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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review

Date	December 7, 2015
From	William Tauber, M.D. Medical Officer
Subject	Clinical Review
NDA/Supplement	NDA 208215
Applicant	Gilead Sciences
Date of Submission	April 4, 2015
PDUFA Goal Date	April 4, 2016
Proprietary Name	Descovy (Emtricitabine/ Tenofovir alafenamide) FDC (FTC/TAF)
Dosage Form/Strengths	2 Dosage forms: Single tablet containing (b) (4) Single tablet containing 200mg/20mg of FTC/TAF
Proposed Indication(s)	Fixed dose combination indicated in combination with other antiretroviral agents for treatment of HIV infection in treatment naïve or virologically suppressed HIV infected treatment naïve or virologically suppressed adults and adolescents
Recommendation	Approval with comments in PI regarding darunavir

1. Background

The Applicant is proposing approval of a fixed-dose combination (FDC) tablet containing emtricitabine and tenofovir alafenamide. Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI) is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Tenofovir alafenamide, a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir (TFV), is a component of the FDC Genvoya (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (10mg). The development program for the emtricitabine/tenofovir alafenamide FDC (F/TAF) (Descovy) is based upon the fact that identical dosages of these antivirals are combined in Genvoya. Genvoya was approved on November 5, 2015.

Demonstration of bioequivalence and bioavailability and the pharmacokinetic (PK) bridging of the corresponding components of the FDC to the respective components of Genvoya form the basis for approval of the Descovy NDA. The following Phase 1 studies of healthy adults were intended to answer the pivotal questions of bioequivalence/bioavailability. Trials GS-US-311-1088, (b) (4) and GS-US-311-1473 are intended as PK bridging between F/TAF and E/C/F/TAF (Genvoya). Study GS-US-311-1386 provides data regarding the impact of food on the PK data of F/TAF.

Additional DDI data was provided in Study GS-US-311-0101 a phase 1 drug interaction study which examined the PK consequences of administration of varying dosages of tenofovir alafenamide/200mg FTC FDC together with efavirenz alone, darunavir/cobicistat FDC or when only cobicistat and tenofovir alafenamide are combined.

The Applicant also submitted Study GS-US-299-0102, a phase 2 study which compared the safety and efficacy of a FDC of darunavir 800mg/cobicistat 150mg/emtricitabine 200mg/tenofovir alafenamide10mg to darunavir 800mg /cobicistat 150mg FDC co-administered with Truvada (FTC 200mg/Tenofovir disoproxil fumarate 300mg). The objective of this study was to demonstrate non-inferiority of the tenofovir alafenamide (b) (4) component as determined by the proportional achievement of HIV-1 RNA < 50 copies/mL at 24 weeks.

Descovy (F/TAF) is not a complete regimen for treatment of HIV-1. It must be combined with a third "anchor" drug to form a compete regimen for HIV-1 infection. The selection of the type of anchor drug has an impact on the dosage of tenofovir alafenamide administered. Protease inhibitors and some integrase inhibitors are generally administered with a pharmacologic boosting agent such as ritonavir or cobicistat. These pharmacoenhancers increase serum exposures of the anchor drug by blocking CYP4A metabolism. These pharmaco-enhancers also increase TAF exposure presumably by blocking the intestinal Pgp efflux pump.

The optimal dosage for TAF was determined in study GS-US-120-0104 to be 25mg per day. (b) (4)

(b) (4)

Boosted darunavir may represent an exception to this rule. Although Study GS-US-299-0102 demonstrated that the D/C/F/TAF was non-inferior to the combination of DRV+COBI + Truvada® (FTC/TDF) the observed TAF exposures resembled those seen when a pharmacoenhancer is not used. TAF exposures measured in Study GS-US-120-0104 with 25 mg of tenofovir alafenamide administered in the fasting state were mean AUC_{last} 115ng▪h/mL. TAF 10mg exposures in 299-0102 in the presence of a pharmacoenhancer and in the fed state were AUC_{last} 131ng▪h/mL. In contrast, TAF

10mg exposures in the Genvoya pivotal studies in the presence of a elvitegravir with cobicistat pharmacoenhancer and in the fed state were AUC_{last} 227ng▪h/mL. It has been previously demonstrated that TAF administration in the fed state results in a 40% increase in TAF levels. The clinical consequences of this lowered TAF exposure are uncertain. In Study 299-0102, the virologic success rates for both arms are assessed as demonstrating non-inferiority at 24 weeks. When assessed at 48 weeks, however, it appears that non-inferiority is lost with the TAF arm at 77% compared to 84% for the comparator arm, with a calculated lower confidence level -19.9%.

***Reviewer comments**: Technically, boosted darunavir does not cause TAF exposure enhancement. It is hypothesized that darunavir does this by increasing the Pgp efflux pump in the gastrointestinal tract. The use of boosted darunavir with the* (b) (4) *dosage results in exposures below those demonstrated to be effective in the Genvoya (E/C/F/TAF) pivotal trials. The efficacy results of 299-0102 at 48 weeks appear to indicate a potential inferior outcome compared to the Truvada containing arm. The use of the 25mg TAF dosage of F/TAF may be appropriate for boosted darunavir use but this was not tested in these studies. On the other hand, the PBMC data appears to indicate 6 times higher levels of TFV-DP (tenofovir diphosphate the active moiety) when TAF is administered with darunavir compared to Truvada with darunavir. Clinical Pharmacology has also pointed out that the TAF exposures with boosted darunavir are on the flat part of the viral activity curve with no significant additional virologic benefit with the higher exposure.* (b) (4)

2. CMC

The selected dosage form of emtricitabine/tenofovir alafenamide (F/TAF) fixed dose combination (FDC) tablets was a 200mg/TAF 25mg FDC (b) (4) (b) (4) (b) (4) (b) (4) /TAF 200/25mg tablets are blue, rectangular-shaped, film coated with GSI debossed on one side and 225 on the other. (b) (4) Please refer to the CMC review of Dr. Haripada Sarker for complete details.

3. Nonclinical Pharmacology/Toxicology

Extensive programs of nonclinical studies with emtricitabine and tenofovir alafenamide have been previously conducted. In view of the of the nonclinical safety profiles for these compounds, additional nonclinical combination safety studies with emtricitabine, and tenofovir alafenamide are not considered necessary to support this application. Therefore, no new nonclinical pharmacology/toxicology data were submitted.

4. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Mario Sampson's Clinical Pharmacology Review for details.

Absorption, Food Effects and Bioavailability

BA/BE Studies Using the FDC (FTC /TAF):

The Applicant conducted BA/BE studies to support the FDC drug product.

Comparative BA and Bioequivalence Studies, Fed Conditions: Studies 311-1088, (b) (4) 311-1473 and 311-1386

The primary objective of Phase 1 **Study 311-1088** was to evaluate the bioequivalence of the fixed drug combination tablet FTC/TAF at dosages of 200mg/25mg to emtricitabine 200mg plus TAF 25 mg coadministered as individual agents. This study utilized a randomized, open-label, single dose, 2-way crossover design in 56 healthy volunteers. Each subject received 2 single doses separated by 15 days; one with the FDC and the other the component agents in identical dosage. A total of 56 subjects were randomized and 54 completed the study. One subject was discontinued due to a protocol violation (illegal drug screen positive) and a second withdrew consent prior to completion.

The results of this study were interpreted to demonstrate F/TAF FDC is bioequivalent to FTC 200mg plus TAF 25mg administered simultaneously as single agents. All parameters were within the prespecified bioequivalence boundary of 80% to 125%. AUC_{last} for tenofovir alafenamide exposure with the F/TAF FDC tablet was 254 ng▪h/mL. AUC_{last} for tenofovir alafenamide exposure with the 25mg tablet was 240 ng▪h/mL.

Table 1 Pharmacokinetic Results Study 311-1088

	GLSMs by Treatment		GLSM Ratio (%)	90% CI (%)
	Test Treatment (F/TAF) (N = 55)	Reference Treatment (FTC+TAF) (N = 55)		
TAF PK Parameter				
AUC_{last} (ng•h/mL)	245.91	239.48	102.68	(95.78, 110.09)
AUC_{inf} (ng•h/mL)	254.18[a]	240.33[b]	105.77	(97.26, 115.01)
C_{max} (ng/mL)	209.36	226.11	92.59	(82.31, 104.16)
FTC PK Parameter				
AUC_{last} (ng•h/mL)	9049.70	9410.78	96.16	(94.29, 98.08)
AUC_{inf} (ng•h/mL)	9259.49	9636.68	96.09	(94.24, 97.96)
C_{max} (ng/mL)	1813.87	1727.84	104.98	(100.75, 109.39)

(b) (4)

(b) (4)

(b) (4)

The primary objective of **Study 311-1473** was to evaluate the bioequivalence of emtricitabine (FTC) and tenofovir alafenamide (TAF) FDC (200/25mg) in the absence of pharmacoenhancement compared to the F/TAF components in Genvoya (E/C/F/TAF) (150/150/200/10mg). This was a randomized, single-dose, 2 ways, crossover study.

Each subject received 2 single doses with food separated by 7 days; once with the F/TAF (25mg) FDC and the other time with Genvoya. A total of 116 healthy volunteers were randomized and all completed the study.

The results of the PK were interpreted to demonstrate the FTC and TAF components of F/TAF (200/25mg) are bioequivalent to their corresponding components in Genvoya (E/C/F/TAF) (150/150/200/10mg). The corresponding 90% CIs of AUC_{last}, $AUC_{Inf,}$ and Cmax for TAF and FTC were contained within the 80% to 125% prespecified for bioequivalence. In this study, AUC_{last} for tenofovir alafenamide exposure with the F/TAF FDC tablet was 374 ng▪h/mL. AUC_{last} for tenofovir alafenamide exposure with the 25mg tablet was 369 ng▪h/mL. In this study the TAF dosage of 25mg in F/TAF resulted in similar exposure as was achieved with 10mg TAF in the presence of a cobicistat.

Table 3 Pharmacokinetic Results Study 311-1473

TAF PK Parameter	N	Test Mean (%CV)	N	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% CI (%)
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h*ng/mL)	116	374.0 (43.4)	116	369.3 (40.6)	100.32	96.48, 104.31
AUC_{inf} (h*ng/mL)	95	396.4 (42.6)	97	389.5 (39.3)	98.54	94.61, 102.62
C_{max} (ng/mL)	116	280.5 (62.9)	116	267.8 (59.8)	103.63	95.46, 112.49
FTC PK Parameter	**N**	**Test Mean (%CV)**	**N**	**Reference Mean (%CV)**	**GLSM Ratio (Test/Reference) (%)**	**90% CI (%)**
F/TAF (200/25 mg) (Test) vs E/C/F/TAF (150/150/200/10 mg) (Reference)						
AUC_{last} (h*ng/mL)	116	9423.9 (19.3)	116	10475.3 (19.7)	90.01	88.88, 91.16
AUC_{inf} (h*ng/mL)	116	9654.6 (19.3)	116	10706.6 (19.6)	90.20	89.06, 91.35
C_{max} (ng/mL)	116	1577.4 (26.8)	116	1601.7 (19.6)	97.26	94.57, 100.03

The primary objective of **Study 311-1386** was to evaluate the effect of food on the pharmacokinetics (PK) of tenofovir alafenamide and emtricitabine when administered as F/TAF. This was a randomized, open label, single-dose, 2 treatment, 2 periods, and crossover food-effect study. Each subject received 2 single doses. One dose was given to subjects in the fasted state and one dose was given with food (high-calorie, high fat meal). The doses were separated by 7 days. A total of 40 healthy volunteers were randomized and 37 completed the study. Two subjects discontinued after receiving the first dose of F/TAF while fasted. One discontinued due to an adverse event and the other due to pregnancy. A third subject withdrew consent after the second dose.

The PK data was assessed to demonstrate overall TAF exposure (AUC_{inf}) increased by 75% when the F/TAF FDC tablet (200/25 mg) was administered under fed conditions compared with fasted conditions. In this study, AUC_{last} for tenofovir alafenamide exposure when F/TAF (25mg) FDC tablet was given with food was 234 ng▪h/mL. AUC_{last} for tenofovir alafenamide exposure when F/TAF (25mg) FDC tablet was given fasted was 134 ng▪h/mL.

Table 4 Pharmacokinetic Results Study 311-1386

	GLSMs by Treatment		GLSM Ratio (Test/Reference) (%)	90% CI (%)
	Test Treatment B (F/TAF Fed) (N = 38)	Reference Treatment A (F/TAF Fasted) (N = 40)		
TAF PK Parameter				
AUC_{inf} (h•ng/mL)	234.86[a]	133.91	175.38	(163.93, 187.63)
AUC_{last} (h•ng/mL)	234.02	132.53	176.57	(166.19, 187.60)
C_{max} (ng/mL)	180.00	212.94	84.53	(74.92, 95.37)
FTC PK Parameter				
AUC_{inf} (h•ng/mL)	9114.01	10,002.77	91.11	(88.84, 93.44)
AUC_{last} (h•ng/mL)	8901.52	9758.42	91.22	(88.90, 93.60)
C_{max} (ng/mL)	1513.12	2058.61	73.50	(69.26, 78.00)

Drug-Drug Interaction Fed Conditions: Studies 311-0101, 120-0118, and 299-0102

The primary objective of **Study 311-0101** was to evaluate the pharmacokinetics of three different dosages of TAF including its impact on TFV when it is given either alone or in combination with FTC, EFV, DRV/COBI and COBI itself. The study design was non-randomized, open label, single site, multiple dose, crossover and multi-cohort study. It was designed to evaluate the drug interaction potential between once daily FTC/TAF (multiple dosages) and EFV or DRV/COBI and between TAF and COBI given in combination. Fifty healthy volunteers were enrolled into one of 4 cohorts of 12 each (one cohort had 14 subjects). Subjects were given daily treatment for 22-26 days. Each cohort underwent two different individual study treatments listed A-H (Table 5). In this table TAF is represented by its development name GS-7340.

Table 5 Study Design Study 311-0101

Cohort 1	Days 1 to 12: Treatment A, FDC oral tablet containing FTC 200 mg and GS-7340 40 mg once daily in the morning, fasted	Days 13 to 26: Treatment B, FDC oral tablet containing FTC 200 mg and GS-7340 40 mg plus EFV 600-mg oral tablet once daily in the morning, fasted
Cohort 2	Days 1 to 12: Treatment C, FDC oral tablet containing FTC 200 mg and GS-7340 25 mg once daily in the morning, fed	Days 13 to 22: Treatment D, FDC oral tablet containing FTC 200 mg and GS-7340 25 mg plus DRV/co 2 × 400/1 × 150-mg oral tablets once daily in the morning, fed
Cohort 3	Days 1 to 10: Treatment E, DRV/co 2 × 400/1 × 150-mg oral tablets once daily in the morning, fed	Days 11 to 22: Treatment F, FDC oral tablet containing FTC 200 mg and GS-7340 25 mg plus DRV/co 2 × 400/1 × 150-mg oral tablets once daily in the morning, fed
Cohort 4	Days 1 to 12: Treatment G, Oral tablet containing single-agent GS-7340 8 mg once daily in the morning, fed	Days 13 to 22: Treatment H, Oral tablet containing single-agent GS-7340 8 mg plus COBI 150-mg oral tablet once daily in the morning, fed

Of the 50 individuals who enrolled in the study, two subjects discontinued because of adverse events.

In cohort 1, the TAF exposures show no interaction of EFV. The TFV exposure decreased in subjects receiving EFV in addition to F/TAF (40mg). The lower confidence limit of the C_{max} parameter was 66.7 ng/mL. This value is slightly below the lower limit of 70 indicating lack of interaction (Table 6). In cohort 2, the co-administration with DRV/COBI with FTC/TAF (25mg) had no impact on TAF exposure but caused a 300% increase in TFV exposure compared to those not receiving DRV/COBI (Table 6). Cohort 3, demonstrated no significant impact of F/TAF (25mg) + DRV/COBI on the pharmacokinetics of cobicistat. In cohort 4 by not administering DRV both TAF and TDF exposures were increased approximately 300% by the co-administration of COBI (Table 6). The Applicant interprets the data in cohort 2 as showing comparable exposures of TAF following multiple dose administration of either FTC/TAF 25mg plus DRV/co versus FTC/TAF alone may be due to an inductive effect of DRV on Pgp efflux pump. This is a reasonable explanation for the lack of boosting of TAF when it is combined with DRV/COBI.

Table 6 Pharmacokinetic Results of Study 311-0101

GS-7340 PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% Confidence Interval
Cohort 1: FTC/GS-7340 200/40 mg + EFV (Test) vs FTC/GS-7340 200/40 mg (Reference), (N = 11)				
AUC_{last} (ng·h/mL)	285.8 (46.4)	344.0 (60.9)	85.54	(72.08, 101.52)
C_{max} (ng/mL)	390.8 (62.2)	499.4 (82.8)	77.92	(57.68, 105.25)
Cohort 2: FTC/GS-7340 200/25 + DRV/co (Test) vs FTC/GS-7340 200/25 mg (Reference), (N = 11)				
AUC_{last} (ng·h/mL)	239.3 (41.0)	245.6 (41.9)	97.64	(80.38, 118.62)
C_{max} (ng/mL)	215.0 (59.2)	208.3 (40.2)	93.43	(72.16, 120.98)
Cohort 4: GS-7340 8 mg + COBI (Test) vs GS-7340 8 mg (Reference), (N = 12)				
AUC_{last} (ng·h/mL)	213.3 (37.7)	81.2 (43.9)	265.06	(229.00, 306.80)
C_{max} (ng/mL)	189.9 (45.6)	71.0 (72.9)	283.31	(219.65, 365.43)

Table 6 continued

TFV PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (Test/Reference) (%)	90% Confidence Interval
Cohort 1: FTC/GS-7340 200/40 mg + EFV (Test) vs FTC/GS-7340 200/40 mg (Reference), (N = 11)				
AUC_{tau} (ng·h/mL)	350.2 (31.7)	430.9 (24.0)	79.72	(73.34, 86.65)
C_{max} (ng·h/mL)	24.0 (34.7)	31.1 (26.2)	75.49	(66.65, 85.50)
C_{tau} (ng/mL)	11.4 (32.4)	13.6 (22.5)	81.61	(74.74, 89.10)
Cohort 2: FTC/GS-7340 200/25 + DRV/co (Test) vs FTC/GS-7340 200/25 mg (Reference), (N = 11)				
AUC_{tau} (ng·h/mL)	953.4 (20.0)	299.3 (29.3)	323.88	(302.11, 347.21)
C_{max} (ng/mL)	57.4 (23.2)	18.3 (27.8)	316.03	(300.13, 332.76)
C_{tau} (ng/mL)	33.7 (19.7)	10.8 (33.2)	320.56	(290.05, 354.27)
Cohort 4: GS-7340 8 mg + COBI (Test) vs GS-7340 8 mg (Reference), (N = 12)				
AUC_{tau} (ng·h/mL)	286.9 (21.9)	86.1 (19.4)	330.88	(310.20, 352.93)
C_{max} (ng/mL)	19.3 (20.5)	5.8 (19.5)	334.09	(301.98, 369.62)
C_{tau} (ng/mL)	10.3 (24.4)	3.0 (19.9)	334.86	(312.43, 358.91)

The primary objective of **Study GS-US-120-0118** was to evaluate the pharmacokinetic drug interaction between independent components TAF and FTC and ritonavir boosted protease inhibitors (PIs) atazanavir, darunavir and lopinavir and unboosted integrase strand-transfer inhibitor (INSTI) dolutegravir (DTG). The study design was open label, single site, multiple dose, and multi-cohort study. Healthy volunteers received a single dose of TAF 10mg+FTC 200mg followed by 13 days of daily standard doses of either ATV/r, DRV/r, LPV/r or DTG. This was followed by an additional single dose of TAF 10mg + FTC 200mg administered in the presence of steady state RTV boosted PI or unboosted DTG. This study did not examine the potential interaction of the F/TAF FDC. Forty healthy volunteers were enrolled in one of 4 cohorts of 10 subjects each. All study

drugs were administered within 5 minutes of the completion of a standard moderate-fat meal.

TAF exposures increased when FTC+TAF was combined with ritonavir boosted atazanavir and lopinavir but not increase when combined with boosted darunavir or unboosted dolutegravir. The pharmacokinetics of the ritonavir boosted protease inhibitors and the dolutegravir were unaffected by the co-administration with FTC+TAF (Table 7).

Table 7 Pharmacokinetic Results of Study 120-0118 (TAF=10mg)

	GLSMs by Treatment			
	Cohort 1			
TAF PK Parameter	FTC+TAF+ATV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)	GLSM Ratio (%)	90% CI (%)
AUC_{inf} (ng•h/mL)	162.62	86.08	188.92	(155.37, 229.71)
AUC_{last} (ng•h/mL)	160.28	83.89	191.06	(155.08, 235.40)
C_{max} (ng/mL)	130.85	74.04	176.72	(128.19, 243.63)
	Cohort 2			
	FTC+TAF+DRV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	76.73	73.54	104.34	(84.14, 129.39)
AUC_{last} (ng•h/mL)	74.76	70.35	106.27	(83.59, 135.10)
C_{max} (ng/mL)	91.16	64.29	141.80	(96.11, 209.22)
	Cohort 3			
	FTC+TAF+LPV/r (Test) (N = 10)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	113.27	78.25	144.75	(114.15, 183.55)
AUC_{last} (ng•h/mL)	111.07	75.70	146.73	(116.60, 184.65)
C_{max} (ng/mL)	145.42	66.41	218.97	(171.88, 278.97)
	Cohort 4			
	FTC+TAF+DTG (Test) (N = 9)	FTC+TAF (Reference) (N = 10)		
AUC_{inf} (ng•h/mL)	106.61	91.42	116.62	(93.49, 145.48)
AUC_{last} (ng•h/mL)	105.29	88.47	119.02	(95.83, 147.82)
C_{max} (ng/mL)	81.74	66.11	123.64	(87.79, 174.13)

A PBMC PK report of **Study 311-1089** was submitted in this NDA. The primary objective of was to evaluate the efficacy of switching FTC/TDF to FTC/TAF provided to describe the intracellular TFV-DP concentrations in PBMCs in subjects receiving FTC/TAF or FTC/TDF in combination with 3rd agents boosted and unboosted. This

study is ongoing but summaries of intracellular PBMC TFV-DP concentrations of individuals receiving either F/TAF 200/25mg for unboosted, [redacted] (b) (4) FTC/TDF 200/300mg were provided and are reproduced below (Table 8). It is important to note that PBMC TFV-DP concentrations were 3 times higher in subjects receiving 25 mg of TAF with anchor unboosted anchor drug and 10mg of TAF with boosted anchor drug was compared to PBMC-TFV-DP concentrations with 300mg of TDF.

Table 8 Pharmacokinetic Results of Study 311-1089

	Intracellular PBMC TFV-DP Concentration (pg/10^6 cell)	
	F/TAF (N = 308)	FTC/TDF (N = 271)
Geometric Mean (95% CI)	14.2 (12.6, 16.0)	3.4 (3.0, 3.8)
GLSM	14.1	3.3
TAF/TDF GLSM Ratio (90% CI) x 100%	424.62 (370.26, 486.97)	

	Geometric Mean (95% CI) by Unboosted 3rd ARV Agent						
	+ DTG (n = 24)	+ EFV (n = 8)	+ MVC (n = 1)	+ NVP (n = 67)	+ RAL (n = 56)	+ RPV (n = 3)	Total (n = 159)
Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	17.2 (10.0, 29.6)	6.4 (2.6, 15.6)	26.8 (NA)	18.3 (14.0, 24.0)	19.6 (14.3, 26.7)	16.1 (0.1, 2271.4)	17.6 (14.7, 21.2)

	Geometric Mean (95% CI) RTV-Boosted 3rd ARV Agent			
	+ ATV+RTV (n = 50)	+ DRV+RTV (n = 82)	+ LPV/r (n = 17)	Total (n = 149)
Intracellular PBMC TFV-DP concentration (pg/10^6 cells)	15.6 (12.3, 19.8)	9.7 (8.0, 11.7)	8.7 (5.4, 14.1)	11.2 (9.7, 13.0)

Study 299-0102 provides additional data on the interaction between cobicistat boosted darunavir and tenofovir alafenamide in HIV-1 infected subjects. The primary objective of **Study 299-0102** was to assess the safety and efficacy of a FDC DRV/COBI/FTC/TAF (800/150/200/10mg) versus DRV+COBI (800,150mg) + Truvada (TVD) (200mg/300mg). The study design was a Phase 2, double-blinded, active controlled study of 150 HIV-1 infected, treatment naïve subjects randomized 2:1 to the 4 drug FDC or the two drugs, two components arm. Treatment duration was 48 weeks.

A total of 153 were randomized into the study (D/C/F/TAF= 103 and DRV+COBI + TVD 50 subjects). There were 27 (18%) discontinuations (D/C/F/TAF=19%) (DRV+COBI + TVD=16%). The most common reasons for discontinuations were lost to follow-up and withdrawal of consent. Discontinuations for AEs were uncommon in both arms. A total of 126 subjects completed study drug treatment and were given the option to enroll in

the extension phase of GS-US-292-0102 to receive open-label treatment with E/C/F/TAF.

The efficacy and safety results of this study will be discussed in subsequent sections.

Steady-state plasma PK parameters were determined for a subset of 21 D/C/F/TAF and 11 DRV+COBI +TVD subjects who participated in the intensive PK substudy. Fourteen and 8 subjects respectively were included in the PBMC substudy analysis set.

The TAF exposures measured for the D/C/F/TAF (10mg) administered (fed) were 130 ng▪h/mL. In Study 120-0104, 25 mg was determined virologically to be the optimal dosage. The TAF PK data for 120-0104 subjects receiving 25mg (fasting) was AUC_{last} 115.2 ng▪h/mL. The measured value of AUC_{last} TAF in the E/C/F/TAF10mg (fed) pivotal studies 292-0104 and 292-0111 was 227 ng▪h/mL. The food effect on TAF is 40% increase compared to fasting.

Table 8 Summary of TAF Pharmacokinetic Parameters D/C/F/TAF 10mg Study 299-0102

	AUC_{last} (ng·h/mL) Mean (%CV) (N = 21)	C_{max} (ng/mL) Mean (%CV) (N = 21)	T_{max} (h) Median (Q1, Q3) (N = 21)	$t_{1/2}$ (h) Median (Q1, Q3) (N = 21)
TAF	130.5 (34.1)	163.0 (51.9)	0.53 (0.50, 1.00)	0.45 (0.38, 0.66)

The tenofovir (TFV) AUC_{tau} of the D/C/F/TAF (10mg) was 339 ng▪h/mL or (9%) compared to 3737 ng▪h/mL measured for the Truvada containing arm.

Table 9 Summary of TFV Pharmacokinetic Parameters Study 299-0102

Parameter	Units	D/C/F/TAF (N = 21)	DRV+COBI+TVD (N = 11)
AUC_{tau}	ng·h/mL	339.0 (37.1)	3737.0 (26.8)
C_{max}	ng/mL	18.8 (37.6)	413.2 (28.3)
T_{max} [a]	h	2.00 (1.50, 3.13)	1.00 (1.00, 3.00)
C_{tau}	ng/mL	11.7 (39.3)	75.4 (30.9)
$t_{½}$ [a]	h	43.82 (32.03, 59.23)	11.85 (11.35, 16.15)

There were 6 fold greater concentrations of PBMC TFV-DP in the subset of 14 D/C/F/TAF substudy participants compared to the 8 DRV+COBI+TVD substudy subjects.
The Agency has asked questions regarding the assay which were answered to the satisfaction of Dr. Sampson. Please see Dr. Sampson's Clinical Pharmacology review for more details. The Applicant has postulated that the PBMC TFV-DP concentrations are more relevant to efficacy than the TAF serum levels.

Table 9 Summary of TFV-DP Pharmacokinetic Parameters Study 299-0102

TFV-DP PK Parameter	GLSM by Treatment		GLSM Ratio (%)	90% CI (%)
	D/C/F/TAF (N = 14)	DRV+COBI+TVD (N = 8)		
AUC_{tau} (µM·h)	17.12	2.62	652.09	(268.28, 1585.00)

5. Clinical Microbiology

There was no clinical microbiology data submitted for the BA/BE studies which enrolled healthy HIV-1 uninfected subjects. Study 299-0102 was the only study in which HIV-1 infected subjects were enrolled. All subjects enrolled showed full sensitivity to darunavir, emtricitabine and tenofovir based on proprietary algorithm from Monogram Biosciences. At baseline, most subjects enrolled in the study (97.4%) had HIV-1 harboring secondary PI-associated mutations. Six subjects had HIV-1 each containing one DRV-specific resistance-associated mutation at screening which did not adversely influence treatment response. NNRTI-associated resistance mutations were found in nearly 20% of subjects at screening with the K103N/S mutation being the most prevalent in this category (10.5%). Finally, 9.8% of subjects were found to harbor HIV-1 with nucleoside-associated resistance mutations, with the V118I being the most prevalent (6.5%).

There were 8 subjects who experienced either confirmed virologic rebound (7) or unconfirmed virological rebound (1). Six (5.8%) of these subjects were receiving D/C/F/TAF and 2 (4%) were receiving DRV+COBI + TVD at the time of their rebound. None of the 8 had any protease resistance mutations at the time of rebound and DRV susceptibility was in the sensitive range. The Applicant interpreted the resistance data as demonstrating evidence of non-compliance with drug treatment as the cause of the virological failure.

Dr. Naeger interpreted the virology data for this NDA. Please see her review for additional details.

6. Clinical/Statistical-Efficacy

No efficacy trials using the FDC drug product, FTC/TAF (Descovy) were submitted in this application. Efficacy assessment of the FDC is based upon demonstration of bioequivalence of the drug exposure. Please refer to NDA 207561 for details regarding the efficacy of the FTC/TAF components of E/C/F/TAF.

The dosage for emtricitabine has been established as 200 mg per day. The optimal dosage for tenofovir alafenamide was determined to be 25 mg based on to virologic findings in study GS-US-120-0104. This 25 mg daily dose could be achieved by administering TAF 25 mg alone or as TAF 10mg with co-administration of a pharmaco-enhancer such as cobicistat. The pivotal trials indicated the desired TAF exposure was

206 ng▪h/mL and virologic data indicates that a minimal exposure of 50 ng▪h/mL is necessary to achieve consistent antiviral activity. In general, proteases and some INSTIs are administered in combination with ritonavir or cobicistat to boost exposures. The dosage of TAF for these individuals would be 10mg. Those ARV agents that do not utilize boosters would be administered TAF 25mg.

The one possible exception to this general rule would be boosted darunavir. In studies 311-0101, 120-0118 and 299-0102 the expected boosting of TAF exposure by cobicistat or ritonavir is diminished by the co-administration of darunavir.

The Applicant submits the efficacy data of Study **299-0102** as evidence that the lowered TAF exposure associated with darunavir/cobicistat co-administration does not have a significant impact on the efficacy of F/TAF (10mg). The 24 week data does appear to indicate non-inferiority. The 48 week efficacy data from Study **299-0102** does not support the conclusion of non-inferiority of D/C/F/TAF compared to F/TDF (Truvada) +DRV+COBI

A total of 153 were randomized into the study (D/C/F/TAF= 103 and DRV+COBI + TVD 50 subjects). The inclusion criteria included HIV-1 RNA levels of ≥ 5000 copies/mL, CD4+ > 50 cells/μL, eGFR ≥ 70 mL/min and no prior use of anti-HIV drug use. Demographic and general baseline characteristics were similar, 93% were male, mean age 35 years, 60% were white or 35% were black. There were 27 (18%) discontinuations (D/C/F/TAF=19%) (DRV+COBI + TVD=16%). The most common reasons for discontinuations were lost to follow-up and withdrawal of consent. Discontinuations for AEs were uncommon in both arms. A total of 126 subjects completed study drug treatment and were given the option to enroll in the extension phase of GS-US-292-0102 to receive open-label treatment with E/C/F/TAF.

The primary efficacy endpoint was the percentage with HIV-1 viral loads < 50 copies/mL using the snapshot algorithm at 24 weeks. Virologic successes for D/C/F/TAF were 75% and DRV+ COBI + TVD were 74%, differences in percentages 3.3% (95% CI: -11.4 to 18.1%). Because the lower bound of the 2-sided CI of the difference was greater than the prespecified -12% non-inferiority margin, D/C/F/TAF was declared by the Applicant as noninferior to DRV+ COBI +TVD. At 48 weeks, the viral success rate was 77% for D/C/F/TAF and 84% for DRV+ COBI + TVD with a difference in percentages of -6.2% and 95% CI of -20% to 7%. In addition, it was noted that the virologic success rates at 48 weeks for D/C/F/TAF were lower than had been observed in the pivotal studies with Genvoya. The Applicant attributed the difference in rates of virologic success at 48 weeks between the D/C/F/TAF in this study and E/C/F/TAF in the Genvoya pivotal studies to differences in the numbers of subjects who discontinuing due to other causes and the overall lowered virologic success rates of protease inhibitors. Dr. Ruben Biostatistician does not find sufficient support for the Applicant's contention that the

difference in rates of virologic success is due to differences in subject discontinuation. Please see the analysis of Dr. Donald Ruben Biostatistician for more details.

Efficacy Summary: Of the 7 studies that were reviewed for this NDA, only **299-0102** enrolled HIV-1 infected subjects. In this study of D/C/F/TAF vs DRV+COBI+TVD, the primary efficacy endpoint at 24 weeks was supportive of non-inferiority of the two arms. The 48 week data did not support the assessment of non-inferiority, however, and the Applicant's assessment that this was the result of imbalance in non-AE discontinuations is not supported by the Agency Biostatistician. The co-administration of DRV+COBI with F/TAF appears to significantly diminish the serum TAF exposure. This could result in a lowered rate of efficacy if F/TAF is given with boosted DRV. The countervailing argument is that the intracellular TFV concentrations are most relevant to efficacy. In multiple studies it has been demonstrated that the PBMC TFV-DP levels with TAF combined with other anchor drugs is many times higher than the PBMC TFV-DP levels found when approved dosages of TDF are administered with these same anchor drugs. The Emax curve derived from GS-US-120-0104 indicates that 146 ng▪h/mL seen with 25 mg given with fasting and 222 ng▪h/mL DRV+COBI + F/TAF (10mg fed) are on the flat part of antiviral activity. The breakpoint for antiviral activity is at a TAF exposure of approximately 50 ng▪h/mL lower than both TAF exposures above.

7. Safety
Emtricitabine at the dosage found in the F/TAF FDC (200mg) has been marketed for several years. The safety profile of this drug when used in combination with other antiretrovirals (ARVs) is also well known.

TAF is a new ARV approved on November 5, 2015 as a component of the FDC Genvoya (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide). Tenofovir alafenamide is a prodrug of tenofovir similar to tenofovir disoproxil fumarate (TDF) whose safety profile is well established. Extensive safety data from clinical trials in which tenofovir alafenamide was administered were considered during the approval of Genvoya. PK data from these studies established the TAF exposures to be equivalent to 25 mg taken once per day. As previously discussed in Section 4 when TAF 10mg is given in combination with a pharmacoenhancer such as cobicistat, the effective exposure resembles that achieved by 25 mg TAF given alone.

Exposure Issues:
The 312 healthy volunteers in the BA/BE studies were administered two doses of study drugs at either 15 days (311-1088) or 7 days (b) (4), 311-1473, 311-1386) intervals. The dosages of F/TAF administered as FDC study drugs were 200mg FTC/25mg TAF except for Study 311-1473 in which cobicistat was also administered and the TAF dosage was therefore 10mg.

The two DDI studies 311-0101 and 120-0118 enrolled a total of 90 healthy volunteers, the TAF dosages were variable in the former and were 10mg in the latter. The durations of exposure were longer in both.

In **Study 311-0101** the dosages of the TAF component varied from 8 mg to 40mg and the FTC component remained stable at 200mg. The co-administered drugs included efavirenz, and darunavir combined with cobicistat. This study enrolled 50 healthy volunteers into one of four cohorts of 12 each. The treatment duration was 22-26 days.

Study 120-0118 enrolled 40 healthy volunteers divided into 4 cohorts of 10 each. The FTC and TAF dosages in all 4 cohorts was 200mg FTC and 10mg TAF which was initially given alone and again after 13 days. Between these two F/TAF doses the subjects received standard dosages of either: atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or dolutegravir. The F/TAF exposure was limited to the two days, one prior to the protease or INSTI and then after 13 days.

Study 299-0102 was the single study in which HIV-1 subjects participated. This study compared the safety and efficacy of 4 drug combinations of darunavir, cobicistat, emtricitabine, and either TAF or TDF. The treatment duration was 48 weeks.
This study enrolled 153 HIV-1 infected subjects randomized to D/C/F/TAF (103) or DRV +COBI + Truvada (FTC/TDF) (50). The F/TAF dosage in both study arms was (b) (4) TAF owing to the co-administration of cobicistat. The treatment duration was 48 weeks although the primary efficacy endpoint was specified as 24 weeks.

Adverse Events

BA/BE Studies 311-1088, (b) (4), 311-1473, 311-1386 FDC (FTC/TAF):

In **Study 311-1088** there were no serious adverse events, deaths, pregnancies or discontinuations due to adverse events. There were a total of 14 adverse events occurring in 56 subjects (25%) in either or both of the treatment arms. The proportions between study arms were similar at 6 in the F/TAF FDC arm compared to 8 in the FTC + TAF arm. All adverse events were grade 1 and the only AE to be recorded in more than one subject was traumatic venipuncture. There were two discontinuations unrelated to adverse events.

Laboratory abnormalities: There was a single F/TAF recipient who developed asymptomatic Grade 3 and subsequently Grade 4 amylase elevations which resolved at study day 16. The only concomitant symptom was unrelated Grade 1 diarrhea. The only other graded laboratory abnormality was Grade 1 glucose elevation in a separate subject.

In **Study 311-1473** there were no deaths and no discontinuations due to adverse events. There were a total of 29 adverse events occurring in 116 subjects (25%) in either or both treatment arms. The proportions between the study arms were similar at 14 in the F/TAF arm compared to 15 in the E/C/F/TAF arm. Grade 2 events were reported in 3 subjects in the F/TAF arm and 2 subjects following E/C/F/TAF. Grade 2 AEs that were reported included gastrointestinal disorders (2 per arm), toothache (1 in F/TAF arm), and headache (2 in the F/TAF arm). There was a single unrelated Grade 3 serious adverse event of peritoneal hemorrhage in a subject with sickle cell disease following a dose of F/TAF.

Laboratory abnormalities: Overall there were graded laboratory abnormalities in 22 individuals out of 116 enrolled. Most of the abnormalities were Grade1 or 2. There was one Grade 4 and 2 Grade 3 laboratory abnormalities. The Grade 4 laboratory abnormality was elevated lipase associated with a Grade 2 amylase abnormality. This subsequently subsided and was never symptomatic. This abnormality did not result in discontinuation of the subject. The two Grade 3 laboratories were occult hematuria in 2 women one of which was experiencing menses at the time of the abnormality.

In **Study 311-1386** there were no deaths, but there were two discontinuations due to adverse events including one Grade 3 neutropenia and one SAE (related) of pregnancy resulting in spontaneous abortion 2 weeks after discontinuation. There were a total of 22 adverse events occurring in 40 subjects, approximately 30% per arm. AEs assessed

as related were balanced between study arms. There were 7 Grade 2 AEs. Six of the 7 Grade 2 adverse events were in the fasted group. The Grade 2 AEs included: muscle tightness, myalgias, gastrointestinal disorders, and vertigo. Both Grade 3 AEs were reported from the F/TAF fasted arm.

Laboratory abnormalities: One subject in the fasted group discontinued with Grade 3 neutropenia which began on Day 3 and reached Grade 3 on Study day 5 where it remained until Day 9. Study drug was discontinued and the event was assessed by the Investigator as related. There were a total of 3 Grade 3 laboratory abnormalities including the neutropenia above and two instances of Grade 3 occult hematuria, one in the fasting and one in the fed arms, both occurring in women participants. The hematuria was assessed as related to menses and the subjects were continued in the study.

DDI Studies (311-0101,120-0118) Using the FDC (FTC/TAF):

Fifty healthy volunteers were enrolled in Drug-Drug Interaction **Study 311-0101.** There were two discontinuations due to AEs. One subject discontinued with Grade 2 anxiety disorder and the other discontinuation was in a 35 year old with an unrelated Grade 2 joint abscess. There were no deaths; no SAEs, no Grade 3 or higher AEs, and only one related AE, the Grade 2 Anxiety resulting in discontinuation. There were a total of 19 AEs reported, the incidence per cohort varied from 0% to a maximum of 33% in treatment arms FTC/TAF 40mg and TAF 8mg respectively. Other than UTI, constipation, venopuncture site pain, no AE was reported in more than one subject. Grade 2 AEs included dyspepsia, vomiting, E. coli UTI, joint abscess, muscle strain, anxiety.

Laboratory Abnormalities: All but one laboratory abnormality was Grade 1 or 2. One woman had isolated asymptomatic Grade 3 occult hematuria. Grade 2 laboratory abnormalities occurring in at least one subject included: hypoglycemia (3), anemia (1), and hematuria (5). Grade 1 amylase elevations were observed in 16 across study arms.

Study 120-0118 was intended to be an open label study of PK drug interaction potential of components TAF (10mg) and FTC with ritonavir boosted protease inhibitors or INSTI DTG. Forty healthy volunteers were enrolled into 4 treatment cohorts of 10 subjects each. There were no SAEs, deaths, pregnancies and discontinuations due to AEs. The numbers of individuals reporting AEs was variable by drug combination ranging from 0 AEs for FTC+TAF + DRV/ritonavir and FTC+TAF+LPV/ritonavir to 100% ocular icterus with atazanavir/ritonavir. All AEs were Grade 1 or 2; there were no Grade 3 or higher AEs. AEs assessed as related to study drug were ocular icterus in 10/10 atazanavir/

ritonavir recipients and diarrhea in 5/10 lopinavir/ritonavir recipients and flatulence in 1/10 FTC/TAF recipients.

Laboratory Abnormalities: Increases from baseline in median values for total bilirubin were observed during treatment with atazanavir/ritonavir which resulted in 100% ocular icterus. No other clinically relevant changes in any other hematology or chemistry parameter were observed.

Safety and Efficacy D/C/F/TAF vs DRV+COBI+ TVD Study 299-0102

Study 299-0102 is the only study reviewed in this submission which enrolled HIV-1 infected subjects and obtained both safety and efficacy data. The efficacy data was discussed in Section 6. The safety data from this study is briefly discussed below.

A total of 153 were randomized into the study. There were no deaths, no pregnancies, 7 serious adverse events and 4 discontinuations due to AEs occurring during the conduct of this trial. As demonstrated below in Table 10, the overall percentages of individuals experiencing an AE, an SAE, a Study Drug related AE, a discontinuation due to an AE, or Grade 2 or higher AE were similar between the two study arms.

Table 10 Adverse Events Summary Study 299-0102

Subjects Experiencing Any	D/C/F/TAF N=103	DRV+COBI +TVD N=50
Adverse Event	95 (92%)	47 (94%)
Grade 2, 3, 4 Adverse Event	57 (55%)	24 (48%)
Grade 3 or 4 Adverse Event	7 (7%)	4 (8%)
Study Drug Related Adverse Event	43 (42%)	19 (38%)
Grade 2, 3, 4 Study Drug Related Adverse Event	10 (10%)	3 (6%)
Grade 3 or 4 Study Drug Related Adverse Event	1 (1%)	1 (2%)
Serious Adverse Event (SAE)	5 (5%)	2 (4%)
Study Drug Related SAE	1 (1%)	0
Discontinuation due to AE	2 (2%)	2 (4%)

There were a total of 7 SAEs, 5 occurring in the D/C/F/TAF arm and 2 occurring in the DRV+COBI+TVD arm. The 5 SAEs in the D/C/F/TAF arm were: allergic-hypersensitivity, substance abuse, psychosis, cellulitis right lower extremity, bloody diarrhea. The two SAEs in the comparator arm were: multiple admissions for pneumonia and bronchitis, subacute renal failure possibly due to renal tubular dysfunction.

Two SAE subjects in each arm discontinued study drug due to adverse events. In the D/C/F/TAF arm SAEs with hypersensitivity/rash and substance abuse were discontinued. In the comparator arm, the SAEs of renal tubular dysfunction and chronic diarrhea were discontinued.

The percentage of Grade 3 and 4 AEs were similar between the two study arms. The only related SAE was the patient with hypersensitivity rash associated with D/C/F/TAF treatment.

The only potential differences in all grade AEs between the two arms might be the higher incidence of psychiatric abnormalities in the D/C/F/TAF arm.

Table 11 Adverse Events Any Grade 299-0102 Reported for ≥5% of Subjects

	D/C/F/TAF N=103	DRV+COBI +TVD N=50
Total Subjects with AEs	95 (92%)	47 (94%)
Musculoskeletal	28 (27%)	18 (36%)
Headache/neuro	16 (16%)	11 (22%)
URI Sx	16 (16%)	7 (14%)
Derm	29 (28%)	13 (26%)
Nausea/Vomiting GI symptoms	54 (53%)	26 (52%)
Psychiatric	19 (18%)	6 (12%)
Fever	7 (7%)	2 (4%)
Infection	62 (60%)	32 (64%)

Ocular Adverse Events: During the development of tenofovir alafenamide pre-clinical data were generated which suggested a possible relationship between TAF administration and the development of posterior uveitis. For more details please see the Genvoya review. Eye AEs were an area of enhanced vigilance during the conduct of all TAF containing trials. No definitive association between TAF and posterior uveitis was documented in the Genvoya (E/C/F/TAF) review. In this study adverse events in the eye disorders system organ class (SOC) were reported in 6 (6%) of subjects in the D/C/F/TAF group compared to none in the DRV+COBI+TVD group. One non-serious AE of photophobia in the D/C/F/TAF group was assessed as related.
The 6 SOC eye disorder AEs are listed below in Table 12. All of the SOC eye disorders were Grade 1 in severity. No eye disorders resulted in discontinuation of study drugs. No AEs of uveitis noted during the study. All of the 6 SOC eye disorders appear to have a potential inflammatory component. The data provided in this submission does not permit further analysis but the imbalance supports continuing concern.

Table 12 Eye Disorders SOC Study 299-0102

Patient Number	Diagnosis	SD Onset	SD End	Severity
0121-3106	Eye Pruritus	151	153	1
0660-3011	Left Eye Irritation	372	406	1
1534-3127	Photophobia (related)	1	1	1
1603-3053	Increased Lacrimation	21	Unknown	1
2157-3063	Bilateral Eye Irritation	2	5	1
6757-3133	Left Eye Redness	77	82	1

Laboratory Abnormalities:
Renal:
One subject in the DRV+COBI+TVD group had an SAE of Grade 2 tubular disorder that resulted in discontinuation. This laboratory abnormality resolved after discontinuation of study drug and was not considered related to study drug by investigator. An additional subject in this group developed Grade 3 proteinuria.

Two subjects in the D/C/F/TAF had AEs of increased serum creatinine (related to study drug in one).

The percentages of Grade 1 and 2 treatments emergent proteinuria reported at 48 weeks in both treatment groups were approximately the same, 32% versus 34%.

Metabolic Laboratory Parameters:
Increases from baseline were observed for fasting total cholesterol, fasting direct LDL cholesterol, fasting HDL cholesterol, and fasting triglycerides at Weeks 24 and 48 for each treatment group, with the exception of a decrease in fasting triglycerides at Week 48 for the DRV+COBI+TVD group.

The median increase from baseline was greater in the D/C/F/TAF group compared with the DRV+COBI+TVD group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for fasting total cholesterol and fasting LDL cholesterol at Week 24, and for all 4 lipid parameters at Week 48.

Median increases from baseline in fasting total cholesterol were as follows:

- At Week 24: D/C/F/TAF 31 mg/dL, DRV+COBI+TVD 14 mg/dL; $p = 0.014$
- At Week 48: D/C/F/TAF 40 mg/dL, DRV+COBI+TVD 5 mg/dL; $p < 0.001$

Median increases from baseline in fasting direct LDL cholesterol were as follows:

- At Week 24: D/C/F/TAF 22 mg/dL, DRV+COBI+TVD 7 mg/dL; $p = 0.004$
- At Week 48: D/C/F/TAF 26 mg/dL, DRV+COBI+TVD 4 mg/dL; $p < 0.001$

Median increases from baseline in fasting HDL cholesterol were as follows:

- At Week 24: D/C/F/TAF 3 mg/dL, DRV+COBI+TVD 2 mg/dL; p = 0.35
- At Week 48: D/C/F/TAF 7 mg/dL, DRV+COBI+TVD 3 mg/dL; p = 0.009

Median changes from baseline in fasting triglycerides were as follows:

- At Week 24: D/C/F/TAF 24 mg/dL, DRV+COBI+TVD 10 mg/dL; p = 0.13
- At Week 48: D/C/F/TAF 29 mg/dL, DRV+COBI+TVD -5 mg/dL; p = 0.007

Reviewer comments: *the laboratory data is similar to what was seen in the Genvoya pivotal studies with some apparent benefits in the renal laboratory parameters and unfavorable laboratory abnormalities in the metabolic lipid areas.*

Safety Summary:
Limited safety data from the BA/BE studies and the Drug-Drug Interaction studies did not generate any new safety concerns for the FTC/TAF FDC.

Data from the Phase 2 Safety and Efficacy Study 299-0102 does not indicate any new safety concerns for the FTC/TAF FDC. An imbalance in numbers of eye disorders was observed with all 6 being noted in the D/C/F/TAF arm. There are no data to indicate that any of the subjects participating in Study 299-0102 had evidence of uveitis, however.

8. Advisory Committee Meeting

An Advisory Committee was not called for this submission.

9. Pediatrics

This NDA does not contain pediatric data. Pediatric trials with tenofovir alafenamide are ongoing. An Agreed Initial Pediatric Study Request (iPSP) has been submitted to the Agency and after discussion agreement was reached. A partial waiver from conducting pediatric studies with FTC /TAF in pediatric subjects < 4 weeks of age was requested. A deferral request of the study of pediatric subjects who are ≥ 4 weeks and < 18 years was also requested in the iPSP. The Division favors approving the waiver and deferral requests. A formal presentation before the PeRC committee is scheduled for January 6, 2016. The study of the deferral age group of pediatric patients is ongoing at this time.

10. Other Relevant Regulatory Issues

As of the completion of this review, the issue of the labeling of F/TAF dosages when combined with boosted darunavir has not been completely resolved. This issue is discussed in Section 6 Clinical/Statistical- Efficacy

11. Labeling

Review and discussions with the Applicant regarding of the contents of this product label are ongoing at the time of the completion of this clinical review.

12. Outstanding Issues

The only issue still requiring resolution at this time is the recommendation of dosage of tenofovir alafenamide in the F/TAF FDC when the third "anchor" drug is boosted darunavir.

13. Recommendations/Risk Benefit Assessment

I recommend approval of (b) (4) Emtricitabine/Tenofovir alafenamide (b) (4) Emtricitabine/Tenofovir alafenamide 200mg/25mg (FTC/TAF), fixed-dose combinations of two nucleoside-nucleotide reverse transcriptase inhibitors to be used in combination with other active ARV agents including: Protease Inhibitors (PIs) given in combination with a pharmacoenhancer such as cobicistat; Integrase Strand Transfer Inhibitors (INSTI); Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) to form a compete regimen for the treatment of HIV-1 infection in treatment naïve adults and adolescents or adults who are fully suppressed on another Antiretroviral Regimen (ARV) for 6 months who have no history of virologic failure but who desire or require for non-virologic reasons a switch of ARV. (b) (4) (b) (4) (b) (4) his recommendation is based on the bioequivalence of the individual component exposures of FTC/TAF in the approved FDC Genvoya (E/C/F/TAF).

I would further recommend that language be added to the product label which discusses (b) (4) This issue remains in active discussion within the Division at this time. The three options being considered would be: recommend the F/TAF 200mg/25mg as ensuring that a sufficient TAF exposure is provided; (b) (4)

The safety data reviewed were limited but did not identify any new safety signals indicating a modification of the risk benefit ratio of the component parts when combined was needed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM B TAUBER
12/07/2015

RUSSELL D FLEISCHER
12/07/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208215 **Applicant: Gilead** **Stamp Date: April 7, 2015**

Drug Name: Descovy (F/TAF) **NDA/BLA Type: Initial**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Summary of development in Module 2.7 with cross-reference to ISS for E/C/F/TAF
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Summary of development in Module 2.7 with cross-reference to ISE for E/C/F/TAF
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	Although not a 505(b)(2) application, this NDA is reliant on bridging BE study to current approved product: E/C/F/TAF (NDA 207561).
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to			X	Dose determined in

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:				development program for E/C/F/TAF.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:		X		NDA is reliant on BE to F/TAF component in E/C/F/TAF. E/C/F/TAF clinical trials provide required efficacy/safety info.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			By cross-reference to NDA 207561 for E/C/F/TAF.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			By cross-reference to NDA 207561 for E/C/F/TAF.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Provided for Phase 2 supporting study submitted under this NDA. Other narratives submitted to NDA 207561.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	None requested for this NDA.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Datasets provided for Phase 2 trial.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		Datasets for pivotal studies submitted to NDA 207561.
37.	Are all datasets to support the critical safety analyses available and complete?		X		Datasets for pivotal studies submitted to NDA 207561.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			Provided for Phase 2 trial
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Provided for Phase 2 trial
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			For investigators participating in Phase 3 trials submitted to NDA 207561. There are a lot of investigators with disclosable interests > $25K.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Approval of this product is dependent on the approval of Genvoya (E/C/F/TAF, NDA 207561) which is currently under review. All efficacy and safety data submitted for review under that NDA are cross-referenced to this NDA. In the event Genvoya is not approved, this NDA will not be approvable. However, the NDA is fileable pending an approval decision for Genvoya.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The pivotal studies for this NDA are being reviewed under NDA 207561. Study GS-US-299-0102, "Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD" will provide minimal additional safety data to support use of F/TAF.

Linda L. Lewis, M.D. — May 19, 2015

Reviewing Medical Officer — Date

same

Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA L LEWIS
05/19/2015