. Drugs that do not have food restrictions are preferred by patients and allow them to take their medications without regard to timing or content of meals. The objective of this study was to evaluate the effect of meals with various fat and caloric contents on the PK of DTG.

(These data were presented in part at the 12th International Workshop on the Clinical Pharmacology of HIV Therapy, Coral Gables, FL, April 2011.)

This was a two-part, single-center, randomized, open-label, crossover study of healthy adult male and female subjects. The sample size was 24 subjects in part 1 and 18 subjects in part 2. In part 1, 24 subjects received DTG at 50 mg as a single dose after an overnight fast of at least 6 h. Eighteen of these subjects were enrolled into part 2 and were randomized to receive a single 50-mg dose on three separate occasions with a low-fat (300 kcal, 7% fat), moderate-fat (600 kcal, 30% fat), or high-fat (870 kcal, 53% fat) meal. To avoid selection bias, the first 18 subjects who were enrolled in part 1 who still met all eligibility criteria continued to part 2. Serial blood samples for PK analysis were collected predosing and 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 h postdosing. There was a washout period of 7 days between doses. Safety evaluations included physical exam, vital signs, electrocardiograms, a full laboratory panel, and daily monitoring for adverse events (AEs). Subjects had a follow-up visit within 7 to 14 days after the last dose.

Subjects were judged to be healthy by physical exam, medical history, and laboratory testing. Exclusion criteria included a positive HIV or hepatitis C virus antibody result, a positive hepatitis B virus surface antigen result, a positive illicit drug or alcohol result, or use of any prescription or nonprescription drugs, including vitamins or herbal products, within 7 days before the first dose and throughout the study. Written informed consent was obtained

from all subjects, and the protocol was approved by the institutional review board of the study site (IncyteReview, Austin, TX [NCT01098513]).

DTG plasma concentrations were determined using a previously described, validated, high-performance liquid chromatography-tandem mass spectrometry method (5). Noncompartmental PK analysis was performed with WinNonlin (version 5.2; Pharsight Corporation, St. Louis, MO) to generate estimated PK parameters, including the area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$), maximum concentration of drug in plasma (C_{max}), C_{24} (concentration at 24 h postdosing), and time to maximum concentration of drug in plasma (T_{max}). Geometric least squares mean ratios and 90% confidence intervals were generated by the mixed effects model for within subject treatment comparisons.

Twenty-four subjects (14 female and 10 male) were enrolled, and 18 completed all four arms of the study. The mean age ($\pm$ standard deviation [SD]) was 36.6 ($\pm$ 14.6) years. The mean body mass index ($\pm$ SD) was 24.8 ($\pm$ 2.6) kg of body weight/m². Twenty-two subjects were Caucasian, one subject was African American, and one subject was of Arabic/North African heritage.

Concentration-time profiles of DTG in the fasting state or with meals of various fat and caloric contents are shown in Fig. 1. Co-administration with food increased plasma DTG exposures and reduced the rate of absorption, as evidenced by a longer T_{max} . Pharmacokinetic parameters are presented in Table 1, and statistical comparisons of these PK parameters are shown in Table 2. The increases in exposure were modest and were observed with increasing fat content. The $AUC_{0-\infty}$ increased by 33%, 41%, and 66% when DTG was administered with low-, moderate-, and high-fat meals, respectively, compared with the fasting state. The plasma DTG C_{max} increased by 45%, 52%, and 67% when DTG was administered with low-, moderate-, and high-fat meals, re-

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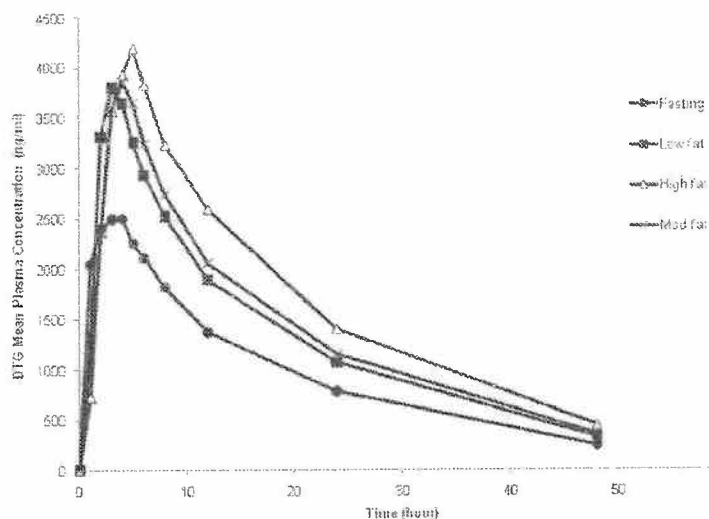


FIG 1 Mean concentration-time profiles of DTG administered in the fasting state or with meals with various fat contents.

spectively. When DTG was administered while subjects were fasting, the median T_{max} was 2.1 h. This increased to 3.0 h for a low-fat meal, 4.0 h for a moderate-fat meal, and 5.0 h for a high-fat meal. The elimination half-life was not affected by food.

DTG was well tolerated, with few AEs reported. No grade 3/grade 4 AEs or withdrawals due to AEs were reported. Two subjects reported gastrointestinal AEs (1 nausea, 1 vomiting, both grade 2) when DTG was administered under fasting conditions. Neither subject enrolled in part 2 of the study. There were no drug-related AEs when DTG was administered with food. Additionally, there were no clinically significant trends in clinical laboratory values, vital signs, or electrocardiograms.

Antiretroviral therapy has evolved to the point where many effective regimens can be administered once daily with one or two tablets or capsules per day. However, many of the most commonly used regimens still have food restrictions, requiring dosing with a meal or on an empty stomach (2, 8). Potent, once-daily antiretrovirals that allow dosing without regard to meals would be advantageous for patient convenience and adherence.

This study demonstrates that food modestly increases the exposure to DTG. The increases demonstrated in this study ranged from 33% to 66%, depending on the meal fat content, and are not

anticipated to impact safety. In a treatment-naïve, phase IIb trial (SPRING-1), HIV-infected subjects who received DTG with or without food tolerated the drug well, as evidenced by the low rate of study withdrawal and favorable adverse event profile (9). In SPRING-1, subjects receiving DTG at 50 mg once daily had a mean (coefficient of variation [CV]) for C_{24} (concentration at the end of the dosing interval) of 1.20 $\mu\text{g}/\text{ml}$ (62%), which is similar to the exposure in this study for the subjects who received a high-fat meal (mean [CV] C_{24} , 1.30 $\mu\text{g}/\text{ml}$ [47%]) (9). Furthermore, data from SPRING-1 demonstrated low to moderate variability in DTG exposures (C_{24} CV range, 62 to 67%) across all DTG doses, suggesting that dosing without regard to food does not lead to unpredictable high exposures in clinical practice (9). Finally, an additional phase IIb study of integrase-resistant, treatment-experienced, HIV-infected subjects (VIKING) in which DTG was administered both at 50 mg once daily and as a twice-daily administration to sequential cohorts of subjects demonstrated comparable safety profiles across both dose groups, despite increases in DTG exposures (7). Thus, as dosing instructions without regard to food have not led to high variability in DTG exposures in patient studies and as increased exposures by dosing twice daily have not shown a different

TABLE 1 Pharmacokinetic parameters of DTG treatment administered in the fasting state or with food

Treatment	N	Geometric mean (% CV)					Median (range)
		C_{max} ($\mu\text{g}/\text{ml}$)	AUC_{0-24} ($\mu\text{g} \cdot \text{h}/\text{ml}$)	C_{24} ($\mu\text{g}/\text{ml}$)	$t_{1/2}$ (h)	T_{max} (h)	
DTG, 50 mg, fasting	18	2.63 (28)	58.3 (27)	0.75 (34)	14.1 (22)	2.06 (1.9–5.0)	
DTG, 50 mg, low-fat meal	18	3.88 (21)	66.7 (35)	1.00 (44)	13.4 (19)	3.00 (2.0–5.1)	
DTG, 50 mg, moderate-fat meal	18	4.03 (19)	71.9 (31)	1.09 (39)	13.5 (19)	4.00 (2.0–6.0)	
DTG, 50 mg, high-fat meal	18	4.44 (24)	83.6 (35)	1.30 (47)	13.4 (21)	5.00 (1.0–8.0)	

TABLE 2 Treatment comparisons for effects of food on DTG pharmacokinetics

DTG PK parameter	Ratio of geometric least squares mean ratio (90% CI) for treatment group compared to fasted group ^a		
	DTG 50 mg + low fat (N = 18)	DTG 50 mg + moderate fat (N = 18)	DTG 50 mg + high fat (N = 18)
AUC _{0-∞}	1.33 (1.23, 1.43)	1.41 (1.29, 1.55)	1.66 (1.52, 1.82)
C _{max}	1.46 (1.34, 1.60)	1.52 (1.39, 1.66)	1.67 (1.53, 1.83)
C _{trough}	1.33 (1.20, 1.48)	1.45 (1.31, 1.61)	1.73 (1.56, 1.92)

^a The fasted group (comparison group) also received DTG at 50 mg.

safety profile, DTG can be dosed with or without food, regardless of the fat content.

Increasing exposure was observed with increasing fat and caloric content, consistent with the solubility-limited absorption of DTG. The presence of food appears to aid in the solubilization of DTG, leading to an overall increase in exposure. However, the food effect with DTG is more consistent than that of the U.S. Food and Drug Administration approved integrase inhibitor raltegravir. The AUC of raltegravir decreased by 46% with a low-fat meal, but it increased by 15% with a moderate-fat meal and increased more than 2-fold with a high-fat meal (1). Furthermore, the interpatient variability in drug exposure observed when subjects were dosed with food was considerably less with DTG than with raltegravir. Given the limitations of a cross-study comparison, the coefficient of variation with various types of meals ranged from 39 to 47% for DTG in this study, compared to previously reported values of 123 to 223% for raltegravir (1).

In summary, DTG is an investigational integrase inhibitor that is being administered in phase III clinical trials without ritonavir boosting and without regard to meals. Although the presence of food modestly increases the exposure to DTG, the effect is not considered clinically significant. Clinical experience from phase IIb trials further support this dosing recommendation. New

agents with flexible and convenient dosing requirements can aid in the construction of efficacious regimens for treatment of patients with HIV infection.

ACKNOWLEDGMENTS

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All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors.

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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: June 8, 2023
Electronic Signature for Frances Tsai: /Frances Tsai/

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 17/738,803

Confirmation No.: 2232

Filed: May 6, 2022

Art Unit: 1615

For: THERAPEUTIC COMPOSITIONS FOR
TREATMENT OF HUMAN
IMMUNODEFICIENCY VIRUS

Examiner: J. N. Worsham

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Dear Commissioner:

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).

#5073296v1

Application No.: 17/738,803

Docket No.: 1147-US-P2C2DC

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.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 07-1250, under Order No. 1147-US-P2C2DC from which the undersigned is authorized to draw.

Dated: June 8, 2023

Respectfully submitted,

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

Substitute for form 1449/PTO		Complete if Known			
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>		Application Number	17/738,803		
		Filing Date	May 6, 2022		
		First Named Inventor	Benjamin Micah Collman		
		Art Unit	1615		
		Examiner Name	J. N. Worsham		
Sheet	2	of	2	Attorney Docket Number	1147-US-P2C2DC

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	JAVOR. (2023) Experimental Report, Novartis, 4 pages.	
	CB	Therapeutic Goods Administration. (2017) Australian Public Assessment Report for emtricitabine / rilpivirine / tenofovir / alafenamide fumarate - Proprietary Product Name: Odefsey, 44 pages.	
	CC	SONG, I. et al. (2012) "Effect of Food on the Pharmacokinetics of the Integrase Inhibitor Dolutegravir" Antimicrobial Agents and Chemotherapy 56(3):1627-1629.	
	CD	Grounds of Appeal from Opponent Teva Pharmaceutical Industries Ltd. dated 2023-04-25 for European Patent No. EP3346995, 28 pages.	
	CE	Grounds of Appeal from Opponent Dr. Richard Cooke dated 2023-05-02 for European Patent No. EP3346995, 11 pages.	
	CF	Grounds of Appeal from Opponent Sandoz GmbH dated 2023-04-28 for European Patent No. EP3346995, 15 pages.	
	CG	Reply to Patentee's Appeal from Opponent Dr. Richard Cooke dated 2023-05-22 for European Patent No. EP3346995, 6 pages.	

Examiner Signature		Date Considered	
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Page 1 of 4
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APPLICATION #
17/738,803

RECEIPT DATE / TIME
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Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 2232

FILED BY Frances Tsai

PATENT CENTER # 62235456

FILING DATE 05/06/2022

CUSTOMER # 25000

FIRST NAMED INVENTOR Benjamin Micah Collman

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Donna Gressler

Documents

TOTAL DOCUMENTS: 11

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
1147-US-P2C2DC_IDS-SB08.pdf	4	-	66 KB
1147-US-P2C2DC_IDS-SB08-TRAN.LET.pdf (1-2)	2	Transmittal Letter	25 KB
1147-US-P2C2DC_IDS-SB08-IDS.pdf (3-4)	2	Information Disclosure Statement (IDS) Form (SB08)	36 KB
1147-US-P2C2DC_RCE.pdf	3	Request for Continued Examination (RCE)	1628 KB
NPL_OPP-O2-SUB_2023-05-22_1147-EP-P2.0.pdf	6	Non Patent Literature	458 KB

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**Petitioner Exhibit 1002
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NPL_SONG_2012.pdf	3	Non Patent Literature	790 KB
NPL_JAVOR_ExpReport_2023.pdf	4	Non Patent Literature	193 KB
NPL_OPP-O2-SUB_2023-05-02_1147-EP-P2.0.pdf	11	Non Patent Literature	1373 KB
NPL_OPP-O3-SUB_2023-04-28_1147-EP-P2.0.pdf	15	Non Patent Literature	2316 KB
NPL_OPP-O1-SUB_2023-04-25_1147-EP-P2.0.pdf	28	Non Patent Literature	2984 KB
NPL_TGA_AU-Public-Assessment-Report_2017.pdf	44	Non Patent Literature	6199 KB
FOR_WO2017-004012A1.pdf	77	Foreign Reference	10079 KB

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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.



Australian Government
Department of Health
Therapeutic Goods Administration

Opposition EP 3 346 995
Appeal T 0355/23
Document D49

Australian Public Assessment Report for emtricitabine / rilpivirine / tenofovir alafenamide fumarate

Proprietary Product Name: Odefsey

Sponsor: Gilead Sciences Pty Ltd

October 2017

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
3TC	lamivudine
ABC	abacavir
ACPM	Advisory Committee on Prescription Medicines
ACTH	adrenocorticotrophic hormone
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of variance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla)
ATV	atazanavir
AZT	zidovudine
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
CD4	cluster determinant 4
CDC	Centres for Disease Control and Prevention
CG	Cockcroft-Gault
CI	confidence interval
CK	creatinine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate

Abbreviation	Meaning
CLcr	creatinine clearance
CMH	Cochran-Mantel-Haenszel
COBI, C	cobicistat (Tybost)
CSR	clinical study report
C-telopeptide	type 1 collagen C-telopeptide
CV	coefficient of variation
DHHS	Department of Health and Human Services
DHEAS	dehydroepiandrosterone sulphate
DRV, D	darunavir
EACS	European AIDS Clinical Society
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
eGFR _{CG}	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
eGFR _{CKD-EPI}	Creatinine estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration serum creatinine equation
eGFR _{creat}	estimated glomerular filtration rate for creatinine as calculated by the Modification of Diet in Renal Disease formula
EQ VAS EQ	visual analogue scale
ETR	etravirine
EVG, E	elvitegravir (Vitekta)
FAS	Full Analysis Set
FDC	fixed-dose combination
FEPO ₄	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC, F	emtricitabine (Emtriva)

Abbreviation	Meaning
GLSM	geometric least-squares mean
HDL	high-density lipoprotein
HIV, HIV-1	human immunodeficiency virus, type 1
HIVTSQ	HIV Treatment Satisfaction Questionnaire
INSTI	integrase strand-transfer inhibitor
IAS-USA	International Antiviral Society of the United States of America
ISE	Integrated Summary of Efficacy
ITT	intent-to-treat
ITT-SS	intent-to-treat population using the snapshot analysis
LDL	low-density lipoprotein
LH	luteinizing hormone
LOCF	last observation carried forward
LPV/r	ritonavir-boosted lopinavir
LSM	least-squares mean
m	module
M = E	missing = excluded
M = F	missing = failure
M = LOCF	missing = last observation carried forward
MH	Mantel-Haenszel
M-MASRI	Modified Medication Adherence Self-Report Inventory
N or n	number of subjects in a population (N) or subset (n)
NCEP	National Cholesterol Education Program
NNRTI	nonnucleoside reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
NVP	nevirapine
OLE	open label extension

Abbreviation	Meaning
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PEP	postexposure prophylaxis
P-gp	P-glycoprotein
PI	Product Information
PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PK	pharmacokinetic(s)
PP	per protocol
PP-SS	per protocol population using the snapshot analysis
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy
PT	preferred term
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAM	resistance-associated mutation
RAP	resistance analysis population
RBP	retinol binding protein
RT	reverse transcriptase
RNA	ribonucleic acid
ROW	Rest of World
RPV, R	rilpivirine

Abbreviation	Meaning
RTV	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SEB	stay on baseline regimen
SD	standard deviation
SF-36	Short Form-36
SF-36v2	Version 2 of the Short Form-36
SOC	system organ class
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild)
STR	single-tablet regimen
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate (Viread)
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TLOVR	time to loss of virologic response
TmP/GFR	renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
TVD	emtricitabine / tenofovir disoproxil fumarate (coformulated; Truvada)
UACR	urine albumin to creatinine ratio
UPCR	urine protein to creatinine ratio
VF	virologic failure
VFres	virologic failure based on resistance criteria
VFss	virological failure according to snapshot analysis

I. Introduction to product submission

Submission details

Type of submission: New fixed dose combination

Decision: Approved

Date of decision: 16 August 2016

Date of entry onto ARTG: 30 August 2016

Active ingredients: Emtricitabine / rilpivirine / tenofovir alafenamide fumarate

Product name: Odefsey

Sponsor's name and address: Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne VIC 3004

Dose form: Fixed dose combination tablet

Strengths: 200 mg emtricitabine / 25 mg rilpivirine / 25 mg tenofovir alafenamide fumarate

Container: HDPE bottles with a child resistant closure

Pack size: 30 tablets

Approved therapeutic use: Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

Route of administration: Oral

Dosage: One tablet per day

ARTG number: 260634

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd to register Odefsey as a new fixed dose combination (FDC) oral tablet containing 200 mg emtricitabine (FTC, F), 25 mg rilpivirine (RPV, R) and 25 mg tenofovir alafenamide (as fumarate) (TAF) for the following proposed indication in Australia:

Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of ODEFSEY and with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy.

FTC/RPV/TAF has been developed for the treatment of HIV-1 infection for once-daily oral administration. The FDC is a combination of a nucleoside reverse transcriptase inhibitor (FTC), a nonnucleoside reverse transcriptase inhibitor (RPV), and a nucleotide reverse transcriptase inhibitor (TAF). There is no currently approved indication for this FDC.

The proposed dose is one tablet taken daily with food. The proposed tradename is Odefsey (FTC/RPV/TAF 200/25/25 mg).

The currently approved equivalent product containing tenofovir disoproxil fumarate (TDF) is Eviplera (FTC/RPV/TDF 200/25/300 mg) approved for the following indication in Australia:

Eviplera is indicated for the treatment of HIV infection in treatment-naïve adult patients with plasma HIV-1 RNA $\leq$ 100,000 copies/mL at the start of therapy.

Eviplera is also indicated in certain virologically-suppressed (HIV-1 RNA $<$ 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of resistance to any of the components of Eviplera (tenofovir DF, emtricitabine or rilpivirine).

The restriction to 'adult' patients for Eviplera relates to its RPV component which, in its registration as single agent Edurant, has restriction of use in children ("Treatment with Edurant is not recommended in paediatric patients ($<$ 18 years) due to insufficient data in this patient population"). Overseas approved prescribing information documents in the USA and EU indicate that paediatric data (Study 213 identified by the sponsor in second round) were used to update recommendations in those jurisdictions but not in Australia.

TAF has been approved in Australia as FDC Genvoya (EVG/COB/FTC/TAF 150/150/200/10 mg) for:

the treatment of HIV-1 infection in adults and adolescents aged 12 years of age and older with body weight at least 35 kg who are either treatment-naïve; or virologically suppressed (HIV-1 RNA $<$ 50 copies/mL) on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Genvoya.

TAF has now been approved as FDC in Descovy (FTC/TAF 200/25 and 200/10 mg) after consideration at the June 2016 meeting of ACPM and is indicated:

in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents aged 12 years and older with body weight at least 35 kg. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Descovy (see PHARMACOLOGY). Descovy is not for use in Pre-Exposure Prophylaxis (PrEP).

Regulatory status

The current international regulatory status is listed in Table 1.

Table 1: International regulatory status for Odefsey at time of submission to TGA.

Country	Submission date	Approval date	Indication (if applicable)
US	1 Jul 2015	1 Mar 2016	ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL, or to replace a stable antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of ODEFSEY.
EU	29 Jul 2015	21 Jun 2016	Odefsey is indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus-1 (HIV-1) without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine and with a viral load $\leq$ 100,000 HIV-1 RNA copies/mL.
Canada	19 Feb 2016	10 Feb 2017	ODEFSEY (200 mg emtricitabine [FTC]/25 mg rilpivirine [RPV]/25 mg tenofovir alafenamide [TAF]) is indicated as a complete regimen for the treatment of adults infected with HIV-1 with no known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or FTC, and with a viral load $\leq$ 100,000 copies/mL.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

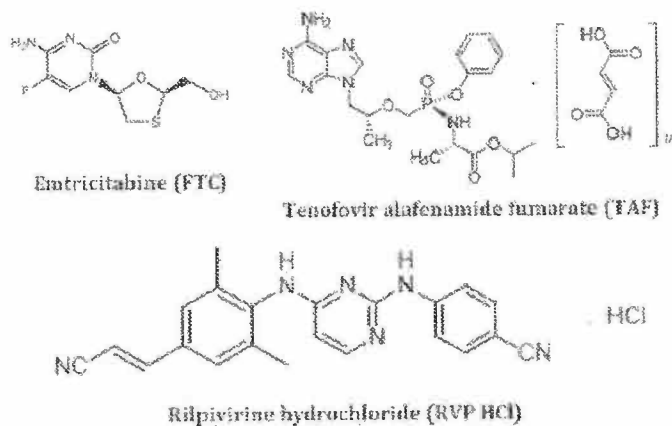
II. Quality findings

Introduction

Drug substance (active ingredient)

The components are shown in Figure 1.

Figure 1: Chemical structures.



Emtricitabine (FTC)

The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for Emtriva FTC 200 mg capsules.

Tenofovir alafenamide (as fumarate) (TAF)

The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for Genvoya Elvitegravir (150 mg), Cobicistat (150 mg), FTC (200 mg) and TAF (10 mg) tablets.

Rilpivirine hydrochloride (RPV HCl)

The chemistry, manufacture, quality control and stability of the drug substance are the same as previously approved for Edurant RPV 25 mg (as hydrochloride) tablets.

Drug product

The proposed FDC tablet is an immediate release, film-coated tablet. The formulation of the tablet is conventional and the tablets are composed of lactose, microcrystalline cellulose, povidone, Polysorbate 20, croscarmellose sodium, and magnesium stearate in the core and Opadry II complete film coating system 85F17636 grey in the film coat. The proposed tablets are packed in HDPE bottles with a child resistant closure containing 30 tablets.

The proposed tablet appearance is below:

60 mg tablet: grey, capsule shaped, film coated tablets debossed with "GSI" on one side and "255" on the other side. The tablet dimensions are 15 mm in length by 7 mm in width.

FTC/RPV/TAF tablets are manufactured in a series of manufacturing steps. RPV HCl is fluid bed granulated with intra granular excipients to produce RPV granules, which are subsequently dried, milled, and blended with extra granular excipients to produce RPV final powder blend. FTC and TAF fumarate are co-dry granulated with intra granular excipients and lubricated with extra granular magnesium stearate to produce FTC/TAF final powder blend. The RPV final powder blend and the FTC/TAF final powder blend are compressed into bilayer tablet cores that are then film coated for appearance using Opadry II Gray 85P17636.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity, water content, assay, degradation products, uniformity of dosage units, dissolution and microbiological content. Specified degradation products at levels above the ICH qualification threshold have been qualified based on toxicological data.

A shelf life of 24 months when stored below 30°C is recommended for the proposed drug product.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

- Study GS-US-366-1159: A Phase I, Randomised, Open Label, Single Dose, Three Way, Six Sequence, Cross Over Study to Evaluate the Bioequivalence of Emtricitabine, Rilpivirine and Tenofovir Alafenamide from a Fixed Dose Combination of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (200/25/25 mg) Relative to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (150/150/200/10 mg) Fixed Dose Combination and Rilpivirine (25 mg)

This study assessed the bioequivalence of a single dose of FTC, RPV and TAF in the proposed tablets to that of 25 mg Edurant tablets (RPV) and 150/150/200/10 mg E/C/F/TAF FDC tablets. The results show that the FTC, RPV and TAF components of the proposed Odefsey FTC/RPV/TAF 200/25/25 mg fixed-dose combination tablet are bioequivalent to the Genvoya E/C/F/TAF 150/150/200/10mg fixed-dose combination tablet and the Edurant (25 mg RPV) tablet.

Table 2: C_{max} and AUC_{0-∞} values for FTV, RPV and TAF.

	FTC		RPV		TAF	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
C _{max}	100.81%	97.52 - 104.21%	113.52%	108.40 - 118.89%	100.78	91.63 - 110.85%
AUC _{0-∞}	92.24%	90.94 - 93.67%	111.70%	106.31 - 117.38%	102.85	98.18 - 107.75%

Quality summary and conclusions

Registration of the product is recommended from a chemistry and quality control perspective.

III. Nonclinical findings

Assessment

In support of the proposed registration, the sponsor submitted data regarding the in vitro anti HIV activity of TAF in combination with FTC and RPV, in a two drug combination assay. Details of this study are included. The submitted in vitro study in acutely infected MT-2 cells clearly demonstrated a synergistic anti HIV activity, with absence of antagonism, when tested in different combinations. Data from a three drug combination were not provided, however since every possible proposed drug combination in the two drug study provided were tested and synergistic anti HIV activity was clearly observed in every combination, further studies were not required.

No nonclinical safety studies with FTC/RPV/TAF combination were provided however, as FDC combinations of these drugs have been previously approved in a number of combination therapies, it is not considered a requirement for approval. FTC (200 mg) and RPV (25 mg) have been approved in combination with 300 mg of TDF in Evipiera. Like TAF, TDF is the first generation prodrug of tenofovir but has higher risks associated with nephrotoxicity and reduction in bone mineral density. TAF (10 mg) has recently been approved in combination with elvitegravir (150 mg), cobicistat (150 mg) and FTC (200 mg) in Genvoya, and TAF (25 mg) in combination with FTC (200 mg) in Descovy. Adequate justification was provided by the sponsor for the lack of nonclinical toxicity studies with the fixed triple combination, which was consistent with EMA guideline on the nonclinical developmental of fixed combination of medicinal products¹ and the ICH M3(R2) guidelines² that state toxicity studies are generally not warranted for drug combinations for HIV.

Nonclinical summary and conclusions

In vitro studies demonstrated synergistic anti HIV activity of the triple drug combination. The sponsor has provided adequate justification for the lack of nonclinical toxicity studies with the triple combination.

There are no nonclinical objections to registration of the FDC of FTC/RPV/TAF, 200/25/25 mg provided that the clinical evaluator is satisfied that bioequivalence has been demonstrated between TAF 25 mg in Odefsey and TAF 10 mg in Descovy, and between RPV 25 mg in Odefsey and RPV 25 mg in Edurant.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

¹ European Medicines Agency, Guidelines on the non-clinical development of fixed combinations in medicinal products, EMEA/CHMP/SWP/258498/2005, 24 January 2008.

² ICH M3 (R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, March 2011.

Introduction

Clinical rationale

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. For ART-naïve HIV-1 infected patients, current treatment guidelines suggest that initial therapy consist of two nucleos(t)ide reverse transcriptase inhibitors (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand-transfer inhibitor (INSTI).

The success of potent and well tolerated ART means that morbidity and mortality in the HIV infected population is increasingly driven by non AIDS associated co-morbidities. Clinical attention has become more focused on the optimisation of tolerability, long term safety, and adherence to potent ART regimens. A medical need remains for new, effective therapies that take into consideration the non HIV co-morbidities, demographics of the aging HIV infected population, ARV resistance, and regimen simplification. Chronic kidney disease is important, since observational studies have demonstrated a relationship between kidney disease and progression to AIDS and death. Moreover, HIV associated nephropathy, present in up to 30% of patients, is a common cause of ESRD requiring dialysis and potential transplantation. ART with proven efficacy and safety in the both elderly and young patients is important; however there are limited data and treatment options are available in both populations. The elderly have increased risks for co-morbidities, including those related to renal function and bone mineralisation. There are specific and complex challenges for the treatment of adolescents, especially related to adherence, and who also represent the population that will require ART for the longest time.

Given the duration for which a newly diagnosed person with HIV-1 may take an ART regimen throughout his or her lifetime, the FTC/RPV/TAF (Odefsey) tablet, may provide the potential for the longevity of treatment that optimizes tolerability, long term safety, and durable efficacy. For HIV infected patients, Odefsey, with its substitution of TDF for TAF, may have advantages over the existing marketed product containing TDF/FTC and RPV (Eviplera); specifically, less proteinuria, less need for renal monitoring, and less impact on bone mineralisation relative to FTC/TDF/RPV treatment. The relatively low dose of TAF (25 mg versus TDF 300 mg) that is used in Odefsey could allow HIV infected, virologically suppressed patients to convert from the TDF based Eviplera regimen with possible renal and bone safety advantages.

Comment: The rationale for developing HIV-1 therapies that have long-term effectiveness, while minimising non-HIV related co-morbidities, is an essential goal to improve long-term HIV management.

Guidance

During the pre-submission assessment, TGA noted the proposed indication is:

as a complete regimen for the treatment of HIV-1 infection in adults and paediatric patients 12 years of age and older without any known mutations associated with resistance to the individual components of FTC/RPV/TAF combination.

TGA further noted:

The proposed F/R/TAF 200/25/25 FDC is supported in principle, given the currently registered F/R/TDF 200/25/300 FDC. It is noted that TAF is currently not on the ARTG as a mono-agent or as a component of any FDC.

Please note that this advice is without prejudice and does not imply adequacy of the BE study to support the registration or the adequacy and relevance of the clinical data for the F/C/F/TAF 150/150/200/10 (Feb 2015 batch) or F/TAF 200/10 and 200/25 (no submission yet) or the data supporting use of TDF. These are evaluation matters and will be dependent on the outcome of the full evaluation process.

At present, the registered products Eviplera (FTC/RPV/TDF), Truvada (FTC/TDF), Edurant (RPV) or Stribild (EVG/COB/FTC/TDF) are approved for use in adults (> 18 years of age). Genvoya and Descovy were not registered at the time of Odefsey submission.

This apparent discrepancy has been addressed in the clinical evaluation report. As noted, one of the major comparator substances, Genvoya, remained under review by TGA at the time of the clinical assessment; therefore, the validity of the use of this comparator remained questionable.

TGA has adopted the following EU guidelines relevant to this submission:

- Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV infection EMEA/CPMP/EWP/633/02 Revision 2,³ which came into effect in June 2009 and as adopted by TGA in July 2009;
- Points to Consider on Switching Between Superiority and Non inferiority CPMP/EWP/482/99,⁴ which came into effect in July 2000 and was adopted by TGA in June 2000;
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses. CHMP/EWP/185990/06,⁵ which came into effect in January 2008 and was adopted by TGA in February 2009.

Contents of the clinical dossier

The clinical dossier is based on a bioequivalence study (GS-US-366-1159) that is intended to provide the 'pharmacokinetic bridge' between the FTC and TAF components of Odefsey and the FTC/TAF components of Genvoya (E/C/F/TAF), although the dose of TAF in Odefsey is 25 mg, whereas the dose in Genvoya is 10 mg, albeit boosted with 150 mg of Cobicistat. The clinical data in the submitted dossier is, to a greater extent, comparable to that in the Genvoya dossier.

As noted by the sponsor there are no data available in this marketing submission on the use of Odefsey in the target population of patients with HIV-1 infection. The only data in this dossier are derived from healthy adult subjects who were administered Odefsey in Phase I bioequivalence studies. There are no clinical data on adolescent subjects who are either healthy or who have HIV-1 infection. All other data are based on evidence from the Genvoya submission, which is not approved at this time.

The submission contains the following clinical information:

- Two clinical pharmacology studies, including two that provided pharmacokinetic data and none that provided pharmacodynamic data. The pharmacokinetic studies are GS-US-366-1159, which is a Phase I two way crossover study comparing the bioequivalence of FTC/TAF administered as Genvoya (E/C/F/TAF) with FTC/TAF administered as Odefsey (F/RPV/TAF), and RPV administered as a single tablet, compared with RPV administered as Odefsey. The second PK study is a Phase I study,

³ European Medicines Agency, Guideline on the clinical development of medicinal products for the treatment of HIV infection, EMEA/CPMP/EWP/633/02 Revision 2, 20 November 2008.

⁴ European Medicines Agency, Points to consider on switching between superiority and non-inferiority, CPMP/EWP/482/99, 27 July 2000.

⁵ European Medicines Agency, Guideline on reporting the results of population pharmacokinetic analyses, CHMP/EWP/185990/06, 21 June 2007.

GS-US-366-1651, describing the PK of Odefsey under fed and fasted conditions, both in healthy subjects. A third study is included, GS-US-366-1689, which is a phase 1 study to determine the possible drug interactions between Odefsey and the combination of Ledipasvir/Sofosbuvir.

- No population pharmacokinetic analyses.
- No pivotal efficacy/safety studies. The dossier for Genvoya is included, but these data are specifically for the combination of E/F/C/TAF at a TAF dose of 10 mg. There are no bioequivalence studies comparing the 10mg TAF dose with the 25mg dose used in the Odefsey FDC, except as Genvoya, which also contains EVG and COBI.
- No dose finding studies.
- There are two post-marketing reports of cumulative clinical experience with Eviplera as related to skin reactions and weight gain. Eviplera is a different FDC to Odefsey as it contains 300mg TDF compared with the 25mg of TAF in Odefsey.

Paediatric data

The submission included paediatric data related to clinical studies on Genvoya, not specifically on Odefsey. The Genvoya data are provided on HIV infected treatment naive adolescents 12 years old or greater (GS-US-292-0106). There are no bioequivalence or clinical data for Odefsey in adolescents. This is especially relevant in relation to the recommended use of Odefsey 200 mg/25 mg/25 mg as there are no bioequivalence studies presented in the dossier to enable determination of the relationship of the 10mg TAF boosted with 150 mg Cobicistat dosage as used in the Genvoya Study GS-US-292-0106.

Good clinical practice

The clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice. All of the studies were conducted under a US Investigational New Drug Application (IND) and in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonisation guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The protocol, consent form, study subject information sheets, and advertisement were submitted by each investigator to a duly constituted Institutional Review Board for review and approval before study initiation. All subjects provided written informed consent after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study related procedures.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic.

Table 3: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Bioequivalence † - Single dose	GS-US-366-1159
	Food effect	GS-US-366-1651
PK interactions	Ledipasvir/Sofosbuvir	GS-US-366-1689

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

This dossier is an application for approval of Odefsey (F/RPV/TAF) as a treatment for HIV-1 infection in adults and adolescents. The pivotal data submitted by the sponsor is limited to three pharmacokinetic studies submitted in this section. There are no other studies in this dossier to include any clinical efficacy or safety data as Odefsey has never been administered to the target population of HIV-1 infected adults or adolescents. The only data available to the assessor are two bioequivalence studies where Odefsey has been compared with Genvoya (E/F/C/TAF), for the TAF/FTC component, and compared with Edurant (RPV) for the RPV component. The assessor is unclear as to why the sponsor has chosen these comparators as Genvoya contains both a booster and an Integrase inhibitor, in addition to TAF/FTC and the dose of TAF is 10 mg rather than 25 mg as in Odefsey, while Edurant is a single agent compound, rather than an FDC and because there are comparator compounds that would have been more appropriate to utilise. As stated previously, Genvoya is currently under review and therefore the selection of this FDC in preference to Descovy (which is also under review) cannot be justified. Moreover, the selection of Edurant, in preference to Eviplera, considering that both are approved, remains to be justified.

The evaluator has the following concerns regarding the current submission:

- Inappropriate selection of comparator compounds; and
- The studies in the current dossier do not involve HIV infected patients, who are the targeted patient population for treatment with Odefsey.

Pharmacodynamics

Studies providing pharmacodynamic data

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration. Considering no pharmacodynamic studies have been done with Odefsey, it is not relevant to ascertain deficiencies.

Evaluator's conclusions on pharmacodynamics

The sponsor has presented no pharmacodynamic studies utilising Odefsey, the FDC, for which this application has been made.⁶ In addition, even in those studies for which the sponsor has included summary statements and made reference to an actual CSR and

⁶ In this dossier, there is a lack of pharmacodynamics studies utilising Odefsey. The corresponding clinical data of those studies summarised were not observed in the clinical evaluation.

provided linked references, the sponsor has not included any of these reference CSRs and therefore the links are non-functional. While this is a valuable resource for noting the sponsor's summary of submitted studies, it is expected that the original studies are included. This is not the case for this section.

Dosage selection for the pivotal studies

As there are no pivotal safety or efficacy studies submitted by the sponsor and as no patients with HIV-1 infection had been administered the FDC, Odefsey, the dosage described below was selected for the pharmacokinetic studies.

The selected dose of TAF single agent is 25 mg, based on the results from Study GS-US-120-0104 (not included in this dossier, although this was included in the Genvoya dossier), in which various doses of TAF (8 mg, 25 mg, and 40 mg) were administered to HIV-1 infected subjects. In this study, TAF 25 mg resulted in near maximal antiviral activity and plasma TFV exposure > 90% lower relative to TDF. TAF 25 mg is recommended with ARV agents that do not have a clinically relevant effect on TAF exposure. Study GS-US-120-1554 showed that RPV does not have a clinically relevant effect on TAF exposure. Therefore, the dose of TAF 25 mg is appropriate for the FTC/RPV/TAF FDC.

RPV 25 mg once daily is the approved dose for Edurant and Eviplera. Co-administration of TAF had no clinically relevant effect on the PK of RPV. Therefore, the dose of RPV 25 mg is appropriate for the FTC/RPV/TAF FDC. FTC 200 mg once daily is the approved dose for Emtriva.

Efficacy

No clinical efficacy studies have been conducted with Odefsey.

Safety

Studies providing safety data

There have been no clinical safety studies conducted with Odefsey in the target population. The only clinical safety studies were conducted during the pharmacokinetic studies in healthy adult subjects. There have been no safety studies conducted with Odefsey in the target population of HIV-1 infected adolescent subjects. It should be noted that only complete Study Reports are included of the three pharmacokinetic studies. While there are study summaries provided for a large number of other studies that have been conducted with Genvoya, Eviplera and Edurant; no CSRs are included. Moreover, the studies with RPV are clinical trial results where RPV is used in combination with multiple other agents.

There are no pivotal safety studies. The safety assessments were included in the pharmacokinetic studies GS-US-366-1651, GS-US-366-1689 and study GS-US-366-1159. Safety observation are summarised below.

Study GS-US-366-1159

All 96 subjects were included in the Safety Analysis Set.

Study GS-US-366-1651

All 60 subjects were included in the FTC, RPV, and TAF Analysis Sets.

Study GS-US-366-1689

All 42 randomised subjects (Randomised Analysis Set) received at least one dose of assigned study drug and were included in the Safety Analysis Set and PK Analysis Set.

Study GS-US-366-1159

Adverse events were reported in 6 subjects (6.3%) following FTC/RPV/TAF (Treatment A), 10 subjects (10.5%) following RPV (Treatment B), and 8 subjects (8.3%) following E/C/F/TAF (Treatment C). Adverse events that were considered related to study drug by the investigator were not reported in any subjects following FTC/RPV/TAF. 1 subject (1.1%) following RPV, and 4 subjects (4.2%) following E/C/F/TAF.

No deaths, SAEs, or AEs leading to premature study drug discontinuation were reported. All AEs were Grade 1 in severity. Overall, the most frequently reported AEs were constipation (9 subjects [9.4%]), nausea, and headache (6 subjects [6.3%] each). Constipation was reported for 2 subjects (2.1%) following FTC/RPV/TAF, 6 subjects (6.3%) following RPV, and 2 subjects (2.1%) following E/C/F/TAF. Nausea was reported for 1 subject (1.1%) following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 4 subjects (4.2%) following E/C/F/TAF. Headache was reported for 3 subjects (3.2%) following FTC/RPV/TAF, 1 subject (1.1%) following RPV, and 2 subjects (2.1%) following E/C/F/TAF.

Study GS-US-366-1651

Adverse events were reported in 8 of 60 subjects (13.3%) following FTC/RPV/TAF administered under fasted conditions, 1 of 30 subjects (3.3%) following FTC/RPV/TAF administered under fed conditions (moderate-fat food), and 4 of 30 subjects (13.3%) following FTC/RPV/TAF administered under fed conditions (high calorie, high fat food). One subject had AEs that were considered by the investigator as related to study drug (nausea, vomiting, and dizziness); these occurred after dosing on the day of administration of FTC/RPV/TAF under fed conditions (high calorie, high fat food), and resolved on the same day without treatment.

No deaths or SAEs were reported, and no subjects discontinued due to an AE. All AEs were Grade 1 (mild). None of the AEs were reported by more than one subject in any treatment group.

Study GS-US-366-1689

Overall, FTC/RPV/TAF and LDV/SOF were generally well tolerated when administered alone or in combination. There were no Grade 3 or 4 AEs, deaths, SAEs, or pregnancies reported and only 1 subject permanently discontinued any study drug due to an AE (non-serious, Grade 2 colitis). By treatment group, the most commonly reported (that is, for > 1 subject) AEs in the LDV/SOF group (Treatment A) were diarrhoea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects); in the FTC/RPV/TAF group (Treatment B) was constipation (9.5%, 4 subjects); and in the LDV/SOF + FTC/RPV/TAF group (Treatment C) were constipation (4.8%, 2 subjects) and headache (4.8%, 2 subjects).

Five subjects (11.9%) had AEs that were considered by the investigator to be treatment related.

AEs considered related to study drug were only reported for > 1 subject following treatment with LDV/SOF: nausea (4.8%, 2 subjects) and vomiting (4.8%, 2 subjects).

Safety issues with the potential for major regulatory impact**Serious skin reactions**

This cumulative review of severe skin and hypersensitivity reactions with Complera/Eviplera was prompted by receipt of a FDA Safety Labelling Change Notification

for Complera (26 February 2015). The FDA has requested that the Complera United States Prescribing Information (US PI) be updated due to "post-marketing reports of skin and hypersensitivity reactions, including but not limited to angioedema, hypotension, Stevens-Johnson syndrome (SJS) and drug rash with eosinophilia and systemic symptoms (DRESS)". The FDA notes that "while some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions had additional organ dysfunctions, including elevations in hepatic serum biochemistries", and the FDA considers this information to be "new safety information" that should be included in labelling for Complera.

The current company core data sheet (CCDS) for Complera/Eviplera describes the undesirable effects of allergic reaction for the FTC and tenofovir DF components and rash for the FTC, RPV and tenofovir DF components. A further description of rash events lists vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus and urticaria and skin discoloration as adverse drug reactions for FTC.

The aim of this cumulative review is to assess all available data to determine whether there is a causal association between severe skin and hypersensitivity reactions and Complera/Eviplera. A comprehensive analysis of severe skin and hypersensitivity reactions for Complera/Eviplera was performed using the following sources of data:

A total of 106 cases were identified on the Gilead DSPH database for Complera/Eviplera with event terms potentially associated with severe skin reactions or hypersensitivity reactions and hypotension. These 106 cases described 136 events, of which 31 were considered serious. None of the events were fatal and one event of anaphylactic reaction was considered life threatening (attributed to almond allergy and considered unrelated to Complera/Eviplera). A total of 27 cases of interest were identified due to either the severity of the reactions or findings of skin or hypersensitivity events of relevance to the proposed US PI. The remaining 79 cases did not describe events of relevance to the US PI or had events that were consistent with current labelling. The 27 cases of interest are described below:

- Stevens-Johnson syndrome: There were no cases of SJS identified from the database for Complera/Eviplera. One consumer (non-medically confirmed) case described an itchy rash with blisters, similar to 'being scalded by hot water, getting itchy and starting to peel off' that the patient believed 'could have led to SJS.' The patient continued treatment with Complera/Eviplera for several weeks prior to discontinuation, which is inconsistent with the clinical course of SJS. Therefore, it is unlikely that the case represents possible SJS.
- DRESS syndrome: There were two cases of potential DRESS syndrome, prompting a cumulative review of DRESS syndrome that will be included in the Complera/Eviplera periodic benefit-risk evaluation report (PBRER) covering the period 11 August 2014 to 10 February 2015. All relevant data from the DRESS syndrome review have been included in this wider and more up to date review of severe skin and hypersensitivity reactions. While both cases had a temporal relationship, rash, eosinophil elevation and abnormal liver function tests (with the former case having a positive de-challenge), in neither case was the diagnosis unequivocal. Clinical details that were lacking in the cases to definitively confirm a diagnosis of DRESS syndrome included: clinical details of the patient's neutropenia, extent of hepatic involvement, the presence or absence of fever and lymphadenopathy, biopsy results and time to regression of the symptoms; and documented temperature meeting true fever criteria, lymphadenopathy and facial oedema. The symptoms in the second case could also occur with a possible viral illness, suggested by the presence of concurrent events of sore throat, congestion and cough. Following review of the cases, there is insufficient evidence for a causal association of DRESS syndrome with Complera/Eviplera.

- Angioedema: Ten cases were identified as potentially associated with angioedema (lip swelling, n = 5; swelling face, n = 2; face oedema, angioedema, lip oedema and pharyngeal oedema, n = 1 each). Seven cases were suggestive of an allergic reaction with possible angioedema. However, one case was confounded by a concomitant medication, one case involved a prior medical history of lip swelling, and one contained limited information on the event. While the events in 5 of the 10 cases were classified as serious, none of the cases were life threatening, none involved hospitalisation or necessitated acute airway management, and none indicated impending shock. Instead, they were consistent with more typical and conventional allergic-mediated angioedema. Allergic reaction involving angioedema is an expected adverse drug reaction to the tenofovir DF component of Complera/Eviplera. These cases are consistent in terms of presentation and severity with current labelling for the event, although it is not possible to attribute causality to a particular component of Complera/Eviplera in these cases.
- Hypotension or blood pressure decreased: Three cases were identified involving hypotension or blood pressure decreased. One case described hypotension in a pregnant patient (with no skin or hypersensitivity reactions). One case described mild hypotension (107/63) in a patient experiencing drug induced allergic hepatitis (without any skin events). One case described a patient collapsing due to hypotension while experiencing an allergic reaction (severe, generalised papular rash with oedema on hands and face with a severe itch). There is currently no evidence to suggest that Complera/Eviplera causes isolated hypotension on its own, and insufficient evidence that skin or hypersensitivity reactions reported with Complera/Eviplera are associated with hypotension.
- Other events of interest: Eleven cases involved other events of interest due to severity or the presence of additional symptoms of relevance to the US PI, including fever, blister, lymphadenopathy, hepatic events, skin exfoliation, conjunctivitis or eosinophilia. Given that some of these symptoms in the 11 cases were also reported in cases described in the categories above (such as SJS, DRESS syndrome and hypotension), the total number of cases out of the 27 cases of interest experiencing fever, hepatic events, blisters, skin exfoliation, conjunctivitis and eosinophilia are described below:
 - Fever: Fever was reported in 5 of the 27 cases of interest, including 1 case of possible DRESS syndrome and 1 case of hypotension with hepatic events and without skin events. Of the 3 remaining cases, fever occurred with rash and lymphadenopathy in one case, in the second case the length of time (9 months) to onset of symptoms suggests alternative aetiology, and the available information in the third case (from a consumer) was limited.
 - Hepatic events: Hepatic events were reported in 5 of the 27 cases of interest, including 2 cases of possible DRESS syndrome and 1 case of hypotension with hepatic events and without skin events. In the remaining 2 cases, transient transaminase elevations occurred around the same time as the rash events, both resolving with Complera/Eviplera discontinuation. Both rash and hepatic events are expected adverse drug reactions to Complera/Eviplera treatment.
 - Blisters, skin exfoliation and conjunctivitis: Blisters, skin exfoliation and conjunctivitis were reported in 7 of the 27 cases of interest, including 1 case where the consumer reported possible SJS (blister, skin exfoliation, not medically confirmed) and 1 case of possible DRESS syndrome (conjunctivitis and blistering). In the remaining 5 cases, rash events occurred in conjunction with blisters (2 cases), skin exfoliation (2 cases) or conjunctivitis (1 case).

- Eosinophilia: Eosinophilia was reported in 3 of the 27 cases of interest, including 2 cases of possible DRESS syndrome. In the remaining case, eosinophil levels increased in a patient experiencing rash.

Conclusions

Upon review of all available data, the following conclusions are made:

- There is insufficient evidence of a causal association between life-threatening hypersensitivity reactions (such as SJS and DRESS syndrome), hypotension and oral lesions with Complera/Eviplera. The current data do not support inclusion of these terms in Complera/Eviplera labelling.
- There have been reports of possible angioedema in patients receiving Complera/Eviplera, and these reports are consistent in terms of nature and severity with current labelling, where angioedema is considered an adverse reaction or undesirable effect to the tenofovir DF component of Complera/Eviplera. However, it is not possible to attribute angioedema to a particular component of Complera/Eviplera from the cases received. Given that none of the cases were life threatening, necessitated acute airway management or hospitalisation, and none involved impending shock, current evidence does not support highlighting angioedema as a potential severe hypersensitivity reaction in the Warnings and Precautions of Complera/Eviplera labelling.
- Cases of serious or severe skin or allergic reactions with systemic symptoms, including fever, blisters, conjunctivitis, elevated liver function tests and eosinophilia have been reported for Complera/Eviplera. Additional wording in Complera/Eviplera labelling is recommended to indicate the severe skin reactions with systemic symptoms that have been reported so far.

Weight gain in patients taking Complera/Eviplera

This cumulative review of weight gain for Complera/Eviplera was prompted following receipt of a literature article describing 4 cases of weight gain in patients switching to Complera/Eviplera and due to the growing number of post-marketing cases of weight gain on the Gilead DSPH database.

Weight gain with Complera/Eviplera has been previously reviewed by Gilead during the analysis of Week 48 and Week 96 data from Study GS-US-264-0110 (A Phase IIIb, Randomised, Open label Study to Evaluate the Safety and Efficacy of a Single Tablet Regimen of FTC/RPV/TDF Compared with a Single Tablet Regimen of EFV/FTC/TDF in HIV-1 Infected, Antiretroviral Treatment Naïve Adults), prompted by a CHMP question upon submission of Week 48 and Week 96 GS-US-264-0110 data on how the weight gain of more than 1 kg in 24 weeks observed in the Complera/Eviplera arm could be reconciled with the known RPV adverse reaction of loss of appetite. At each analysis (Week 48 and Week 96), weight gain was not considered a validated signal due to insufficient evidence for a causal association. A response to specifically address the CHMP's question regarding weight gain and appetite was submitted in June 2014 (response to a RSI dated 17 June 2014). In this response, Gilead concluded that the relationship between weight gain and appetite is complex and the minimal mean and median increases in weight observed in subjects receiving RPV in the clinical studies is clinically insignificant. The CHMP endorsed Gilead's conclusions on the GS-US-264-0110 Week 96 weight gain analyses in correspondence dated 24 July 2014.

In this review, an analysis of weight gain was performed using the following sources of data:

- Cases on the Gilead DSPH database: A search of Complera/Eviplera cases on the Gilead DSPH database revealed 51 cases involving events potentially associated with weight

gain, of which 45 cases described actual weight gain and 6 cases did not report weight gain. The 45 cases describing weight gain are summarised below.

- Of these 45 cases, 5 cases were considered cases of interest due to being fairly well documented, having a temporal association to Complera/Eviplera and absence of alternative aetiologies for the weight gain; 3 of these cases also reported a positive de-challenge. In these 5 cases, weight gain ranged from 1.8 kg to 13.2 kg over a time period of 1 to 5 months; in the 3 positive de-challenge cases, time for weight to return to baseline following discontinuation was 1 month in 1 case, 6 months in another, and not specified in the third case. Of the remaining 40 cases, 6 cases had potential alternative explanations for the weight gain, 2 cases reported the weight gain occurring prior to initiation of Complera/Eviplera, 1 case reported the weight gain resolving with Complera/Eviplera continued, and 31 cases were considered poorly documented.
- The magnitude of weight gain was specified in 27 of the 45 cases: weight gained was ≤ 5 kg in 7 cases, between > 5 to ≤ 10 kg in 14 cases, > 10 to ≤ 20 kg in 5 cases and > 20 to ≤ 30 kg in 1 case. The mean weight gain in the 27 cases was 8.1 kg (median 7.0 kg, range 1.8 kg to 25 kg). The time period of the weight gain was reported in 22 of the 45 cases, with weight gain occurring over a mean time period of 4.9 months (median 4.5 months, range 10 days to 27 months).
- Thirteen of the 45 cases specified the type of weight gain. Eleven cases involved central fat accumulation or chest/mammary fat accumulation (of which 3 had central fat accumulation alone, 2 had central fat accumulation and chest/mammary fat accumulation, 1 had gynaecomastia, 1 had breast enlargement, and 4 had central fat accumulation and acquired lipodystrophy). One case reported gain of muscle mass and not fat mass. One further case of acquired lipodystrophy was reported, but the event started prior to initiation of Complera/Eviplera therapy. While lipodystrophy has been associated with combination antiretroviral therapy, it is unclear whether the 4 cases of central fat accumulation and lipodystrophy acquired in patients receiving Complera/Eviplera represent true fat redistribution (lipodystrophy) or simply weight gain and fat deposition in the abdominal area.
- Disproportionality analysis: Five events potentially associated with weight gain cumulative to Q1 2014 were identified on the FDA SRS/AERS database for FTC + RPV +tenofovir/tenofovir disoproxil (increased appetite, eating disorder, hunger, hyperphagia, weight increased). There was no evidence of any disproportional reporting (EB05 > 2.0).
- Information from clinical trials: A trend towards greater mean increase in weight from baseline was observed in the RPV arm versus EFV arm in ECHO/THRIVE studies (2.9 kg versus 1.8 kg at Week 96) and in the Complera/Eviplera arm versus Atripla arm in Study GS-US-264-0110 (2.6 kg versus 1.3 kg at Week 96). TEAEs potentially associated with weight gain were reported at a low frequency in the Week 96 analyses of both ECHO/THRIVE and GS-US-264-0110 studies and no consistent or significant differences were observed between the arms in the studies. There were consistent trends towards higher proportions of subjects experiencing > 15 kg increases in weight from baseline in the RPV versus EFV arms in ECHO/THRIVE (3.64% versus 2.01%, or 2.73% versus 0.73% when considering only subjects who had > 15 kg weight gain on 2 consecutive visits [$p = 0.0182$]) and in the Complera/Eviplera versus Atripla arms in GS-US-264-0110 (5.08% versus 2.81%, or 3.55% versus 2.04% on 2 consecutive visits). Similar trends were observed for subjects experiencing > 20 kg increase in weight from baseline in subjects receiving a RPV- versus EFV-containing regimen in ECHO/THRIVE (1.45% versus 0.73%, or 0.73% versus 0.37% on 2 consecutive visits) and in GS-US-264-0110 (1.78% versus 1.02%, or 0.76% versus 0.26% on 2 consecutive visits).

- Information from epidemiological studies: Two sources of epidemiological data were assessed:
 - In limited data in the latest report from the Janssen-sponsored Drug Utilisation Study of RPV versus EFV, no adverse events describing weight gain were reported.
 - In a separate epidemiological study utilizing administrative healthcare claims data, there was no evidence of an association of weight gain with Complera/Eviplera. This non-concurrent, prospective cohort study was based on a large set (n = 35,167) of patients in the US receiving an antiretroviral regimen in the IMS Pharmetrics Plus claims database. After adjusting for prior medical conditions and other potential confounding factors, these analyses did not demonstrate any elevated risk of weight gain (obesity/overweight, polyphagia, abnormal weight gain) associated with RPV containing regimens (Complera/Eviplera and Edurant [RPV]) when compared to other antiretroviral regimens.
- Information from the published literature: Five individual case safety reports that were identified from the literature have been included in the review of cases on the Gilead DSPH safety database (including the 4 cases which prompted this cumulative review). No additional literature articles were identified in the published literature describing a possible association between RPV or Complera/Eviplera and weight gain.
- Information from nonclinical studies: Findings from nonclinical studies are inconsistent with respect to weight gain. One 3 month repeat dose study in mice (Study TMC278-NC119 [TOX6739]) showed weight gain in both males and females throughout the dosing period for the highest RPV dose tested (320 mg/kg/day), in line with increased food consumption throughout the dosing period (mice could feed ad libitum in this study). Other animal studies instead showed no effects on body weight or showed reduced body weight gain.

The reason for reported weight gain in some patients receiving Complera/Eviplera is unclear, but the following factors could potentially play a role:

- Improvement of general health status: Minimal weight gain following initiation of Complera/Eviplera could potentially reflect the effectiveness of the anti HIV-1 medication and represent improvement of general health status. One of the 45 cases of weight gain noted that she considered the reported weight gain as a positive change. Such effects have been observed with other antiretroviral medications in other studies of HIV infected subjects receiving combination antiretroviral therapy.
- Awareness of the caloric requirement of RPV dosing: Patient awareness of the caloric requirement of 500 kcal for RPV dosing may have potentially led to increased total food consumption, or consumption of foods with a higher fat content, which in turn would have led to weight gain. Four of the 45 weight gain cases attributed the weight gain to the calorie requirement or fat requirement of RPV dosing.
- Increased appetite/hunger: Five of the 45 cases reporting weight gain noted that the patient experienced increased appetite (n = 3) or hunger (n = 2) after initiation of Complera/Eviplera. In addition, 3 of the 6 cases in which no weight gain was reported described increased appetite (n = 2) or hunger (n = 1) following initiation of Complera/Eviplera. Increased appetite and hunger are unlisted events for Complera/Eviplera; to the contrary, decreased appetite is a listed event for the RPV component of Complera/Eviplera. The increased appetite reported in a small number of patients receiving Complera/Eviplera could potentially be linked to improvement of general health status upon initiation of an effective antiretroviral regimen.

Accentuated weight gain with Complera/Eviplera when using Atripla as a comparator

A trend towards higher mean weight gain was observed with RPV versus EFV and Complera/Eviplera versus Atripla in the ECHO/THRIVE and GS-US-264-0110 clinical studies, respectively. Differences in weight gain may be accentuated when using Atripla as the comparator, given that EFV is dosed on an empty stomach and decreased appetite due to gastrointestinal events is common when starting a new antiretroviral regimen, particularly Atripla.

Following review of the cumulative data, in particular the post-marketing data (with supporting data from clinical trials), it is considered that there is sufficient evidence to add weight gain (preferred term 'weight increased') to the CCDS as an adverse drug reaction for Complera/Eviplera identified through post-marketing experience.

Post marketing data

The sponsor has included two reports of post-marketing AEs related to Eviplera (PTC/RPV/TDF). These reports do not have study numbers and are not link referenced in the safety summary. One report relates to severe skin reactions and allergies and the other report relates to weight gain in patients taking Eviplera/Complera.

Evaluator's conclusions on safety

Considering the total absence of any clinical safety data on Odefsey in the target population, the only conclusion that can be drawn is that it is not possible to determine the safety profile of Odefsey in patients who have HIV-1 infection. As such, it is not possible to recommend Odefsey as meeting the minimum safety requirements for approval. The sponsor has used data on adverse events from the Genvoya versus Stribild clinical studies to extrapolate the potential renal and bone mineral density problems from Stribild to Odefsey, and then concluding that by replacing TDF as in Eviplera with TAF in Odefsey these adverse events will be ameliorated. However, the sponsor has not mentioned if the same renal and BMD adverse events noted in the Genvoya/Stribild studies have been observed in patients who are being administered Complera/Eviplera, given there are around 200,000 patient years of experience with Eviplera. The evaluator has concerns regarding lack of treatment-related safety data for Odefsey in the targeted patient population with HIV infection.

First round benefit-risk assessment**First round assessment of benefits**

The benefits of Odefsey in the proposed usage are:

- There may be a hypothetical benefit of Odefsey, compared with Eviplera, in relation to the substitution of TDF (in Eviplera) for TAF (in Odefsey) in the potential reduction of renal and bone mineral density adverse events. However, this submission does not provide evidence to support this possibility and the extrapolations of clinical study results from the Genvoya dossier do not appear to be relevant.

First round assessment of risks

The risks of Odefsey in the proposed usage are:

- The sponsor proposes to extend the indication of Odefsey to adolescents 12 to 18 years of age. Currently, Eviplera is approved for adults > 18 years old. There is insufficient evidence to support sponsor's proposal to extended indication to

adolescents. The rationale for extrapolation of evidence from Genvoya dossier does not seem to be acceptable.

- As Odefsey has not been administered, in any context, to the target population, it is not possible to determine the clinical or safety potential risks.

First round assessment of benefit-risk balance

The benefit-risk balance of Odefsey is neither favourable nor unfavourable given the proposed usage, but could become favourable if the changes recommended are adopted.

First round recommendation regarding authorisation

The recommendation is that this application should be rejected.

Clinical questions

Pharmacokinetics

1. It is unclear why the sponsor chose the bioequivalent comparators of Genvoya and Edurant and, while in the summary, the sponsor has focussed on using Eviplera as the main clinical comparator to Odefsey. It is suggested the sponsor consider conducting bioequivalent studies with Descovy and Eviplera, which would then provide some evidential basis for using Eviplera as a clinical comparator.
2. It is unclear why the sponsor has decided that while the exposure to RPV increases more with a high-fat meal compared with a moderate fat meal there is no specific instruction as to the composition of the meal and how Odefsey should be taken, for example, before, with or just after the meal.
3. As in the Descovy application, administration of TAF 10 mg with a meal results in almost the same bioequivalence exposure as administering TAF 25 mg, why the sponsor dismisses the possibility of having a 10 mg dose of TAF in Odefsey is not explained in the dossier, other than to dismiss the increased exposure to TAF when administered with food as 'not clinically relevant'.
4. It is unclear why the sponsor chose to conduct the single bioequivalence study on a drug-drug interaction with Ledipasvir/Sofosbuvir (LDV/SOF) FDC tablets. No rationale is given for this choice as it does not necessarily fit with the context of the application or with the recommended clinical indications.

Pharmacodynamics

5. There are no pharmacodynamic data on Odefsey FDC. The pharmacokinetic data are derived from Genvoya and Eviplera studies and may not be applicable to the Odefsey FDC. It is unclear why the sponsor chose not to conduct a single pharmacodynamic study using Odefsey in the target population.

Efficacy

6. As stated previously, Odefsey has never been administered to the target population and therefore the sponsor has extrapolated efficacy results from Genvoya (currently not approved and not relevant as a comparator) for the FTC/TAF component of Odefsey and results from Eviplera studies for the RPV component of Odefsey. While the Genvoya dossier is attached to the submission, there is no clinical study reports related to Eviplera or Edurant, even though these studies are referenced and linked to

the clinical summaries. It is strongly recommended that the sponsor consider conducting a clinical equivalence study comparing Eviplera and Odefsey. There are a number of study designs that would meet this recommendation.

From a regulatory perspective, the clinical and scientific rationale for extrapolating data from unrelated compounds does not seem to be acceptable.

Safety

7. Specifically, the sponsor should be conducting a safety study on adolescents in the target group to determine safety aspects of Odefsey prior to making application for approval of Odefsey for this age group. The pivotal safety study currently underway where Odefsey equivalent constituents are being trialled was briefly described in the Descovy submission as GS-US-311-1089, which is an ongoing Phase 3, randomised, double-blind, switch study to evaluate the efficacy of switching FTC/TDF to F/TAF versus maintaining FTC/TDF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF as determined by the proportion of subjects with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48. In this trial there will be patients who remain on Eviplera and those who switch to FTC/RPV/TAF and these subjects in the target population may provide data to support both the safety and efficacy aspects of this submission. The preliminary PBMC data on TFV-DP concentration in the three (3) subjects reported indicated a range of intracellular concentration of 0.1-2271.4 pg per 10⁶ cells with a geometric mean of 16.1 TFV-DP concentration in pg per 10⁶ cells. These data need further clarification and consideration by the sponsor in light of availability of clinical safety and efficacy results. Clinical data from this ongoing safety study was not included in the dossier. The evaluator considers that the preliminary efficacy and safety results from this study would also contribute to the overall benefit-risk assessment of Odefsey.

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Odefsey are unchanged from those identified in the first round.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Odefsey are unchanged from those identified in the first round.

Second round assessment of benefit-risk balance

The benefit-risk balance of Odefsey, given the proposed usage, is favourable because the sponsor has provided additional information in the response.

Second round recommendation regarding authorisation

It is recommended that Odefsey should be granted authorisation. This is a shift from the recommendation of the first round. The reason for this change is based on the provision of additional data by the sponsor with respect of the summary table from clinical Study GS-US-366-1881. This table provides bioequivalence data for Eviplera versus Odefsey and demonstrates no difference. In addition, Odefsey has now been approved in the US and EU. The evaluator concludes that on-balance the dossier supports patients with HIV-1 infection to have TDF replaced by TAF in Odefsey as this will reduce the risk of renal and bone mineral density adverse effects for patients. Study C231, has data to extend approval for adolescents.

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted a Risk Management Plan (EU-RMP Version 0.1 [dated 14 July 2015, Data Lock Point 28 April 2015]) and Australian Specific Annex (ASA) Version 0.1 (dated September 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Ongoing safety concerns.

Safety Concerns		FDC component
Important identified risks	Post-treatment hepatic flares in HIV/HBV co-infected patients	FTC, TAF
	Development of drug resistance	RPV
	Depression	
	Severe skin reactions	
Important potential risks	Overdose (including overdose through accidental concurrent use of FTC/RPV/TAF with RPV-containing products)	FTC/RPV/TAF ^a , RPV
	Off-label use in patients with a baseline viral load >100,000 HIV-1 RNA copies/mL	RPV
	QT interval prolongation	
	Hepatotoxicity	
	Blood cortisol decreased	
Missing information	Long-term safety information in adults and adolescents	FTC/RPV/TAF ^a , TAF (adolescents)
	Safety in children aged 4 weeks to < 12 years	RPV, TAF
	Safety in elderly patients	RPV
	Safety in pregnancy	FTC, RPV, TAF
	Safety in lactation	
	Safety in patients with severe hepatic impairment (CPT score C)	RPV, TAF

Safety Concerns		FDC component
	Safety in patients with HBV or HCV coinfection	TAF
	Safety in patients with renal impairment (eGFR _{creat} <50 L/min/1.73 m ²)	RPV

FTC = Emtricitabine; RPV = Rilpivirine; TAF = Tenofovir Alafenamide; ^ = as single tablet

RMP reviewer comment

The listed safety concerns are generally consistent with those for Descovy and Genvoya, and for the RPV component of Eviplera. However, "drug-drug interactions" is listed as missing information for the RPV component of Eviplera. Therefore, the Sponsor should provide a justification for this difference, or add the concern as missing information for Odefsey.

The missing information safety concern of "Safety in children aged 4 weeks to <12 years" should be modified to include paediatric patients aged 12 years or over but weighing <35 kg.

The clinical evaluator's concerns regarding renal and bone toxicity are noted. However, the approach taken is consistent with other FDC involving TAF.

The omission of lactic acidosis and lipodystrophy as important identified risks is supported by a PRAC review which recommended the removal of these warnings for this class of medicines.

Pharmacovigilance plan

Routine pharmacovigilance⁷ is proposed for all safety concerns except "missing information - long-term safety information in adults and adolescents". Additional pharmacovigilance activities for specified safety concerns are summarised in Table 5.

Table 5: Additional pharmacovigilance activities for missing information.

Assigned safety concern	Additional activity	Actions/outcome proposed	Est. planned submission of final data
Safety in pregnancy (RPV, TAF, FTC)	<i>Antiretroviral pregnancy registry</i>	Collection of information on the risk of birth defects in patients exposed to antiretrovirals, including ODEFSEY during pregnancy.	Interim reports to be included in ODEFSEY PSURs
	<i>Clinical trial</i> Study TMC114HIV3015	Pharmacokinetic study of RPV in HIV-1 infected pregnant women	Q4 2016 (EU)
Safety in children aged 4 weeks to <12 years (RPV, TAF)	<i>Clinical trials</i>		
	GENVOYA in HIV-1 infected patients aged 6 to <18 years - GS-US-292-0106 (ASA)	Pharmacokinetics, safety, and antiviral activity of the GENVOYA STR in HIV-1 infected antiretroviral	48 wk report Q1 2016 (EU); final report Q2

⁷ Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

Assigned safety concern	Additional activity	Actions/outcome proposed	Est. planned submission of final data
	GS-US-292-0113 (EU-RMP)	treatment naive adolescents	2022
	GS-US-292-1515	In ASA only; no study details given	Not indicated
	RPV - clinical study in HIV-1 infected adolescents from 6 to <12 years of age - C220 (ASA) and/or C213 (EU-RMP).	<i>Note - indicated as Study C213 in ASA</i> efficacy, pharmacokinetics, safety, and tolerability, of RPV in antiretroviral treatment-naïve HIV-1 infected children (<12 Years).	Q2 2019 (EU)
Long-term safety information in adults and adolescents (F/R/TAF as STR) (TAF for adolescents)	Phase 3 clinical trials		
	• HIV-1 infected adults:		
	GS-US-292-0104* & GS-US-292-0111	Comparison of safety and efficacy of STRIBILD and GENVOYA (TDF <i>cf</i> TAF)	96 wk report Q3 2016 (EU)
	GS-US-292-0109*	Evaluate switching from TDF and TAF containing single tablet regimens	96 wk report Q1 2017 (EU)
	• HIV-1 infected adolescent patients:		
	GS-US-292-0106	See above	See above
	GS-US-292-1515	In ASA only; no study details given	Not indicated
	• RPV clinical study in HIV-1 infected adolescents (C213).	pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine in antiretroviral naïve HIV-1 infected adolescents aged 12 to <18 Years.	Final report (incl. long-term extension <240 wks); Q4 2018 (EU)
	• ODESEY clinical studies in HIV-infected adult patients: GS-US-366-1166	Switching from a Regimen Consisting of ATRILA to ODESEY in Virologically-Suppressed, HIV-1 Infected Subjects	Final report Q4 2017 (EU)
	GS-US-366-1216	Safety and Efficacy of ODESEY in HIV-1 Positive Subjects who are Virologically Suppressed on EVIPLERA	Final report Q3 2017 (EU)
Safety in patients with HBV or HCV coinfection (TAF)	Clinical trial GS-US-292-1249	Efficacy and Safety of GENVOYA in HIV 1/Hepatitis B Coinfected Adults	Q3 2016 (EU)

FTC = emtricitabine; RPV = rilpivirine; STR = single tablet regimen; TAF = tenofovir alafenamide fumarate;
 ATRILA = efavirenz/emtricitabine/tenofovir disoproxil fumarate;

STRIBILD = Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate

* = study includes Australian patients

RMP reviewer comment

The pharmacovigilance activities reported in the ASA is incomplete as it does not report all studies referenced in the EU-RMP. Similarly, the summary of pharmacovigilance activities in the ASA is inconsistent with those listed in the EU-RMP. The sponsor should also clarify any Australian involvement in the studies that are added to the revised ASA. The following safety concerns have additional pharmacovigilance activities reported in the EU-RMP, which should also be included in the ASA:

- Development of drug resistance
- Depression
- QT prolongation
- Hepatotoxicity
- Safety in children aged 4 weeks to <12 years (studies reported in ASA inconsistent with those in EU-RMP)
- Safety in pregnancy (additional pharmacovigilance study in EU-RMP)

Study GS-US-292-0112 is reported as being underway, and should be included in Table 6 as addressing the missing information for safety in patients with mild to moderate renal impairment. It should also be added to the EU-RMP.

Details of Study GS-US-292-1515 should be provided, and the sponsor should incorporate the anticipated dates for the submission of pharmacovigilance study reports in Australia into the ASA.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities⁶ for all the specified safety concerns and missing information are sufficient, except for the important potential risk: 'blood cortisol decreased', and the missing information: 'Long-term safety information in adults and adolescents' for which no risk minimisation is proposed.

RMP reviewer comment

As indicated above, the ASA states that no routine risk minimisation activities are planned for effects on blood cortisol levels. However, statements regarding effects on cortisol levels in the context of adrenal function in the Australian PI are comparable to those in the SmPC, and therefore PI statements should be included as routine risk minimisation for this important potential risk.

The potential for overdose is addressed as an important potential risk. The sponsor concluded there is a low risk for Odefsey to transmit infectious disease, or to be misused for illegal purposes. This conclusion is supported by the tablet formulation and mechanism of action which does not involve the CNS.

The potential for off-label use included use in patients with a baseline viral load of >100,000 HIV-1 RNA copies/mL, which is identified as an important potential risk. In addition, the potential for paediatric off-label use in children aged <12 years of age was considered. The sponsor claims that minimal use of other single tablet regimens have been reported in children aged <12 years of age in PSURs/PBRERs for these products. The sponsor has committed to investigating the extent of adult and paediatric off-label uses in PSURs/PBRERs for Odefsey.

⁶ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the PI or by careful use of labelling and packaging.

One patient population that may be at risk of off-label use is children aged ≥ 12 years of age but weighing < 35 kg. It is recommended that the proposed indication be modified to address this concern by including the minimum weight in the indication, as has been done in the EU.

Summary of recommendations

Issues in relation to the RMP

The sponsor should revise the ASA to:

- Align its contents with that of the EU-RMP with respect to the summary of pharmacovigilance activities described in ASA;
- Indicate Australian involvement in the pharmacovigilance activities, and indicate their anticipated date of submission to TGA;
- Clarify the proposed additional risk minimisation activities for QT prolongation in Australia (none or n/a; clarify the meaning of n/a if required);
- Include the exact wording of statements in the EU SmPC and proposed Australian PI in the ASA;
- If retained, the proposed removal of advice to not use Odefsey in patients with severe hepatic impairment from the PI should be reflected in the ASA.

Recommendation to the Delegate

The suggested wording for the conditions of registration is:

The European RMP (dated 14 July 2015, DLP 28 April 2015), with ASA (Version 0.1, dated September 2015), to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no outstanding issues. Approval is recommended. The submission was not sent to the PSC.

Nonclinical

There are no toxicology objections to the approval. Recommendations for PI have been provided.

Clinical

The clinical dossier is based on 2 Bioequivalence studies, 1 food study, and 1 drug-drug interaction study.

Bioequivalence (BE)

The dossier supporting Odefsey consists of 2 relative bioequivalence studies, Study 1159 & Study 1881 as follows.

BE Study 1159

This was 2 separate, single dose, randomised, crossover trials in healthy volunteers under fed state, to ascertain pharmacokinetic bioequivalence of:

- FTC & TAF in ODEFSEY (FTC/RPV/TAF 200/25/25 mg)
versus
FTC & TAF in GENVOYA (EVG/COB/FTC/TAF 150/150/200/10 mg)
- RPV in ODEFSEY (FTC/RPV/TAF 200/25/25 mg)
versus
RPV in EDURANT (RPV 25mg)

The results were as follows.

Table 6: BE Study 1159 PK parameters.

FTC PK Parameter	N	Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs FTC/TAF (150/150/200/10 mg) (Reference)						
AUC ₀₋₂₄ (hrng/mL)	95	9351.9 (23.7)	96	10159.4 (21.8)	92.24	90.84, 93.67
AUC _{inf} (hrng/mL)	95	9603.2 (21.6)	96	10387.1 (21.5)	92.37	90.93, 93.83
C _{max} (ng/mL)	95	1608.6 (25.5)	96	1583.8 (23.3)	100.83	97.52, 104.24
RPV PK Parameter	N	Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs RPV (25 mg) (Reference)						
AUC ₀₋₂₄ (hrng/mL)	95	3609.6 (34.9)	95	3373.4 (40.0)	111.76	106.31, 117.58
AUC _{inf} (hrng/mL)	95	3843.1 (36.2)	95	3540.7 (43.0)	110.51	105.82, 115.42
C _{max} (ng/mL)	95	121.4 (26.1)	95	108.0 (28.7)	113.52	108.40, 118.80
TAF PK Parameter	N	Test Mean (CV%)	N	Reference Mean (CV%)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
FTC/RPV/TAF (200/25/25 mg) (Test) vs FTC/TAF (150/150/200/10 mg) (Reference)						
AUC ₀₋₂₄ (hrng/mL)	95	280.0 (43.3)	96	234.4 (36.5)	102.85	98.18, 107.75
AUC _{inf} (hrng/mL)	82	263.6 (42.0)	83	247.4 (36.1)	105.85	98.27, 109.74
C _{max} (ng/mL)	95	188.0 (57.7)	96	191.8 (48.2)	100.78	91.63, 110.85

Thus, bioequivalence was satisfactorily demonstrated, based on conventional criterion of 90% confidence interval for the ratio of means for AUC and C_{max} to be within 80-125% equivalence margin, for all 3 components, including TAF 25mg unboosted in Odefsey versus TAF 10mg boosted with cobicistat in Genvoya.

BE Study 1881

This study was initially not included in the dossier and was identified only in the Section 31 response. The report was supplied at the conclusion of evaluation process. The sponsor explained that the US FDA declared a preference for comparison of Odefsey with Genvoya and Edurant rather than with Eviplera. The reasons are not clear, but may have to do with the need to prioritise the equivalence of TAF and link it to the clinical efficacy of Genvoya in the absence of clinical studies of Odefsey.

This was a single dose, randomised, crossover trial in healthy volunteers under fed state, to ascertain relative bioequivalence of RPV in Odefsey (FTC/RPV/TAF 200/25/25 mg) versus Eviplera (FTC/RPV/TDF 200/25/300 mg). The results were as follows.

Table 7: GS-US-366-1881: statistical comparisons of PK parameter estimates between test and reference treatments (RPV PK analysis set).

RPV PK Parameter	GLSM		GLSM Ratio (%) (90% CI)
	Test (N = 28)	Reference (N = 27)	
ODE (Test) vs CPA (Reference)			
AUC ₀₋₂₄ (ng·h/mL)	2079.45	2100.75	100.99 (90.31, 110.68)
AUC _{0-∞} (ng·h/mL)	2084.55	2071.05	100.52 (90.40, 110.80)
C _{max} (ng/mL)	105.05	91.71	104.76 (90.82, 118.82)

Thus, the bioequivalence was satisfactorily demonstrated with respect to RPV component in Odefsey and Eviplera.

Clinical Efficacy/Safety

No clinical efficacy/safety data are available for Odefsey at present.

Risk management plan

The EU-RMP (dated 14 July 2015, BLP 28 April 2015), with ASA (Version 0.1, dated September 2015) applies to this submission.

Risk-benefit analysis

Delegate's considerations

The FTC, RPV and TAF components in Odefsey were found to be bioequivalent to the respective components in Genvoya, Edurant and Eviplera.

The selected 25mg dose of TAF in Odefsey (FTC/RPV/TAF 200/25/25 mg) is based on results of Study GS-US-120-0104 in the previously evaluated GENVOYA dossier in which 3 dose levels of TAF (8, 25 and 40 mg) were examined in HIV patients as monotherapy. TAF 8 mg was found to be equipotent to TDF 300 mg, whereas TAF 25 mg resulted in near maximal antiviral activity with plasma TFV exposure lower by more than 90% relative to TDF 300 mg.

TAF 25 mg is also a component in Descovy (FTC/TAF 200/25), which will also be made available in 200/10 mg strength in Australia for use in the presence of a boosting agent.

Genvoya contains 10mg TAF due to inclusion of cobicistat as boosting agent in this product. Unboosted TAF 25 mg and boosted TAF 10 mg are considered bioequivalent based on data seen previously, as well as data in this submission (Study 1159).

In terms of suitability of the Odefsey as a fixed dose formulation, a single dose study (GS-US-120-0117) of RPV (25 mg) and TAF (25 mg) in healthy volunteers in Genvoya dossier did not show clinically relevant changes in TAF, TFV and RPV exposure levels on co-administration compared to administration alone. Furthermore, multiple dose study (GS-US-120-1554) of RPV (25 mg) and TAF (25 mg) in Descovy dossier also did not show clinically relevant changes in TAF, TFV and RPV exposure levels on co-administration. The amount of FTC (200 mg) and RPV (25 mg) in Odefsey are same as in the currently approved Eviplera.

This submission also included a food study (GS-US-366-1651) of Odefsey and a drug-drug interaction study (GS-US-366-1689) of Odefsey with ledipasvir/sofosbuvir (90/400 mg). A clinically significant food effect (AUC of 87%, 172% and 153% for FTC, RPV & TAF respectively with high fat diet compared to fasting) or a pharmacokinetic interaction with ledipasvir or sofosbuvir (all 5 components) was not demonstrated.

The bioequivalence strategy supporting Odefsey is based on implied extrapolation of clinical efficacy and safety of Genvoya, Edurant and Eviplera to Odefsey. The known drug interactions also apply to Odefsey by extrapolation.

A very small amount of relevant clinical exposure data was identified in Study GS-US-311-1089 which was evaluated in the Descovy submission. This was a Phase III, randomised, double-blind study to examine switching to Descovy (FTC/TAF) in virologically-suppressed HIV patients stable on regimens containing Truvada (FTC/TDF) plus a third agent. At Week 48, it is noted that 9/663 (0.5%) patients received RPV as the 3rd agent (3 patients in FTC/TAF and 6 patients in FTC/TDF group) in this study.

An additional issue is that Edurant and Eviplera are not approved for use in children <18 years of age in Australia. These are approved for use in adults and adolescents aged 12 years or older in EU and USA. The approved prescribing information from these jurisdictions indicates that a single arm, Phase II, Study C213 in 36 treatment naïve adolescent (≥12 to <18 years age) HIV patients was used to expand the use to adolescent population. This update was not done in Australia. The clinical study report for this trial has now been provided and a description of it is also proposed for inclusion in the Odefsey PI. This study involved the use of RPV (25mg daily) in combination with a regimen containing 2 NRTIs (67% of which were FTC+TDF). The PK results were as follows and were demonstrative of PK bioequivalence with respect to RPV exposure (AUC) in treatment-naïve adolescents and treatment naïve adult HIV patients (reference group).

Table 8: Summary of statistical analysis of the steady-state PK parameters of RPV after multiple dose administration of RPV 25 mg qd in adolescents (this study Part 1) and in adults (pooled data of TMC278-C209/C215 PK sub studies).

Parameter	LS means*		LS means ratio, %	90% CI, %
	TMC278-C209 + TMC278-C215 (reference)	TMC278-C213 (Part 1 + 1b) (test)		
C _{max} (ng/ml)	58.5	70.8	121.07	95.45 – 155.36
C _{min} (ng/ml)	47.5	51.3	108.09	87.44 – 133.64
C _{avg} (ng/ml)	116	102	88.24	71.08 – 109.64
AUC ₀₋₂₄ (ng.h/ml)	1782	1709	96.19	80.51 – 116.73

* N=44 for reference and N=23 for test

LS=least squares

90% confidence intervals

LS=least squares

The Week 48 efficacy data in Study 213 were also reported as follows.

Table 9: Virologic outcome at Week 24 and 48 (<50 copies/ml, TLOVR); ITT.

n (%)	RPV 25 mg qd (N=36)	
	Week 24	Week 48
Responder	27 (75.0%)	26 (72.2%)
Virologic failure	7 (19.4%)	8 (22.2%)
never suppressed	6 (16.7%)	6 (11.1%)
initial lack of response	1 (2.8%)	1 (2.8%)
relapsing	1 (2.8%)	1 (1.1%)
Discontinued due to AE**	1 (2.8%)	1 (2.8%)
Discontinued due to reason other than AE	1 (2.8%)	1 (2.8%)

Responder: number of subjects with data, n=number of subjects with data observation

* Confirmed decrease in plasma viral load of <-1.0 log₁₀ at Week 12 from the baseline plasma viral load (i.e. 2 consecutive measurements at least 2 weeks apart)

** One subject (213-0026) discontinued due to AE of pulmonary tuberculosis (mandatory withdrawal criteria)

In addition, data from study GS-US-292-0106 in Genvoya dossier have also been previously evaluated which formed the basis of approval of Genvoya of use in adolescent patients above 12 years of age and subsequent approval of Descovy in this age group. Hence, the proposed use of Odefsey in adolescents >12 years of age is supported.

Proposed action

Pending advice from the ACPM, approval is supported for the following indication:

*ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older and with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. The patients **must not have history of treatment failure** or known mutations associated with resistance to the individual components of ODEFSEY.*

Note restriction to patients with baseline viral RNA $\leq 100,000$ copies/mL is based on Edurant/Eviplera dossiers.

The following clinical efficacy studies of Odefsey are currently underway and provision of results and clinical study reports to TGA as soon as available will be included as a condition of approval:

- Study GS-US-366-1160 is a randomised, double blind study to evaluate maintenance of virologic suppression in virologically suppressed, HIV-1 patients on switching from EFV/FTC/TDF (Atripla) to FTC/RPV/TAF (Odefsey).
- Study GS-US-366-1216 is a randomised, double blind study to evaluate maintenance of virologic suppression in virologically suppressed, HIV-1 patients on switching from FTC/RPV/TDF (Eviplera) to FTC/RPV/TAF (Odefsey).

The Delegate has no reason to say, at this time, that the application for Odefsey should not be approved for registration.

This report is submitted to the ACPM for advice.

Request for ACPM advice

The ACPM is requested to provide advice on the following specific issues:

1. Does the ACPM support approval based on bioequivalence data only, with extrapolation of clinical efficacy/safety from related but not equivalent products?
2. Could the ACPM please provide advice on appropriate the therapeutic indication to capture the relevant patient population?

The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Summary

Gilead agrees with the Delegates recommendation that the application for Odefsey should be approved for registration with the indication statement as follows:

ODEFSEY is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of ODEFSEY.

Discussion of Delegate's comments*ACPM advice being sought by the TGA Delegate*

- 1. Does the ACPM support approval based on bioequivalence data only, with extrapolation of clinical efficacy/safety from related but not equivalent products?

Scientific advice on the development of Odefsey tablets, and consequently the approach to the registration strategy of Odefsey tablets was sought from the Medicinal Products Agency (MPA), Medicines and Healthcare products Regulatory Agency (MHRA), National Agency of Medicine and Health Products Safety (ANSM), and Medicines Evaluation Board (MEB), as well as in consultation with the US FDA. Based on these discussions, Odefsey was registered based on a bioequivalent strategy. This registration approach is consistent with the TGA adopted industry guideline on the investigation of bioequivalence.⁹ Acceptability of the BE strategy as outlined above has been validated by the recent approval of Odefsey by the US FDA on 1 March 2016, and EMA on 21 June 2016.

Similarly, Eviplera was approved by the TGA based on a BE strategy supported by data demonstrating that Eviplera was bioequivalent to the individual dosage forms administered concurrently, and by cross reference to the clinical efficacy and safety data previously provided to TGA for the products Viread, Emtriva, Truvada and Edurant.

In its entirety, the clinical evidence provided supports the conclusion that the administration of Odefsey is non-inferior to Eviplera in terms of comparative safety and efficacy, with a favourable profile in terms of renal and bone safety:

The pivotal bioequivalence study (GS-US-366-1159) demonstrated the following:

- Bioequivalence of TAF and FTC exposures between the Odefsey FDC and Genvoya FDC, thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the Odefsey FDC to those from Genvoya.
- Bioequivalence of RPV exposure between the Odefsey FDC tablet and Edurant, thereby supporting extrapolation of the demonstrated safety and efficacy of RPV exposures in the Odefsey FDC to those from Edurant.

In accordance with the bioequivalence approach outlined above, the safety and efficacy of Odefsey in various patient populations is derived from clinical studies previously evaluated by TGA in registration applications for Genvoya and Eviplera as follows:

- ART naive adult patients
 - Two pivotal Phase III studies conducted with Genvoya (Studies GS-US-292-0104 and GS-US-292-0111)
 - Two pivotal Phase III studies conducted with RPV in combination with a N(t)RTI backbone, which included FTC and TDF (Studies TMC278-TIDP6-C209 [C209] and TMC278-TIDP6-C215 [C215]).
- Virologically suppressed adult patients
 - One Phase III Genvoya study (GS-US-292-0109)
 - Two Phase IIb and Phase III Eviplera studies (GS-US-264-0111 and GS-US-264-0106)
- Adult patients with mild to moderate renal impairment
 - One Phase III Genvoya study (GS-US-292-0112)

⁹ European Medicines Agency, Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 January 2010.

- RPV is approved without dose adjustment for patients with mild to moderate renal impairment
- Adolescent patients
 - One Phase II/III Genvoya study (GS-US-292-0106)
 - One Phase II RPV study (TMC278 TDP38-C213 [C213]) (provided to TGA during current evaluation).

Extrapolation to Odefsey is further supported by the bioequivalence of RPV exposures between Eviplera and Edurant (Study GS-US-264-0103).

While conducting clinical trials in every possible population, would simplify evaluation, it would also unnecessarily delay registration, when in accordance with the TGA adopted industry guideline on the investigation of bioequivalence,¹⁰ such studies are not required for the purposes of registration.

In addition to clinical evidence provided, as a sponsor of therapeutic goods, Gilead continues to conduct clinical trials throughout the lifecycle of a product in order to provide physicians with additional data regarding efficacy and safety of a product. Studies GS-US-366-1160 and GS-US-366-1216 are randomized, double blinded, ongoing Phase IIb switch studies investigating Odefsey:

- Study GS-US-366-1160 is a randomised, double blind study designed to evaluate maintenance of virologic suppression (HIV-1 RNA < 50 copies/mL at Week 48) in virologically suppressed, HIV-1 infected patients when switching from a regimen consisting of Atripla (FTC/TDF/EFV 200/300/600) FDC to Odefsey FDC.
- Study GS-US-366-1216 is a randomised, double blind study designed to evaluate maintenance of virologic suppression (HIV-1 RNA < 50 copies/mL at Week 48) in virologically suppressed, HIV-1 infected patients when switching from Eviplera FDC to Odefsey FDC.

Gilead has noted the Delegate's comments that provision of these studies will be included as a condition of approval and commit to provide the data to TGA for review in a post approval application when available.

- 2. Could the ACPM please provide advice on the therapeutic indication to capture the relevant patient population?

Gilead agrees with the Delegate's recommendation that the application for Odefsey should be approved for registration with the indication statement as follows:

Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq$ 100,000 copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

As outlined in response to question 1, exposures to the FTC and TAF components of the Odefsey FDC have been shown to be bioequivalent to the exposures to those components obtained from Genvoya, therefore the safety and efficacy data for Genvoya can be reliably extrapolated to Odefsey. Likewise, since exposure to the RPV component of Odefsey has been shown to be bioequivalent to the RPV exposure obtained from Edurant, the safety and efficacy data for Edurant (and therefore Eviplera) can be reliably extrapolated to Odefsey.

¹⁰ European Medicines Agency, Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1491/98 Rev. 1/ Corr ***, 20 January 2010.

Overall, a comprehensive program of 64 clinical studies characterises the PK of Odefsey and its components. This includes data from studies conducted with Odefsey, Genvoya, Descovy, TAF, RPV, Eviplera, Emtriva, and Truvada. The data provided in support of this application includes treatment naïve adults and adolescents, virologically suppressed adults who switched from protease inhibitor based regimens, NNRTI based regimens, or integrase strand transfer inhibitor based regimens, and virologically suppressed adults with mild-to-moderate renal impairment. As such, Gilead believes the totality of data supports the therapeutic indication in capturing the relevant patient population.

It is noted by the Delegate that Edurant and Eviplera are not approved for use in children <18 years of age in Australia. Genvoya is similar to the TGA approved Stribild, and Descovy is similar to the TGA approved Truvada, which are both likely to be replaced in clinical practice following the availability of Genvoya and Descovy. Neither Stribild nor Truvada are approved for the treatment of HIV-1 infection in children <18 years of age in Australia.

Genvoya was approved by TGA on 12 January 2016, and Descovy on 28 June 2016 for use in adults and adolescents aged 12 years of age and older with body weight at least 35 kg. These indications were supported by results from the Genvoya study GS-US-292-0106 (Study 0106).

In addition to Study 0106, Study C213 supports the proposed indication of Odefsey FDC tablets in adolescents. Study C213 is a Phase II, open label, single arm study evaluating the PK, safety, tolerability, and antiviral activity of RPV plus an investigator selected regimen containing 2 NRTIs (67% of which were FTC+TDF, referred to as the FTC/TDF subset) in ART naïve adolescent patients with HIV-1 infection. The PK of RPV in Study C213 supports the efficacy of the RPV component of Odefsey as well as Eviplera in adolescent patients. The 48 week efficacy and safety results demonstrate that RPV 25 mg once daily, in combination with 2 NRTIs, is efficacious, safe and well tolerated in adolescents. A summary of the results from Study C213 are included in the proposed PI.

Indication

Gilead agrees with the Delegate's recommendation that the application for ODEFSEY should be approved for registration with the indication statement as follows:

Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

Advisory Committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of bioequivalence, efficacy, safety and quality, agreed with the delegate and considered Odefsey tablet containing FTC 200 mg/RPV 25 mg/TAF 25 mg to have an overall positive benefit-risk profile for the amended indication:

Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. The patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

In making this recommendation, the ACPM:

- Noted that the comparable efficacy of Truvada and Descovy and Stribild and Genvoya and the bioequivalence of each of TAF, FTC and RPV in the pharmacokinetic studies

provided sufficient evidence to allow extrapolation of clinical efficacy and safety for Odefsey.

- Was of the view that dose combination delivers sufficient TAF to achieve reasonable efficacy for the proposed indication with no major safety issues.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration

Proposed PI/ CMI amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the ACPM support approval based on bioequivalence data only, with extrapolation of clinical efficacy/safety from related but not equivalent products?*

The ACPM supported approval of new combination of active ingredients based on the comparable efficacy of Truvada and Descovy and Stribild and Genvoya and the bioequivalence of each of TAF, FTC and RPV in the pharmacokinetic studies provided.

2. *Could the ACPM please provide advice on the appropriate therapeutic indication to capture the relevant patient population?*

The ACPM advised on the following indication to appropriately capture the relevant patient population:

Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in treatment-naïve adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. ODEFSEY is also indicated in certain virologically-suppressed (HIV-1 RNA < 50 copies/mL) adult patients and adolescents ≥ 12 years with body weight ≥ 35 Kg on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen. Patients must not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

3. *The Committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

Prescribers of this formulation should be aware that FTC and tenofovir alafenamide have activity against HBV. This could be better addressed in the PI.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Odefsey (200 mg emtricitabine/25 mg rilpivirine/25 mg tenofovir alafenamide fumarate) FDC tablets, indicated for:

Odefsey is indicated as a complete regimen for the treatment of HIV-1 infection in adults and adolescents (12 years and older with body weight at least 35 kg) with plasma HIV-1 RNA $\leq 100,000$ copies/mL at the start of therapy. The patients must

not have a history of treatment failure or known mutations associated with resistance to the individual components of Odefsey.

Specific conditions of registration applying to these goods

- The Odefsey fixed dose combination of (200 mg emtricitabine/25 mg rilpivirine/25 mg tenofovir alafenamide fumarate) RMP: EU-RMP Version 0.1 (dated 14 July 2015, DLP 28 April 2015) and ASA Version 0.1 (dated September 2015), and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Odefsey at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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Datum/Date
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Zeichen/Reference/Référence	
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Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire	
Gilead Sciences, Inc.	

Appeal number: T0355/23-3.3.07

Please find enclosed a copy of the statement setting out the grounds of Appeal filed by Opponent 01 (Teva Pharmaceutical Industries Ltd.), Opponent 02 (Dr. Richard Cooke) and Opponent 03 (Sandoz GmbH).

Any reply must be filed within **4 months** of this notification.

The Registry B. Atienza Vivancos
Tel.: 089 / 2399 - 3371

Annex(es):

- Letter of Opponent 01 dated 25.04.2023
- Letter of Opponent 02 dated 02.05.2023
- Letter of Opponent 03 dated 28.04.2023

Registered letter



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Registergericht: AG München PR1207

VAT Reg. No: DE 130 747 219

St.-Nr./ Tax No: 143/573/80654

Appeal number: T0355/23-3.3.07

Opposition against EP 3 346 995 (16 798 063.0)

"Therapeutic compositions for treatment of human
immunodeficiency virus"

Patentee: Gilead Sciences, Inc.

Opponent O3: Sandoz GmbH

28.04.2023

Ae/Or/ms

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Further to the Notice of Appeal filed on February 17, 2023 on behalf of Opponent 3 (O3, Sandoz GmbH), we herewith provide the Grounds of Appeal.

I. Prior Art

Reference is made to documents **D1** to **D46** as cited by the parties during the first instance procedure, maintaining the document numbering as used by the opposition division (OD) in the appealed decision dated December 23, 2022 on pages 3 to 9.

In addition, the following documents **D47** to **51** are further submitted herewith:

D47: Experimental Report

D48: WO 2017/004012 A1

* Büro Bielefeld: Artur-Ladebeck-Str. 51, 33617 BIELEFELD

Telefon: (0521) 914 940 Telefax: (0521) 914 94 20

D49: Australian Public Assessment Report for emtricitabine / rilpivirine / tenofovir alafenamide fumarate

D50: Song et al., Antimicrob Agents Chemother 2012, 56(3), 1627-1629

D51: Patentee's response dated March 20, 2019 in view of US 15/346,335 (US counterpart of the opposed patent)

It is herewith requested to admit these documents into the proceedings, which are considered to be of *prima facie* relevance for the present proceedings.

In particular, the additionally filed documents D47-D51 show that the alleged "food effect", on which the OD has based its conclusions on the presence of an inventive step, is not reasonable, and the alleged effect cannot be achieved over the entire scope of the claims. Further, these documents could not have been filed during the first instance proceedings, since the OD's conclusions on inventive step were surprising and could not have been predicted from the OD's preliminary opinion. In the OD's preliminary opinion dated June 24, 2021, the OD concluded that the Main Request and Auxiliary Requests did not comply with the requirements of the EPC due to non-compliance with Art. 123(2) EPC (items 6.1 and 7.1 of the preliminary opinion). Thus, no specific reasoning with respect to inventive step of the opposed patent was provided by the OD. Thus, it could not be expected by the opponents that the alleged "food effect" is considered to be of particular relevance for the presence of an inventive step. Further, the OD's decision that the opposed patent surprisingly shows a "food effect" is erroneous and justifies the filing of additional documents, showing that the OD's conclusions are incorrect.

Moreover, D51 is a document submitted by the proprietor during prosecution of the corresponding US application. Hence, filing of this document cannot take the proprietor by surprise, since its content is well known to the proprietor.

II. Facts and Arguments

1. Main Request

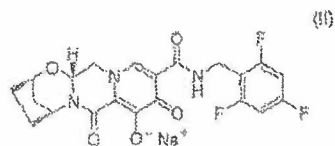
We fully agree with the OD's reasoning given in item 2 of the decision that claim 1 of the Main Request's claims (filed by the patentee with submission dated August 26, 2022) extend beyond the content of the application as filed. In particular, we fully agree with the OD's reasoning that introducing the feature "*emtricitabine salt*" is not admissible under Art. 123(2) EPC, since all paragraphs, which disclose this feature, comprise further additional technical features or are not specifically directed to a solid dosage form as claimed in claim 1.

2. Auxiliary Request 1

2.1 Lack of Novelty in View of WO 2015/196116 A1 (D1/TM14)

The objection of lack of novelty over D1 is maintained. The reasons as outlined in the Notice of Opposition still apply:

D1 is directed to sodium (2R,5S,13aR)-8-hydroxy-7,9-dioxo-N-(2,4,6-trifluorobenzyl)-2,3,4,5,7,9,13,13a-oceathydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazepine-10-carboxamide, i.e. to sodium bictegrovir, pharmaceutical formulations and therapeutic uses thereof. The structure of sodium bictegrovir is depicted as formula (II) (D1, [0002], [0008]).



In other words, the compound of formula (II) of D1 represents sodium bictegrovir.

In addition, D1 discloses the following:

"In certain embodiments, a compound disclosed herein is combined with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate, or tenofovir alafenamide and 200 mg emtricitabine. A compound as disclosed herein (e.g., a compound of formula (II)) may be combined with the agents provided herein in any dosage amount of the compound (e.g., from 50 mg to 500 mg of compound) the same as if each combination of dosages were specifically and individually listed." (TM14, [0096], emphasis added)

As outlined above, the compound of formula (II) of D1 represents sodium bictegrovir.

Hence, D1 discloses the combination of 50 mg to 500 mg of sodium bictegrovir with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate or tenofovir alafenamide and 200 mg emtricitabine.

More than this, the general section of D1 concerning the administration of the compounds discloses that tablets are preferred pharmaceutical compositions (D1, [0065]).

Thus, D1 unambiguously and directly discloses tablets comprising 50 mg to 500 mg of sodium bictegravir with 25 mg tenofovir alafenamide fumarate, tenofovir alafenamide hemifumarate or tenofovir alafenamide and 200 mg emtricitabine.

Finally, D1 discloses the use of the disclosed compounds for the treatment or prevention of an HIV infection (D1, [0069], claims 22-25).

The subject-matter of claims 1, 2 and 10 of the opposed patent is therefore anticipated by the disclosure of D1.

2.2 Lack of an Inventive Step

2.2.1 In the opposition division's decision, D5 was chosen to represent the **closest prior art** (CPA) document. We fully agree with this choice of the CPA. D5 discloses a composition comprising 50 mg dolutegravir (DTG) as integrase inhibitor (INSTI), 200 mg emtricitabine (EMC) and 25 mg tenofovir alafenamide (TAF, p. 19-20 of D5), wherein the most preferred composition is a tablet (p. 23 of D5).

2.2.2 As confirmed by the OD in the appealed decision, the **distinguishing feature** between the claimed subject-matter and the teaching of D5 is the use of 50 mg bictegravir as integrase inhibitor instead of 50 mg dolutegravir in D5, i.e. the INSTI is exchanged, while its dose of 50 mg is maintained.

2.2.3 According to the decision under appeal, "*Examples 3 and 9 of the patent demonstrate that it*" (i.e. the claimed tablet) "*possesses good food effects*" (p. 15, first sentence). The OD thus formulated the technical problem with respect to the teaching of D5 as providing "*an alternative composition (to that of D5) with good food effects to treat HIV infection*" (p. 14, penultimate sentence).

However, as we will show in the following, the alleged "*food effect*" cannot unambiguously be attributed to the distinguishing feature. In addition, we will show that this alleged effect cannot be achieved over the entire breadth of the claims.

(i) The patentee alleges that a "*food effect*", i.e. an independence of the bioavailability of bictegravir irrespective on whether the tablet is administered with or without food, is demonstrated in Examples 3 and 9 of the opposed patent.

In **Example 3**, the relative bioavailability of a **bilayer tablet** containing bictegravir, emtricitabine, and tenofovir alafenamide (75/200/25 mg - Tablet F2) administered under

fasted and fed conditions is compared with simultaneous administration under fasted conditions of a **fixed dose combination** tablet containing emtricitabine and tenofovir alafenamide (200/25 mg - Tablet F3) and a tablet containing bictegravir (75 mg - Tablet F1) as single active agent (see paragraph [0315] of the opposed patent).

In **Example 9**, the relative bioavailability of a **bilayer tablet** containing bictegravir, emtricitabine, and tenofovir alafenamide (50/200/25 mg - Tablet F7) administered under fasted and fed conditions (high-fat meal and moderate-fat meal) is compared with simultaneous administration under fasted conditions of a **fixed dose combination** tablet containing emtricitabine and tenofovir alafenamide (200/25 mg - Tablet F3) and a tablet containing bictegravir (75 mg - Tablet F1) as single active agent (see paragraph [0346] of the opposed patent).

According to paragraphs [0355] and [0356] of the opposed patent, the data presented in these Examples show that *"a fixed dosed combination tablet formulation of the compound of Formula I, emtricitabine, and tenofovir alafenamide may be taken without regard to food"*.

However, it is evident from the above-provided summary of Examples 3 and 9 of the opposed patent that no comparison with the closest prior art tablet is provided, which already discloses a fixed dose tablet comprising 50 mg of the INSTI, i.e. dolutegravir, and which thus uses the same dose as claimed in the opposed patent. Therefore, the comparison of a fixed dose combination tablet comprising the three components in a dose of 50/200/25 mg with a tablet comprising the same ingredients in a different dose, i.e. 75/200/25 mg is not a comparison with the CPA, which differs from the claimed tablet in a replacement of the INSTI while maintaining the amount of the INSTI, whereas Examples 3 and 9 instead provide a comparison of different amounts of the INSTI, i.e. bictegravir. In consequence, Examples 3 and 9 do not provide a comparison with the closest prior art.

In other words, the alleged *"food effect"* demonstrated in Examples 3 and 9 is based on a difference in the amount of bictegravir. However, the amount of bictegravir is not a distinguishing feature of the claimed subject-matter compared with the disclosure of the CPA. Hence, the comparison provided in Examples 3 and 9 of the opposed patent is irrelevant for the purposes of the problem-and-solution approach.

(ii) In addition, the comparison provided in Examples 3 and 9 is not a valid comparison, since the excipient formulations of the bilayer tablets F2 and F7 are different to those of the fixed dose tablet formulations F1 and F3. Tablet formulation F1 contains lactose monohydrate, which is not contained in any of the bilayer tablets F2 and F7. Further, the tablet formulation F1 contains sodium stearyl fumarate, which is also not contained in the

bilayer tablets F2 and F7. In addition, also the quantitative excipient composition of the tablets is different, since the excipients are used in different amounts in the fixed dose tablets and the bilayer tablets.

In consequence, any differences in the relative bioavailability could also result from the different tablet formulations, and are not necessarily the result of providing the three active agents in a single fixed dose combination tablet instead of administering bictegrovir in a single tablet together with emtricitabine and tenofovir alafenamide hemifumarate in a separate tablet.

Provided that the proprietor should base the alleged food effect on the comparison of the bioavailability achieved with the bilayer tablet of 75/200/25 mg F2 in Example 3 with the bilayer tablet 50/200/25 mg F7 in Example 9, this would result in a comparison across different studies, which is not a valid comparison. Instead, no direct comparison is provided. Thus, the alleged “food effect” is not credibly demonstrated.

In consequence, the alleged “food effect” based on Examples 3 and 9 of the opposed patent cannot be attributed to the distinguishing feature and is not demonstrated to be achieved over the entire scope of the claims.

(iii) In addition, the Tables in paragraphs [0309] and [0335] describe the specific composition of the tablets F2 (being a reference tablet) and F7 used in the pharmacokinetic studies referred to in Examples 3 and 9. It is evident from these tables that both tablets F2 and F7 are specific bilayer tablets containing a specific excipient composition and which is manufactured using the process as described in Example 8, i.e. in which the compound bictegrovir is contained in a first layer and the emtricitabine/tenofovir alafenamide hemifumarate is contained in a separate second layer.

However, claim 1 of the Auxiliary Request 1 is not restricted to such a specific bilayer tablet, but instead encompasses *any* tablet comprising a combination of the three active agents as claimed and even encompasses single layer tablets containing a mixture of all three active agents.

It is, in particular, not demonstrated in the opposed patent that the alleged “*food effect*” can also be achieved for any other tablet than the specific tablet formulation of tablet F7. Instead, further structural limitations, such as the requirement of a multilayer tablet and specific excipient composition as used in the specific tablet formulation F7 of the opposed patent, are only required by claim 1 of Auxiliary Request 10. Hence, the comparison of Examples 3

and 9 of the opposed patent introduces specific structural limitations, which are not required by claim 1 of Auxiliary Request 1.

The provision of a relatively complicated and demanding tablet design in form of a bilayer tablet, separating the active agents of a formulation in different layers, compared to a much simpler monolayer tablet, does only make sense in case there is an incompatibility between the active agents of a combination. Such an incompatibility might lead to increased and therapeutically unacceptable degradation of one or more of the active agents. Indeed, as described in **D15**, page 412, left-hand column, fourth para., multilayer tablets *"are made primarily to separate incompatible drugs from each other, i.e. incompatible drugs can be incorporated into the same tablet"*.

The experimental report submitted herewith as **D47** shows and confirms that there is an incompatibility between bicitgravir (BIC) and tenofovir alafenamide (TAF). As evident from the results reported in **D47**, granulation of both BIC and TAF leads to significant degradation of TAF when stored at stress conditions of 60°C and 30% rel. humidity (RH) for seven days. The presence of an excipient mixture corresponding to that used in the tablet formulations of the opposed patent slightly reduced this incompatibility. Nevertheless, under these stress conditions, about 6% of degradation products of BIC and TAF could be detected in a formulation containing all three ingredients in the amounts as claimed in the opposed patent plus excipients (see "Results" and "Conclusions" of **D47**). In consequence, it can be concluded from **D47** that the combination of both active agents bicitgravir and tenofovir alafenamide in a single layer of a tablet, as in the tablet formulations of the opposed patent, would lead to unacceptable degradation of tenofovir alafenamide in the presence of bicitgravir.

The presence of an incompatibility between the active agents tenofovir alafenamide (TAF) and other anti-HIV active agents, including emtricitabine, is confirmed in the art and is described in **D48**. Although **D48** is published after the filing date of the opposed patent, this document is submitted herewith as a confirmation that TAF shows incompatibility problems when formulated with other anti-HIV active agents, including emtricitabine, as combined in the formulations of the opposed patent. In particular, **D48** describes (page 16, lines 13-14):

"As mentioned above and as explained in more detail in the examples below, the stability of tenofovir alafenamide deteriorates in the presence of emtricitabine."

D48 further describes that the incompatibility is further accelerated by the presence of the active agent rilpivirine (**D48**, p. 16, l. 14-15). The stability problems associated with TAF are overcome in **D48** by formulating multilayer tablets for separating the active agents (**D48**,

p. 17, l. 20-21). Indeed, the commercial product Odefsey®, which includes the triple combination described in D48, i.e. 200 mg emtricitabine, 27.5 mg rilpivirine hydrochloride (equivalent to 25 mg rilpivirine), and 28 mg tenofovir alafenamide fumarate (equivalent to 25 mg tenofovir alafenamide) is marketed as a bilayer tablet (see D49, p. 14, first paragraph).

Thus, separating bictegravir in the bilayer tablets F2 and F7 from the other two active agents tenofovir and emtricitabine by formulating bictegravir in one layer and tenofovir and emtricitabine in a separate layer is necessary to overcome the incompatibility of the active agents. Instead, a physical mixture of the three active agents as claimed, as e.g. in a monolayer tablet, leads to unacceptable incompatibilities, which would make such a formulation unsuitable for any pharmaceutical applications. In addition, it is not demonstrated that the alleged “food effect” could even be obtained for any other tablet formulation than the very specific bilayer tablet used in Example 9 of the opposed patent.

In consequence, it is not credible that the alleged “food effect” if at all, can also be achieved with any other tablet than that of tablet F7 of the opposed patent, such as any monolayer tablet, in which all three components are contained in a single layer.

To summarize from the above (i) to (iii), **no technical effect** is demonstrated by the proprietor, which can be unambiguously attributed to the distinguishing feature in comparison with the closest prior art, and which can be achieved across the entire scope of the claims.

2.2.4 Thus, the **objective technical problem** to be solved is the provision of an alternative tablet formulation based on the back-bone anti-HIV-therapy emtricitabine/tenofovir alafenamide hemifumarate.

2.2.4.1 Starting from the CPA D5, the skilled person would have arrived at the claimed technical solution in view of D3, which already highlights bictegravir as a suitable INSTI to be combined with the emtricitabine/tenofovir alafenamide hemifumarate backbone therapy, i.e., D3 teaches that bictegravir is a suitable and readily available alternative to dolutegravir of D5.

In that respect, the OD has correctly concluded that D3 describes bictegravir as INSTI with adequate properties, as demonstrated in examples 106 and 107 of D3, and which is specifically exemplified in claim 32 of D3.

The OD has also correctly concluded that the skilled person would consider bictegavir disclosed in D3 as a suitable alternative to dolutegravir of D5, and thus the skilled person would have replaced dolutegravir of D5 with bictegavir of D3 without any inventive step.

2.2.4.2 Even in case the Board of Appeal should confirm the technical problem as formulated by the OD, i.e. as the provision of an alternative formulation with good food effects to treat HIV (page 14, penultimate paragraph of the contested decision), the technical solution lacks an inventive step.

In particular, the OD has failed to provide any reasoning, why the skilled person, for any unknown reason and starting from the amount of dolutegravir of 50 mg, i.e. the very same amount as claimed in claim 1 of the Auxiliary Request 1, should have deviated from this amount.

Instead, considering the structural similarities between dolutegravir and bictegavir, both sharing the core chemical structure comprising three fused rings, the skilled person could and would have started from the amount of 50 mg dolutegravir disclosed in D5 as a promising starting point. Hence, the skilled person would have used the very same amount of 50 mg of bictegavir for combination with the tenofovir/emtricitabine backbone.

In that respect, the OD has argued that D5 indicates that *"the daily dose of dolutegravir can vary from 20 to 75 mg per day, i.e. leading to tablets possibly comprising amounts of dolutegravir different from 50 mg"*. This reasoning is, however, not justified, since the most promising starting point within D5 is the embodiment disclosing a composition comprising 50 mg dolutegravir. Hence, there was no reason for the skilled person to change this amount, which thus lies in the middle of the range of 20 to 75 mg disclosed in D5. Hence, this range instead confirms that an amount of 50 mg is a good starting point.

2.2.4.3 In addition, the effect of food on the bioavailability of the 50 mg dose of dolutegravir was assessed in the art and the results published in D50. Therein, it was concluded that *"dolutegravir can be taken with or without food and without regard to fat content"* (last sentence of the abstract of D50). As is evident from Table 1, page 1628 of D50, this effect was observed for the 50 mg dose of dolutegravir.

In consequence, the skilled person starting from a dose of 50 mg dolutegravir as disclosed in D5 and knowing that this dose can be taken without regard to food had no reason whatsoever to deviate from this 50 mg dose, but instead would have replaced this 50 mg dose of dolutegravir by the same dose of bictegavir. Finding that this 50 mg dose of bictegavir can be administered without regard to food is not surprising in view of the same finding in

D50 with respect to the same amount of dolutegravir. The finding reported in the opposed patent and D36 that a higher dose of bictegravir has different bioavailability dependent on whether this amount is taken with or without food is thus without relevance, since this higher dose of 75 mg is based on a further technical difference compared to the CPA.

In other words, since the distinguishing feature is the replacement of the INSTI dolutegravir of D5 with bictegravir in the opposed patent, an inventive step may not be based on the specific amount of 50 mg bictegravir as providing for any alleged unexpected technical effect compared to a higher dose of 75 mg bictegravir, since the dose of bictegravir is not the distinguishing feature.

2.2.4.4 In addition, the OD's conclusions on inventive step clearly result from an inconsistent, and thus incorrect, problem-and-solution approach.

The OD, in the first paragraph on page 15 of the decision, argues that the patent in Examples 3 and 9 would show "good food effects". However, as discussed above, this alleged effect is based on a comparison of a tablet containing 75 mg bictegravir with a tablet containing 50 mg bictegravir.

Since, however, the OD has also acknowledged that D5 is the closest prior art and the distinguishing feature is the small structural difference between the INSTIs dolutegravir and bictegravir, i.e., the replacement of 50 mg DTG with 50 mg bictegravir, the OD should also have acknowledged that the alleged "food effect" shown in Examples 3 and 9 of the opposed patent does not result from the distinguishing feature.

Consistently following the correct problem-and-solution approach, the OD should have acknowledged that no technical effect is demonstrated in the opposed patent, which results from the distinguishing feature, i.e., the replacement of 50 mg DTG with 50 mg bictegravir.

Instead, the OD seems to have followed the proprietor's argumentation presented during the first instance proceedings (see item 5.5 of the proprietor's response dated November 01, 2021). Therein, the proprietor stated that the skilled person would allegedly not have considered the 50 mg bictegravir dose, since it was found during Phase I clinical studies that 75 mg BIC is the optimum dose. The proprietor further argued that, allegedly, 50 mg bictegravir resulted in an unexpected "food effect" in comparison with the 75 bictegravir dose.

However, this argumentation is, on the one hand side, not reasonable and, on the other side, would not change the conclusions reached above that the claimed subject-matter is rendered

obvious in view of D5. The approach applied by the proprietor only shows that, starting from the 50 mg dolutegravir dose of D5, the skilled person, in a first step and based on routine Phase I clinical studies, would have replaced the 50 mg dose by the 75 mg dose as being the optimum bictegravir dose, and then, in a second step based on routine experimentation for evaluating the impact of food on the bioavailability, would have gone back to the 50 mg dose due to the alleged "food effect", leading the skilled person again to the starting dose of 50 mg. In other words, routine experimentation would have led the skilled person to the selection of 75 mg bictegravir as the dose having maximum anti-HIV activity, thereby allegedly creating a teaching away from the 50 mg dose. Further routine experimentation would have then again led the skilled person to the starting amount of 50 mg of bictegravir.

Hence, even in case the skilled person would indeed have followed the line of arguments presented by the proprietor, this would not have changed the overall conclusions that the opposed patent lacks an inventive step.

The OD has initially correctly formulated the technical problem as the provision of an alternative formulation (to the DTG-FTC-TAF combination disclosed in D5) with good food effect. However, in this case, the technical effect would need to be demonstrated by the proprietor in comparison with the formulation disclosed in D5, i.e. the triple combination combining 50 mg dolutegravir with the FTC/TAF backbone formulation. The OD, however, has failed to recognize that no such technical effects have been demonstrated by the proprietor.

The approach applied by the OD in the next-step of the problem-and-solution approach seems instead to follow the proprietor's incorrect line of arguments of a BIC containing FTC-TAF formulation having a good food effect. However, such an approach is not based on a comparison with the closest prior art. Concluding, the approach applied by the OD in the contested decision is clearly inconsistent and thus reaches the incorrect conclusions.

2.2.4.5 In addition, the proprietor has confirmed during the proceedings of the US counterpart of the opposed patent that "*the unexpected results obtained using the instantly claimed formulation of Formula I, tenofovir alafenamide, and emtricitabine*" are not based on a specific amount of the active agents. Reference is made in that respect to a statement dated March 20, 2019 by the patent proprietor during prosecution of the corresponding US counterpart US 15/346,335 of the opposed patent, which is submitted herewith as D51. Corresponding to the presently claimed subject-matter, also the subject-matter claimed in the application US 15/346,335 was a fixed dose combination of three active agents, the combination comprising 50 mg bictegravir. In the submission dated March 20, 2019, the proprietor stated:

“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.” (page 7, penultimate par. of D51, underlining added)

“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.” (page 7, final par. of D51)

Hence, the proprietor confirmed that the alleged unexpected technical effects, including the alleged “food effect” result from the specific combination of active agents but do not result from their specific amounts as claimed, i.e., do not result from the specific amount of 50 mg bictegravir. The proprietor’s statement is thus in full consistency with the above-provided observations according to which the “food effect” alleged by the proprietor is not reasonably shown to result from the distinguishing feature of the specific amount of 50 mg bictegravir.

Concluding, the OD’s reasoning provided on page 15 of the appealed decision is erroneous, since the skilled person would not have deviated from the amount of the INSTI of 50 mg disclosed in the CPA D5. The mere replacement of dolutegravir of D5 by bictegravir of D3 is, however, clearly rendered obvious in view of the combination of D5 and D3 and thus does not involve an inventive step.

3. Lack of patentability of Auxiliary Requests 2-10 (AR 2-10) filed by the proprietor on August 26, 2022

3.1 Lack of patentability of Auxiliary Request 2

The objections as raised for the AR 1 apply in the same way to the claims of AR 2.

3.1.1 In particular, claim 1 of AR 2 extends beyond the content of the application as filed for the same reason as the Main Request, i.e. due to the presence of the feature of a salt of emtricitabine, which was cancelled from the claims of AR 1 in order to resolve the added-matter objections, but which is reintroduced into the claims of AR 2.

3.1.2 In addition, the claims lack an inventive step for the same reasons as the claims of AR 1. Claim 1 is amended in the AR 2 by specifying the drug amount based on the respective salts of the active agents. No surprising or unexpected technical effect is demonstrated for

these additional distinguishing features. In the absence of any unexpected technical effect, the mere provision of a specific salt of bictegravir and tenofovir does not involve any inventive activity. Thus, the above-provided argumentation of lack of an inventive step of the claims of AR 1 still applies.

3.2 Lack of patentability of Auxiliary Request 3

Claim 1 of AR 3 requires that the tablet is a coated tablet. No surprising beneficial technical effect is demonstrated for this additional feature. Instead, coating of tablets is a routine option for the skilled person, which may be applied for various different purposes. Hence, providing a coated tablet clearly belongs to the skilled person's common general knowledge and thus does not involve any inventive activity.

3.3 Lack of patentability of Auxiliary Requests 4-6

Claim 1 of AR 4-6 is limited to a multilayer tablet, in which bictegravir is present in one layer and emtricitabine and tenofovir are present in a second, separate layer. Claim 1 of AR 4 further requires that the tablet has a total weight of less than 1 g. Claims 5 and 6 instead require that the amount of active agents bictegravir and tenofovir is that of the specific salts as claimed.

However, no surprising or unexpected technical effect is demonstrated in the opposed patent resulting from any of these additional distinguishing features compared to any other tablet formulation. Instead, the alleged "*food effect*" is anyway only disclosed for a specific bilayer tablet, as already discussed above with respect to the Auxiliary Request 1. Therefore, the technical problem for this partial problem would be the provision of an alternative tablet formulation. However, multilayer tablet formulations are well-known to the skilled person (D15, page 412, left-hand column, 4th para.). Thus, the skilled person would have considered such a two-layer tablet in an obvious manner when formulating the claimed tablet without involving any inventive step.

3.4 Lack of patentability of Auxiliary Requests 7-10

Claim 1 of each of AR 7-10 further defines the multilayer tablet by incorporating further features specifying the tablet F7 of Example 9, such as the specific quantitative and qualitative excipient formulation of the respective layers.

No surprising or unexpected technical effect is demonstrated for any of the additional distinguishing features specifying the excipient composition. Instead, in the absence of any

surprising technical effect, finding a suitable excipient formulation belongs to the skilled person's daily practice and thus would be achieved based on routine experimentation. Thus, claim 1 of each of AR 7-10 lacks an inventive step.

4. Conclusions

In view of the above-presented arguments, it becomes evident that the request of the Notice of Appeal to set the OD's decision aside and to revoke the opposed patent in its entirety is reasonable and justified.

Respectfully submitted for the appellant/opponent (O3)



Dr. Bernd Aechter
European Patent Attorney
Association No. 6



Dr. Ingo Ortel
European Patent Attorney
Association No. 6

Enclosures:
D47 to D51

Experimental Report

Purpose of the experiments was to demonstrate a possible incompatibility between the active agents bictegravir sodium (BIC), tenofovir alafenamide hemifumarate (TAF) and emtricitabine (EMT). Formulations were prepared using the amounts of active agents as used in the tablet F7 of EP 3 346 995 (EP995), i.e. 50 mg BIC, 200 mg EMT, 25 mg TAF. In addition, the excipients and their amounts correspond to those of the tablet formulation F7 of EP995 (see paragraph [0335] of EP995). Degradation of active agents was analysed after storage at stress conditions.

The following formulations were prepared:

001KZ

Ingredient	Amount [mg]
Bictegravir sodium	52.500
Emtricitabine	200.000
SUM	252.50

002KZ

Ingredient	Amount [mg]
Tenofovir alafenamide hemifumarate	28.000
Emtricitabine	200.000
SUM	228.00

003KZ

Ingredient	Amount [mg]
Bictegravir sodium	52.500
Tenofovir alafenamide hemifumarate	28.000
SUM	80.50

004KZ

Ingredient	Amount [mg]
Bictegravir sodium	52.500
Tenofovir alafenamide hemifumarate	28.000
Emtricitabine	200.000
SUM	280.50

001EXC – excipient mixture

Ingredient	Amount [mg]
Microcrystalline cellulose	359.500
Croscarmellose sodium	49.600
Magnesium stearate	10.600
SUM	419.70

005KZ

Ingredient	Blend label	Amount [mg]
Bictegravir sodium + emtricitabine	001KZ	252.500
Excipient mixture	001EXC	419.700
SUM		672.20

006KZ

Ingredient	Blend label	Amount [mg]
Tenofovir alafenamide hemifumarate + emtricitabine	002KZ	228.000
Excipient mixture	001EXC	419.700
SUM		647.70

007KZ

Ingredient	Blend label	Amount [mg]
Bictegravir sodium + tenofovir alafenamide hemifumarate	003KZ	80.500
Excipient mixture	001EXC	419.700
SUM		500.20

008KZ

Ingredient	Blend label	Amount [mg]
Bictegravir sodium + tenofovir alafenamide hemifumarate + emtricitabine	004KZ	280.500
Excipient mixture	001EXC	419.700
SUM		700.20

Biktarvy (EP 3 346 995)

009KZ

Ingredient	Amount [mg]	
Bictegravir sodium	52.500	
Microcrystalline cellulose	52.500	
SUM	105.00	

010KZ

Ingredient	Amount [mg]	
Bictegravir sodium	52.500	
Croscarmellose sodium	52.500	
SUM	105.00	

011KZ

Ingredient	Amount [mg]	
Bictegravir sodium	52.500	
Magnesium stearate	5.250	
SUM	57.75	

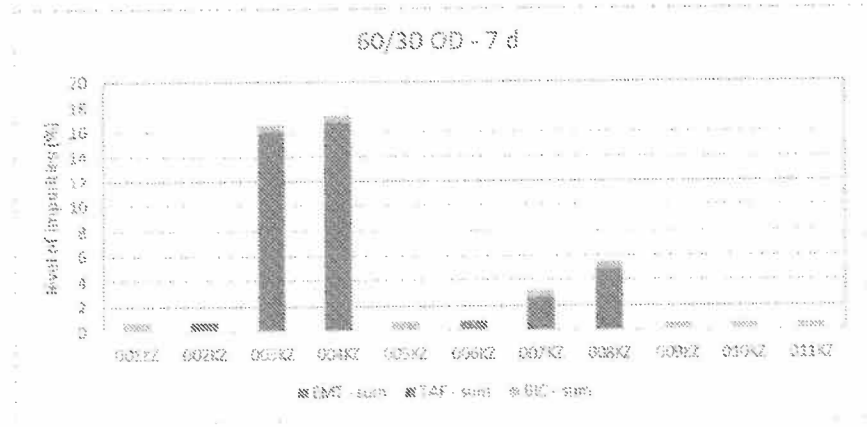
Mixture 001KZ-011KZ were prepared by following procedures: Ingredients were weighed and blended. The mixture from previous step was sieved and blended again to obtain final mixture.

The formulations were stored in a glass container at room temperature before testing. For stress tests, the formulations were exposed to 60°C / 30% relative humidity in open dish for 7 days.

Impurities of all three drug substances were analysed using a gradient UPLC method with UV detection.

Biktarvy (EP 3 346 995)

Results:



Conclusions:

It could be shown that tenofovir alafenamide is incompatible in the presence of bictegravir sodium in formulations after storage for 7 days at 60°C/30%rH, since the combination of both active agents leads to a high amount of degradation products.

Kac Javor

Digitally signed by Kac Javor
DN: c=slovakia, o=Kac Javor
Date: 2025.04.21 12:22:14.00



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Page 1 of 2

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/738,803

RECEIPT DATE / TIME
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ATTORNEY DOCKET #
1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 2232

FILED BY Frances Tsai

PATENT CENTER # 62235548

FILING DATE 05/06/2022

CUSTOMER # 25000

FIRST NAMED INVENTOR Benjamin Micah Collman

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Donna Gressler

Documents

TOTAL DOCUMENTS: 0

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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DOCUMENT	MESSAGE DIGEST(SHA-512)
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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.

Cipla v. Gilead

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Petitioner Exhibit 1002
1042 of 1074

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

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APPLICATION #
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1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 2232

FILED BY Frances Tsai

PATENT CENTER # 62235548

AUTHORIZED BY Donna Gressler

CUSTOMER # 25000

FILING DATE 05/06/2022

CORRESPONDENCE
ADDRESS -

FIRST NAMED
INVENTOR Benjamin Micah Collman

Payment Information

PAYMENT METHOD
DA / 071250

PAYMENT TRANSACTION ID
E202368136119681

PAYMENT AUTHORIZED BY
Frances Tsai

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	2000.00	1	2000.00
TOTAL AMOUNT:				\$2,000.00

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Cipla v. Gilead

IPR2025-00033

Petitioner Exhibit 1002
1044 of 1074

National Stage of an International Application under 35 U.S.C. 371

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

EXAMINER	
WORSHAM, JESSICA N	
ART UNIT	PAPER NUMBER
1615	

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

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	\$1200	\$0.00	\$0.00	\$1200	10/02/2023

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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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

25000 7590 06/30/2023
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.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232

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	\$1200	\$0.00	\$0.00	\$1200	10/02/2023

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/AIA/122 or PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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, 1 _____
- (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. 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)

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

- ☐ Electronic Payment via Patent Center or 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. _____



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 22312-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232
25000 7590 06/30/2023				
GILEAD SCIENCES, INC				
333 LAKESIDE DR				
FOSTER CITY, CA 94404				
EXAMINER				
WORSHAM, JESSICA N				
ART UNIT		PAPER NUMBER		
1615				

DATE MAILED: 06/30/2023

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.

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. 17/738,803	Applicant(s) Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 1615	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

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 8 June 2023.
☐ 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 52-64. 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)	5. ☒ Examiner's Amendment/Comment
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 6/8/2023.	6. ☒ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.	7. ☐ Other _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	
--	--

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 8 June 2023 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.

Terminal Disclaimer

2. The terminal disclaimer filed on 5 April 2023 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **U.S. Patent No. 10,548,846** has been reviewed and is accepted. The terminal disclaimer has been recorded.

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 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 Monday-Friday (8-5).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center

Application/Control Number: 17/738,803
Art Unit: 1615

Page 4

and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JESSICA WORSHAM/
Primary Examiner, Art Unit 1615

Search Notes 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 1615

CPC - Searched*		
Symbol	Date	Examiner
(A61K9/209 or A61K9/0053 or A61K9/2013 or A61K9/2027 or A61K9/2054 or A61K9/2086 or A61K9/2095 or A61K9/28 or A61K9/2833 or A61K31/513 or A61K31/5365 or A61K31/537 or A61K31/553 or A61K31/675 or A61P31/18 or A61K9/282 or A61K9/20 or A61K2300/00).cpc.	04/12/2023	JW

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: PE2E, PALM	12/01/2022	JW
PE2E: See attached	12/01/2022	JW
SciFinder: See attached	12/01/2022	JW
PE2E: See attached	04/12/2023	JW

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	
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Search Notes 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 1615

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	(emtricitabine and tenofovir and tablet and bictegravir).clm.	04/12/2023	JW

/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	
--	--

Issue Classification 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.	
	Examiner JESSICA WORSHAM	Art Unit 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	/	2027	I	2013-01-01
A61K	/	9	/	2833	I	2013-01-01
A61K	/	31	/	537	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

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)	13	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	22 June 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20230622

Issue Classification 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 1615

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	7	31	5365

NON-CLAIMED			
	7		

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

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

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	13	
JESSICA WORSHAM/ Primary Examiner, Art Unit 1615	22 June 2023	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office

Part of Paper No.: 20230622

Issue Classification 	Application/Control No. 17/738,803	Applicant(s)/Patent Under Reexamination Collman et al.
	Examiner JESSICA WORSHAM	Art Unit 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		10		19		28		37		46	4	55	13	64
	2		11		20		29		38		47	5	56		
	3		12		21		30		39		48	6	57		
	4		13		22		31		40		49	7	58		
	5		14		23		32		41		50	8	59		
	6		15		24		33		42		51	9	60		
	7		16		25		34		43	1	52	10	61		
	8		17		26		35		44	2	53	11	62		
	9		18		27		36		45	3	54	12	63		

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 13	
/JESSICA WORSHAM/ Primary Examiner, Art Unit 1615 (Primary Examiner) _____ (Date) 22 June 2023		O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office

Part of Paper No.: 20230622

Approved for use through 05/31/2024. 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				Complete if Known Application Number17738,803 Filing DateMay 6, 2022 First Named InventorBenjamin Micah Collman Art Unit1615 Examiner NameJ. N. Worsham Attorney Docket Number1147-US-P2C2DC	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)					
Sheet	1	of	2		

[illegible][illegible]

Examiner Signature	/JESSICA WORSHAM/	Date Considered	06/22/2023
-----------------------	-------------------	--------------------	------------

*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: June 8, 2023

Electronic Signature for Donna Johnson Gressler: /Donna Johnson Gressler/

#5073295v1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

PTO/SB/08b (07-09)
 Approved for use through 05/31/2024. 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		Complete if Known			
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)		Application Number	17/738,803		
		Filing Date	May 6, 2022		
		First Named Inventor	Benjamin Micah Collman		
		Art Unit	1615		
		Examiner Name	J. N. Worsham		
Sheet	2	of	2	Attorney Docket Number	1147-US-P2C2DC

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.†	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.	T²
	CA	JAVOR. (2023) Experimental Report, Novartis, 4 pages.	
	CB	Therapeutic Goods Administration. (2017) Australian Public Assessment Report for emtricitabine / rilpivirine / tenofovir / alafenamide fumarate - Proprietary Product Name: Odefsey, 44 pages.	
	CC	SONG, I. et al. (2012) "Effect of Food on the Pharmacokinetics of the Integrase Inhibitor Dolutegravir" Antimicrobial Agents and Chemotherapy 56(3):1627-1629.	
	CD	Grounds of Appeal from Opponent Teva Pharmaceutical Industries Ltd. dated 2023-04-25 for European Patent No. EP3346995, 28 pages.	
	CE	Grounds of Appeal from Opponent Dr. Richard Cooke dated 2023-05-02 for European Patent No. EP3346995, 11 pages.	
	CF	Grounds of Appeal from Opponent Sandoz GmbH dated 2023-04-28 for European Patent No. EP3346995, 15 pages.	
	CG	Reply to Patentee's Appeal from Opponent Dr. Richard Cooke dated 2023-05-22 for European Patent No. EP3346995, 6 pages.	

Examiner Signature	/JESSICA WORSHAM/	Date Considered	06/22/2023
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*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.

† Applicant's unique citation designation number (optional). ‡ Applicant is to place a check mark here if English language Translation is attached.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.W/

TO: IPDocketing@gilead.com,IPUS2@gilead.com
FROM: noreply@uspto.gov
CC: patentcenter_eofficeaction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - Correspondence Notification for Customer Number 25000

Fri Jun 30 05:19:42 EDT 2023

Dear Patent Center Customer:

Correspondence Address:

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FOSTER CITY,CALIFORNIA,94404
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Application	Document	Mailroom Date	Attorney Docket No.
17738803	NOA	06/30/2023	1147-US-P2C2DC
17738803	1449	06/30/2023	1147-US-P2C2DC

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PART B - FEE(S) TRANSMITTAL

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

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Alexandria, Virginia 22313-1450

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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 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. Because electronic patent issuance may occur shortly after issue for payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize expediency.

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

05000 7500 06/10/2023
GILEAD SCIENCES, INC
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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.

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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.

Frances Tsai	(Typed or printed name)
/Frances Tsai/	(Signature)
7/10/2023	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17735,803	05/06/2022	Benjamin Michael Coleman	1147-US-E2C2DC	2272

TITLE OF INVENTION: THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

APPL. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	FEE PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	10/02/2023

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

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

- ☐ Change of correspondence address for Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122 attached.
- ☐ "Free Address" indication (or "Free Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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. _____
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 3.51(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, CA

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)

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

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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 1.51 and 1.55. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Donna Johnson Gressler/

Date 7/10/2023

Typed or printed name Donna Johnson Gressler

Registration No. 45,544



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Page 1 of 2
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www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/738,803

RECEIPT DATE / TIME
07/10/2023 08:35:00 PM ET

ATTORNEY DOCKET #
1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	2232	FILED BY	Frances Tsai
PATENT CENTER #	62415191	AUTHORIZED BY	Donna Gressler
CUSTOMER #	25000	FILING DATE	05/06/2022
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Benjamin Micah Collman

Payment Information

PAYMENT METHOD
DA / 071250

PAYMENT TRANSACTION ID
E202370K36046504

PAYMENT AUTHORIZED BY
Frances Tsai

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1501	UTILITY ISSUE FEE	1200.00	1	1200.00
TOTAL AMOUNT:				\$1,200.00

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Cipla v. Gilead

IPR2025-00033

**Petitioner Exhibit 1002
1063 of 1074**

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APPLICATION #
17/738,803

RECEIPT DATE / TIME
07/10/2023 08:35:00 PM ET

ATTORNEY DOCKET #
1147-US-P2C2DC

Title of Invention

THERAPEUTIC COMPOSITIONS FOR TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 2232

FILED BY Frances Tsai

PATENT CENTER # 62415191

FILING DATE 05/06/2022

CUSTOMER # 25000

FIRST NAMED INVENTOR Benjamin Micah Collman

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Donna Gressler

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
1147-US-P2C2DC_IssueFeeTransmittal.pdf	1	Issue Fee Payment (PTO-85B)	1002 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
1147-US-P2C2DC_IssueFeeTransmittal.pdf	26E6E813F907B1251A69F53348F480244409A28D4D606870F90 AAD0566C8ADED992CF1D75D677D2770DDD31DBB68B9B336 C2BE5C9398E520890ACDEE9190702C

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National Stage of an International Application under 35 U.S.C. 371

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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)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/738,803
				Filing Date	May 6, 2022
				First Named Inventor	Benjamin Micah Collman
				Art Unit	1615
				Examiner Name	J. N. Worsham
Sheet	2	of	13	Attorney Docket Number	1147-US-P2C2DC

U. S. PATENT DOCUMENTS					
Examiner Initials ¹	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			
	AT	US-2016/0194335-A1	07-07-2016	Jin et al.	
	AU	US-2017/0000807-A1	01-05-2017	Koziara et al.	
	AV	US-2017/0027967-A1	02-02-2017	Koziara et al.	
	AW	US-2017/0079999-A1	03-23-2017	DAHL et al.	
	AX	US-2017/0114074-A1	04-27-2017	Jin et al.	
	AY	US-2017/0197985-A1	07-13-2017	Carra et al.	
	AZ	US-2018/0022757-A1	01-25-2018	Chiu et al.	
	AA1	US-2018-0065986-A1	03-08-2018	Carra et al.	
	AB1	US-2018-0215769-A1	08-02-2018	Jin et al.	
	AC1	US-2019-0015420-A1	01-17-2019	Carra et al.	
	AD1	US-7,390,791	06-24-2008	Becker et al.	
	AE1	US-7,803,788	09-28-2010	Becker et al.	
	AF1	US-8,592,397	11-26-2013	Dahl et al.	
	AG1	US-8,598,185	12-03-2013	Dahl et al.	
	AH1	US-8,716,264	05-06-2014	Dahl et al.	
	AI1	US-8,754,065	06-17-2014	Liu et al.	
	AJ1	US-8,841,310	09-23-2014	Jensen R & D Ireland	Stoffels
	AK1	US-9,018,192	04-28-2015	Dahl et al.	
	AL1	US-9,216,996	12-22-2015	Jin et al.	

Change(s) applied
to document,

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4/28/2023

FOREIGN PATENT DOCUMENTS						
Examiner Initials ¹	Cite No. ¹	Foreign Patent Document	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
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
	BG**	WO-2014100323-A1	06-26-2014	Gilead Sciences, Inc		
	BH**	WO-2015/022351-A1	02-19-2015	Ratiopharm GmbH		
	BI**	WO-2015039348-A1	03-26-2015	Merck Sharp & Dohme		
	BJ**	WO-2015/196116-A1	12-23-2015	Gilead Sciences, Inc		
	BK**	WO-2015/196137-A1	12-23-2015	Gilead Sciences, Inc		
	BL**	WO-2017/083304-A1	05-18-2017	Gilead Sciences, Inc		

Examiner Signature		Date Considered	
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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	17/738,803
				Filing Date	May 6, 2022
				First Named Inventor	Benjamin Micah Collman
				Art Unit	1615
				Examiner Name	J. N. Worsham
Sheet	1	of	13	Attorney Docket Number:	1147-US-P2C2DC

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-2002-0119443-A1	08-29-2002	Becker et al.	
	AB	US-2003-0219727-A1	11-27-2003	Becker et al.	
	AC	US-2005-0124583-A1	06-09-2005	Becker et al.	
	AD	US-2005-0124584-A1	06-09-2005	Becker et al.	
	AE	US-2005-0124585-A1	06-09-2005	Becker et al.	
	AF	US-2006-0024659-A1	02-02-2006	Becker et al.	
	AG	US-20070099902-A1	05-03-2007	Dahl et al.	
	AH	US-2007/0219243-A1	09-20-2007	Kearney et al.	
	AI	US-2008/0200435-A1	08-21-2008	Stoffels	
	AJ	US-20100285122-A1	11-11-2010	Oliyai et al.	
	AK	US-2013/0243857-A1	09-19-2013	Oliyai et al.	
	AL	US-2014/0142070-A1	05-22-2014	Delaet et al.	
	AM	US-2014/0213556-A1	07-31-2014	DAHL et al.	
	AN	US-2014/0221355-A1	08-07-2014	Lazerwith et al.	
	AO	US-2014/0349971-A1	11-27-2014	Janssen R & D Ireland	Stoffels
	AP	US-2015/0111856-A1	04-23-2015	Dahl et al.	
	AQ	US-2015/0150810-A1	06-04-2015	OLIYAI et al.	
	AR	US-2015/0283135-A1	10-08-2015	Janssen R & D Ireland	Stoffels
	AS	US-2016/0016973-A1	01-21-2016	Carra et al.	

Change(s) applied
to document,
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4/26/2023

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-2004024078-A2	03-25-2004	Merck & Co., Inc		
	BB**	WO-2006030807-A1	03-23-2006	Shionogi & Co., Ltd		
	BC**	WO-2006116764-A1	11-02-2006	Shionogi & Co., Ltd		
	BD**	WO-2008/043829-A2	04-17-2008	Boehringer Ingelheim Int		
	BE**	WO-2013/116720-A1	08-08-2013	Gilead Sciences, Inc		
	BF**	WO-2013/115916-A1	08-08-2013	Gilead Sciences, Inc		

Examiner Signature	Date Considered
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Dated: April 5, 2023

Electronic Signature for Donna Johnson Gressler: /Donna Johnson Gressler/

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	09/05/2023	11744802	1147-US-P2C2DC	2232

25000 7590 08/16/2023
GILEAD SCIENCES, INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

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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 Center (<https://patentcenter.uspto.gov>).

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IR103 (Rev. 10/09)

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Benjamin Micah Collman, San Mateo, CA;

Lei Hong, Cupertino, CA;

Joanna M. Koziara, Foster City, CA;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

Gilead Sciences, Inc., Foster City, CA;

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TO: IPDocketing@gilead.com,IPUS2@gilead.com
FROM: noreply@uspto.gov
CC: patentcenter_eofficeaction@uspto.gov
SUBJECT: USPTO: Patent Electronic System - Correspondence Notification for Customer Number 25000

Thu Aug 17 05:59:55 EDT 2023

Dear Patent Center Customer:

Correspondence Address:

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FOSTER CITY,CALIFORNIA,94404
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Application	Document	Mailroom Date	Attorney Docket No.
17738803	ISSUE.NTF	08/16/2023	1147-US-P2C2DC

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/738,803	05/06/2022	Benjamin Micah Collman	1147-US-P2C2DC	2232
25000 7590 GILEAD SCIENCES, INC 333 LAKESIDE DR FOSTER CITY, CA 94404			EXAMINER WORSHAM, JESSICA N	
			ART UNIT 1615	PAPER NUMBER
			NOTIFICATION DATE 09/05/2023	DELIVERY MODE ELECTRONIC

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PTOL-90A (Rev. 04/07)



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APPLICATION NO.	ISSUE DATE	PATENT NO.
17/738,803	05-Sep-2023	11744802

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17738803	11744802	EGRANT.NTF	09/05/2023	1147-US-P2C2DC

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