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APPLICATION NUMBER:

205551Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 205551 SDN: 000 DATE REVIEWED: 07/14/2014
Virology Reviewer: Lisa K. Naeger, Ph.D

NDA#: 205,551

Serial #: 000

Reviewer's Name(s): Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:

ViiV Healthcare Company
 5 Moore Drive
 Research Triangle Park, NC 27709

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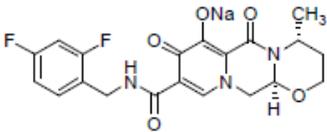
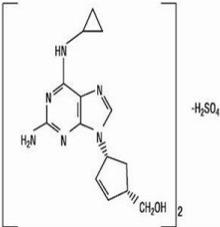
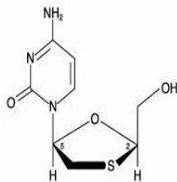
Related/Supporting Documents: IND75382, NDA204790

Product Name(s)

Proprietary: Triumeq

Non-Proprietary/USAN: dolutegravir, abacavir, lamivudine

Code Name/Number: GSK1349572A

Non-Proprietary/USAN	Dolutegravir (DTG)	Abacavir (ABC)	Lamivudine (LAM)
Chemical Name	Sodium (4R,12aS)-9-[[[(2,4-difluorophenyl)methyl]carbamoyl]-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate	1S,cis)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)	(2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one
Molecular Weight	441.36 g/mol (dolutegravir sodium)	670.7 ^(b)	229.1 ^(b) ₍₄₎
Molecular Formula	C ₂₀ H ₁₈ F ₂ N ₃ NaO ₅	(C ₁₄ H ₁₈ N ₆ O) ₂ •H ₂ SO ₄	C ₈ H ₁₁ N ₃ O ₃ S
Structural Formula			

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Dosage Form(s): tablet

Route(s) of Administration: Oral

Indication(s): An integrase strand transfer inhibitor (b) (4) combination (b) (4) abacavir and lamivudine (both nucleoside analogue (b) (4) reverse transcriptase inhibitors) indicated as a complete regimen for the treatment of HIV-1 infection.

Limitations of Use:

- TRIUMEQ alone (b) (4) in patients with history of resistance to any (b) (4) components of TRIUMEQ. (b) (4)

Dispensed: Rx

Abbreviations: ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BL, baseline; DRV, darunavir; DTG, dolutegravir; EC₅₀, effective concentration at 50%; EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; EVG, elvitegravir; FC, fold-change; FPV, fosamprenavir; FTC, emtricitabine; HSA, human serum albumin; IC₅₀, inhibitory concentration at 50%; IN, integrase; INSTI, integrase strand transfer inhibitor; LAM, lamivudine; LTR, long terminal repeat; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OSS, overall susceptibility score; PBL, peripheral blood lymphocytes; PDVF, protocol defined virologic failure; PI, protease inhibitor; PR, protease; RAL, raltegravir; RT, reverse transcriptase; SDM, site-directed mutants; SQV, saquinavir; TDF, tenofovir disoproxil fumarate; TPV, tipranavir;

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EXECUTIVE SUMMARY

This NDA for dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), in a fixed-dose combination with the nucleoside analog reverse transcriptase inhibitors abacavir (ABC) and lamivudine (LAM) is approvable with respect to virology for the treatment of HIV-1 in combination with other antiretrovirals in patients who are susceptible to each component of this fixed-dose combination.

Limitations of Use:

- TRIUMEQ alone (b) (4) in patients with history of resistance to any (b) (4) components of TRIUMEQ. (u) (4)

(b) (4)

In support of this indication, the sponsor submitted updated Week 96 results from the phase 3 treatment-naïve studies (SPRING-2 [ING113086] and SINGLE [ING114467]) and updated Week 48 data from the phase 3 treatment-experienced INSTI-naïve study (SAILING [ING111762]). The updated Week 96 and Week 48 results did not significantly change the conclusions from the clinical virology review of the original NDA.

In the DTG phase 3 clinical studies in treatment-naïve subjects (Studies ING113086 and ING114467), no subjects in either treatment-naïve study had viral isolates with a decrease in DTG susceptibility or background NRTIs. One subject in Study ING114467 had a treatment-emergent INSTI resistance substitution, E157E/Q, detected at Week 24 but no change in DTG susceptibility. In the comparator arms of these studies, 3 subjects' isolates on the raltegravir (RAL) treatment regimen in Study ING113086 had emergent INSTI resistance substitutions and 4 subjects' isolates had emergent NRTI resistance substitutions associated with the background NRTIs; and 8 subjects' isolates in the Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate) arm of Study ING114467 had emergent EFV resistance substitutions with one of these also having emergent NRTI resistance substitutions.

In FLAMINGO, an open-labeled study in treatment-naïve subjects comparing DTG vs. darunavir (DRV)/r with Epzicom or Truvada as background at Week 48, 4 subjects met the criteria for protocol-defined virologic failure (2 in each arm). None of the subjects had treatment-emergent resistance substitutions in integrase or phenotypic resistance to DTG. No subjects had treatment-emergent primary resistance substitutions in RT or PR.

In Study ING111762, DTG efficacy was compared to RAL efficacy in treatment-experienced subjects with no INSTI experience. Based on the FDA criteria for resistance analysis (>400 copies/mL HIV-1 RNA at the failure timepoint, Week 24 or having resistance data at failure), there were 10% of subjects (37/357) in the DTG arm compared to 17% (60/362) of subjects in the RAL arm who were eligible for resistance analysis at Week 48.

Twenty-one percent (6/28) of subjects' isolates with post-baseline integrase (IN) resistance data in the DTG arm had emergent INSTI resistance substitutions (L74M or I, Q95Q/L, T97A, E138T/A, V151V/I, and R263K) compared to 43% (21/49) in the RAL arm with emergent INSTI

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resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E/Q and G163G/R). In the DTG arm, one of the subjects' isolates with emergent INSTI resistance substitutions had decreased susceptibility to both DTG and RAL while the remaining 5 subjects had <2-fold change in DTG susceptibility and no RAL cross-resistance. Overall, emergent resistance to drugs in the background regimen was lower in the DTG arm compared to the RAL arm (30% in DTG vs. 50% in RAL). Two subjects (2/23; 9%) in the DTG arm had emergent NRTI-resistance substitutions compared to 12 subjects (12/48; 25%) in the RAL arm. Two subject's isolates (9%) on a PI-containing regimen had emergent PI resistance substitutions in the DTG arm of this study compared to 19% (9/48) in the RAL arm. However, 3 subjects (3/23; 13%) in the DTG arm taking a background NNRTI had emergent NNRTI resistance substitutions [2 subjects were taking efavirenz (EFV)] compared to 3 subjects (3/48; 6%) with emergent NNRTI resistance substitutions in the RAL arm. One subject in the RAL arm also had emergent CXCR4-tropic virus at failure on maraviroc (MVC). The 21 subjects' isolates in the RAL arm with emergent INSTI resistance substitutions all had RAL phenotypic resistance and 7 (33%) of the RAL-resistant subject isolates were cross-resistant to DTG (≥ 2 -fold change in DTG susceptibility)

1. RECOMMENDATIONS

1.1. Recommendation and Conclusion on Approvability

This NDA for a fixed dose combination tablet of dolutegravir (DTG; TIVICAY), an integrase strand transfer inhibitor (INSTI), and nucleoside analog reverse transcriptase inhibitors abacavir and lamivudine is approvable with respect to virology as a complete regimen for the treatment of HIV-1 infection.

1.2. Recommendation on Phase IV (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

There are no virology recommendations for Phase IV commitments or requirements.

2. ADMINISTRATIVE

2.1. Reviewer's Signature

[Lisa K. Naeger, Ph.D.]
Sr. Virologist, HFD-530

2.2 Concurrence

HFD-530/Micro TL _____ Date _____

3. CLINICAL VIROLOGY

ING113086 (SPRING-2)

Treatment-Naive 96 Week Results: DTG 50 mg once daily compared to RAL 400 mg twice daily both administered with fixed-dose dual NRTI therapy

Protocol-defined virology failure (PDVF) in this study was defined as two consecutive HIV-1 RNA values ≥ 50 copies/mL HIV-1 RNA on or after Week 24), which mandated withdrawal from the trial (if confirmed before Week 48) and testing for resistance. There were fewer subjects with PDVF in the DTG treatment group than in the RAL treatment group. In the DTG treatment group, 5% of subjects (n=19) met the definition of PDVF while 7% of (n=30) subjects in the RAL treatment group met the definition of PDVF (Table 1).

In the submitted resistance dataset for Study ING113086, there were 24 subjects in the DTG arm and 33 subjects in the RAL arm. The majority of subjects in the Study ING113086 resistance dataset had low-level viremia at the failure timepoint (HIV-1 RNA viral loads ≥ 50 copies and ≤ 400 copies/mL at the failure timepoint (Table 1). Forty-two percent (n=8) of the sponsor's PDVF in the DTG arm were on ABC/LAM. This was comparable to the 40% of PDVFs on ABC/LAM in the RAL arm.

Table 1. Disposition of Virologic Failures in SPRING-2

	DTG 50 mg QD N=411	RAL 400 mg BID N=411
Subjects in Resistance Dataset	24	33
Subjects on ABC/LAM	10 (42%)	12 (36%)
HIV-1 RNA at failure timepoint		
<50 copies/mL	2	
≥ 50 to ≤ 400 copies/mL	16	27
>400 copies/mL	6	6
Sponsor PDVF Subjects	19	30
Sponsor PDVF Subjects on ABC/LAM	8 (42%)	12 (40%)
FDA-Defined Failures	1 (#3999)	9

For the FDA virologic failure analysis, in order to take into account “blips” observed in the viral load assay, the virologic failure “rebound” criteria were modified to “confirmed >400 copies/mL after confirmed suppression to <50 copies/mL” or evidence of resistance emergence. The 6 subjects with >400 copies/mL in the DTG arm are listed in Table 2, but only one (Subject 3999) had confirmed >400 copies/mL and was considered a virologic failure in the FDA analysis.

Table 2. Listing of Subjects with >400 copies/mL in the DTG arm

Subjects with >400 copies/mL at failure (n=6)	ARM	Viral Load	Genotype
3015	DTG/ABC LAM	Week 48 Viral load >400 then <50 then >1000 at Week	Week 60: P90P/S

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		60 then <400; not confirmed >400	
3093	DTG/ABC LAM	Week 24 >1000 then <50; not confirmed	
3296	DTG/FTC TDF	Week 32 >400 then <400; not confirmed	
3734	DTG/ABC LAM	Week 72 >400 then <400; not confirmed	
3999	DTG/FTC TDF	Week 32 >10,000 then 632; confirmed	A21T from mixture at BL
4335	DTG/ABC LAM	Week 40 >400 then <400 at Week 48; not confirmed	M50M/V

There was 1 FDA-defined virologic failures in the DTG arm (Subject 3999) and 9 FDA-defined virologic failures in the RAL arm (Subjects 3073, 3173, 3617, 3864, 4130, 4314, 4316, 4424, and 4640) (Table 3). In the DTG arm, Subject 4335 had VL>400 copies/mL at Week 40 but was not confirmed >400 copies/mL and resuppressed at Week 48. This subject had an emergent substitution (M50M/V) in IN at Week 24 (Table 3). One subject (Subject 4424) in the RAL arm had <400 copies/mL at Week 24, but also had emergent substitutions at Week 24, so this subject was included in the FDA virologic failure analysis. Subjects 3864 and 4640 in the RAL arm are included in the FDA-defined Failures, but not in the sponsor's PDVF.

Table 3. Genotypic or Phenotypic Evidence of Resistance in Study ING113086

PID	Arm	Failure Week	Baseline INSTI Subst	Emergent INSTI Subst	Emergent RT Subst	Emergent PI Subst	Phenotype Changes
3999	DTG TDF/ FTC	Week 32		A21T	None	None	None
4335*	DTG LAM/ ABC	Week 40	L74I	M50M/V	None	None	None
3073	RAL TDF/ FTC	Week 32		None	None	None	None
3617	RAL TDF/ FTC	Week 24		T97T/A S119S/R E138E/D V151V/I N155H D232D/N	A62A/V K65K/R K70K/E M184V		LAM-R FTC-R ABC-R RAL-R (34X) DTG 2.2X
3864	RAL TDF/ FTC	Week 8		--	None	None	--
4130	RAL TDF/ FTC	Week 24		--	None	None	None
4314	RAL LAM/ ABC	Week 24		R20K L74I (BL)			

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4316	RAL LAM/ ABC	Week 24		No BL; V37I M50I I60V T122I V113I E157Q K160Q A205S K211R V234L N254S S255G	Q102K		0.82 RAL
4640	RAL LAM/ ABC	Week 24		--	None	None	FTC 1.6 LAM 1.38
3173 [#]	RAL TDF/ FTC	Week 24 (52 copies/mL)		D167E R284G	M184M/I V189V/I		FTC 1.64
4424 [#]	RAL LAM/ ABC/	Week 24	L74L/I G193I/V	L74I S81S/R T125A V176L G193V K211R	E44E/K M184M/V		LAM-R FTC-R ABC 2.6X RAL 1.49

Bolded substitutions are INSTI-, NRTI- or NNRTI-resistance associated substitutions.

* Subject 4335 had VL>400 copies/mL at Week 40 but not confirmed >400 copies/mL; resuppressed at Week 48
[#]VL=<400 copies/mL at Week 24 but had emergent substitutions at Week 24

No subjects in the DTG 50 mg once daily treatment arms of Study ING113086 had a detectable decrease in phenotypic susceptibility to DTG or background NRTIs in the resistance analysis subset (n=1 with >400 copies/mL HIV-1 RNA at Week 32). In the comparator arm, 3 subjects on the RAL treatment regimen had emergent INSTI resistance substitutions in their viral isolates and 4 had emergent NRTI substitutions associated with the background NRTIs (Table 4). Two subjects also have evidence of phenotypic resistance to RAL and the NRTIs.

Table 4. Study ING113086

	DTG 50 mg QD	RAL 400 mg BID
FDA-Defined Failures	1	9
Subjects with Emergent INSTI Substitutions in FDA-Defined Failures	0	3
Subjects with Emergent NRTI Substitutions	0	4
Subjects with Phenotypic Resistance at Failure in FDA-Defined Failures	0	2

^a Subjects 3999 (Subject 4335 had VL>400 copies/mL at Week 40 but not confirmed >400 copies/mL; resuppressed at Week 48)

^b Subjects 3073, 3617, 3864, 4130, 4314, 4316, 4424, and 4640

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ING114467 (SINGLE)

Treatment-Naïve 96 Week Results: DTG 50 mg once daily plus ABC/LAM fixed dose combination (FDC) compared to fixed-dose dual EFV/FTC/TDF (Atripla)

In the submitted 96 Week resistance dataset for Study ING114467, there were 31 subjects in the DTG arm and 32 subjects in the Atripla arm. In both the DTG and Atripla treatment arm, 25 subjects (6%) met the definition of PDVF (Table 5). The majority of subjects in the Study ING114467 resistance dataset had low-level viremia (had HIV-1 RNA viral loads ≥ 50 copies and ≤ 400 copies/mL at the failure timepoint) at the failure timepoint: 71% (22/31) of subjects in the DTG arm and 63% (20/32) in the Atripla arm (Table 5). Based on the FDA criteria for virologic failure analysis at Week 96, there were 8 subjects (1.9%) in the DTG arm and 13 subjects (3%) in the Atripla arm with confirmed >400 copies/mL HIV RNA at the failure timepoint or resistance data at failure.

Subjects 5141, 5233, 5910, 5920, 6926, 6934, 7856 and 7912 in the DTG arm were analyzed for emergent substitutions in the FDA resistance analysis. Subject 7912 had an emergent INSTI substitution E157Q/P in addition to substitutions K173K/E and K266K/R at Week 24 with no change in DTG susceptibility (fold-change = 1.1). Subject 6926 had emergent G193D from a mixture of G193G/D/E at baseline, but no change in DTG susceptibility (fold-change = 1.1). None of these subjects had emergent NRTI-resistance associated substitutions in RT (Table 5 and 6). In the comparator Atripla arm, 8 subjects had emergent EFV resistance substitutions of which 6 had corresponding EFV phenotypic resistance (Table 5 and 6). One of these subjects also had emergent mixtures of NRTI resistance substitutions with no change in TDF or FTC susceptibility.

Table 5. Study ING114467 RESISTANCE ANALYSIS

	DTG/ABC/LAM N=414	ATRIPLA N=419
Subjects in Resistance Dataset	31	32
Subjects with PDVF (sponsor)	25	25
HIV-1 RNA at failure timepoint/resistance analysis timepoint		
<50 copies/mL	0	1
≥ 50 to ≤ 400 copies/mL	22	20
>400 copies/mL	9	11
FDA-Resistance Analysis Set (>400 copies/mL or resistance data at failure)	8 ^a (2%)	13 ^c (3%)
Subjects with Post BL IN	7	
Subjects with Emergent INSTI-Resistance Substitutions	1 ^b (13%)	--
Subjects with Post BL RT	8	13
Subjects with Emergent NNRTI-Resistance Substitutions	--	8 (62%)
Subjects with Emergent NRTI – Resistance Substitutions	0	1 (8%)

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Subjects with Phenotypic Resistance at Failure	0	6 (46%)
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^a Subjects 5141, 5233, 5910, 5920, 6926, 6934, 7856, 7912

^b Subject 7912 (E157Q/P)

^c Subjects 5441, 5506, 5576, 5772, 6033, 6084, 6186, 6707, 6856, 6886, 6921, 6924, 7817

Table 6. Genotypic and Phenotypic Changes in FDA Resistance Analysis of Study ING114467

PID	ARM	Week of Failure Timept	Baseline RT Subst	Emerging RT Subst	Baseline INSTI Subst and BL Phenotype	Emerging INSTI Subst	Phenotypic Fold Change at Failure
5141	DTG	Week 84	K101R		L74L/M/I G163E		DTG 0.93
5233	DTG	WK24 FU	S68G			A128A/V	DTG 1.0
5910	DTG	WK84			No BL	M50I V72I G106A	DTG 0.97
5920	DTG	WK72				S153S/A I200I/M I204I/L	DTG 0.86
6926	DTG	WK84			G193G/D/E	G193D	DTG 1.1
6934	DTG	WK24		W88W/R	V72I G193E	--	--
7856	DTG	WK84	S68G V106I	E42E/K I50I/V V90V/I G190G/E D237D/N	V72I D167D/E	D167E S283G	DTG 0.79
7912	DTG	WK24	E138G	Q91Q/R E138A	V72I L74L/V E157Q	E157Q/P K173K/E K266K/R	DTG 1.1
5541	Atripla	WK24					
5506	Atripla	WK48	A98P	K101E			EFV 1.9X (2.5X from BL)
5576	Atripla	WK32		K103K/N I178I/M	NA	NA	EFV-R 14X
5772	Atripla	WK24 FU	TDF-R (1.6)		NA	NA	
6033	Atripla	WK24	A98S	V35V/I K103N G190G/A			EFV-R 22X
6084	Atripla	WK96	G196G/E	I178M V189I			
6186	Atripla	WK24	K43R				
6707	Atripla	WK24		K65K/R D67D/G G190G/E Q197Q/R			TDF 0.7 FTC 1.3

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6856	Atripla	WK24	K103R	V179V/D G190G/A L264L/S			EFV-R 20X
6886	Atripla	WK48		V90V/I K103N C162S A272P			EFV-R 18X
6921	Atripla	WK60	K43K/R V118I	K103K/N			EFV-R 12X
6924	Atripla	WK60	K104R				
7817	Atripla	WK72	S68G I135R	K103N I135K			EFV-R 11X

ING114915 FLAMINGO

Treatment Naïve Randomized Open-label trial comparing DTG 50 mg QD vs. DRV/r QE with Epzicom or Truvada as background: 48 week analysis

The primary analysis demonstrated that DTG is non-inferior to DRV+RTV for the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 based on the FDA snapshot algorithm. Differences in virologic response rates between DTG and DRV+RTV were primarily driven by discontinuations due to AEs (DTG 1%, DRV+RTV 4%) and other reasons (DTG 2%, DRV+RTV 5%) prior to Week 48. The proportion of virologic nonresponders by the FDA “snapshot” algorithm though Week 48 was 6% in the DTG group and 7% in the DRV+RTV group, while 4% of subjects in the DTG treatment group and 10% in the DRV+RTV treatment group were considered virologic non-responders due to lack of virologic data at Week 48 (Table 7). Superiority of DTG versus DRV+RTV was then considered as per the pre-specified criteria. The lower end of the 95% CI for the treatment difference from the primary analysis (+0.9%) is above 0% and hence superiority of DTG is concluded.

Table 7. ING114915 FLAMINGO Week 48 Outcome, Snapshot Analysis

Outcome	Week 48	
	DTG QD N= 242	DRV/r QD N=242
Virologic Success (HIV RNA <50 copies/mL)	217 (90)	200 (83)
Virologic Non-response (HIV RNA ≥ 50 copies/mL)	15 (6)	18 (7)
Data in window not below threshold	6 (2)	11 (5)
Discontinued for lack of efficacy	1 (<1)	1 (<1)
Discontinued for other reason while not below threshold	3 (1)	5 (2)
Change in ART	5 (2)	1 (<1)
No Virologic Data	10 (4)	24 (10)

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Discontinued due to AE or Death	3 (1)	9 (4)
Discontinued for Other Reasons	6 (2)	11 (5)
Missing data during window but on study	1 (<1)	4 (2)

The PDVF criteria in the FLAMINGO trial was confirmed HIV-1 RNA >200 copies/mL at or after Week 24. There were 4 subjects that met criteria for PDVF and were included in the resistance dataset: 2 in the DTG arm (both had TDF/FTC as backbone) and 2 in the DRV/r arm (both had ABC/3TC as backbone). Genotype and phenotype for integrase were obtained at Baseline and at the time of PDVF for each subject who met PDVF. None of the subjects had treatment-emergent resistance substitutions in integrase or phenotypic resistance to DTG. No subjects had treatment-emergent primary resistance substitutions in RT or PR.

Table 8. Resistance Analysis of Protocol-Defined Virologic Failures in FLAMINGO

PID	Arm	Failure Week	Viral Load at Failure (copies/mL)	Emergent IN substitutions	Emergent PR/RT substitutions	Phenotype at Failure
468702	DTG	Week 24	668	S17N L28L/P	PR: V77V/I RT: L173K/E	DTG: 0.86
476401	DRV/r	Week 48	218		RT: E40D I167T	DRV: 0.22
476808	DRV/r	Week 36	61754		PR: I72I/V	DRV: 1.1
485805	DTG	Week 24	2270			DTG: 0.97

ING111762 (SAILING)

Treatment-Experienced INSTI-Naïve Week 48 Results: DTG 50 mg once daily (354 subjects) or RAL 400 mg twice daily (361 subjects), each added to an investigator selected background regimen consisting of one fully active single agent plus no more than one second single agent which may or may not have been active.

At Week 48, 71% of subjects receiving DTG and 64% of subjects receiving RAL achieved the primary endpoint the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 based on the outcomes of the FDA “Snapshot” algorithm. The study demonstrated non-inferiority of DTG versus RAL and statistical superiority was concluded as part of a pre-specified testing procedure. This finding was primarily driven by virologic outcomes: more subjects on RAL had ‘data within the window not <50 copies/mL’ (DTG: 10%; RAL: 13%) and discontinuations due to lack of efficacy (DTG: 5%; RAL: 10%).

Protocol-defined virological failure was defined as the following:

Virologic Non-response

- A decrease in plasma HIV-1 RNA of less than 1 log₁₀ copies/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 copies/mL.
- Confirmed plasma HIV-1 RNA levels ≥400 copies/mL on or after Week 24.

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Virologic Rebound

- Confirmed rebound in plasma HIV-1 RNA levels to ≥ 400 copies/mL after prior confirmed suppression to < 400 copies/mL.
- Confirmed plasma HIV-1 RNA levels $> 1 \log_{10}$ copies/mL above the nadir value where nadir is the lowest HIV-1 RNA value ≥ 400 copies/mL.

Virologic failure through Week 48 occurred earlier and more frequently in the RAL arm. At Week 24, there were 14 (4%) confirmed virologic failures for the DTG arm and 34 (9%) for the RAL arm. The difference through Week 24 was driven by a greater proportion of protocol-defined virologic non-response in the RAL arm 5% versus $< 1\%$ in the DTG arm, with a similar proportion of virologic rebound in both arms (4%). Between Week 32 and Week 48 there were no additional PDVFs in the DTG arm, and 6 additional PDVFs in the RAL arm, resulting at Week 48 in 21 (6%) and 45 (12%) cumulative virologic failures for DTG and RAL respectively.

The Week 48 PDVF Genotypic and Phenotypic populations were used for analysis of genotype and phenotype and changes from Baseline (Day 1) in genotype and phenotype at the time of protocol defined virologic failure. Integrase, RT and PR genotypes and phenotypes were attempted at Baseline and time of PVDF for all subjects with PDVF, while CCR5 co-receptor antagonist (maraviroc) and fusion inhibitor (T20; enfuvirtide) data was generated for subjects who included those antiretroviral agents in their background regimen.

In the submitted 48 Week resistance dataset for Study ING111762, there were 106 subjects in the DTG arm and 132 subjects in the RAL arm (Table 9). The proportion of subjects with lack of protocol-defined efficacy was 8% (27/357) in the DTG arm and 13% (46/362) in the RAL arm. Based on the FDA criteria for virologic failure analysis at Week 48 (confirmed > 400 copies/mL or resistance data at failure), there were 37 subjects (10%) in the DTG arm and 60 subjects (17%) in the RAL arm (Table 9). The majority of these subjects had post-baseline resistance data: 81% in the DTG arm and 92% in the RAL arm. Not all subjects had both IN and RT/PR resistance data.

In the DTG arm, 6 subjects (21%) had detectable emergent INSTI substitutions (L74L/M/I, Q95Q/L, T97A, E138A/T, V151V/I, R263K) (Table 10). Five of the six subjects in the DTG arm who had failure isolates with emergent INSTI substitutions had a < 2 -fold change in DTG susceptibility. However, subject isolate 9402 which had INSTI substitutions E138A, G140S and Q148H at baseline had a change in DTG susceptibility from 12-fold at baseline to 148-fold at Week 16 with the emergence of E138T/A and T97A. All subject isolates (5/6; 83%) except Subject 9402 had no cross-resistance with RAL. Subject 9402 had 110-fold reduced susceptibility to RAL at baseline with the presence of E138A, G140S and Q148H.

In comparison, in the RAL arm, there were 21 subject isolates (43%) with emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E, and G163K/R) and/or emergent phenotypic RAL resistance (≥ 1.5 -fold) (Table 9 and 11). Seven (33%) of the RAL resistant subject isolates were cross-resistant to DTG (≥ 2 -fold reduction in DTG susceptibility) (Subjects 260, 384, 785, 963, 2426, 2427 and 2769).

Overall, the proportion of subjects with emergent resistance substitutions to a background drug was lower in the DTG arm compared to the RAL arm. In the DTG arm, a total of 7 subjects (30%) had emergent RT or PR resistance substitutions and/or emergent phenotypic resistance to a background drug compared to a total of 23 subjects (48%) with emergent RT or PR

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resistance substitutions and/or phenotypic resistance to a background drug in the RAL arm (Table 9 and Appendix A). Additionally, one subject (Subject 977) in the RAL arm had a tropism switch from CCR5-tropic virus to CXCR4-tropic virus on MVC. When comparing the emergent substitutions to a class of drugs, a lower proportion of NRTI and PI resistance substitutions emerged in the DTG arm compared to the RAL arm (9% DTG vs. 25% RAL with emergent NRTI resistance-associated substitutions and/or phenotypic resistance; 9% DTG vs. 19% RAL with PI resistance-associated substitutions and/or phenotypic resistance) (Table 9). However, 3 subjects (13%) in the DTG arm had emergent NNRTI resistance-associated substitutions compared to 3 subjects (6%) with in the RAL arm. The addition of EFV as the background drug in a DTG regimen was primarily associated with this increase in emergent NNRTI substitutions (2 of the 3 had EFV in the regimen and the other had FPV) (Table 10).

Table 9. ING111762 RESISTANCE ANALYSIS (Week 48)

	DTG 50 mg once daily (N=357)	RAL 400 mg twice daily (N=362)
Failure Subjects in Dataset	106 (30%)	132 (36%)
Subjects with Lack of Efficacy	27 (8%)	46 (13%)
FDA-Defined Resistance Analysis Set (>400 copies/mL or resistance data at failure)	37 (10%)	60 (17%)
With Post-Baseline Data	30 (81%)	55 (92%)
INSTI Post-Baseline Data	28	49
Emergent INSTI Resistance Substitutions and/or phenotypic resistance	6 ^a (21%)	21 ^b (43%)
RT/PR Post- Baseline Data	23	48
Emergent NRTI-Resistance Substitutions and/or Phenotypic Resistance	2 ^c (9%)	12 (25%)
Emergent NNRTI-Resistance Substitutions and/or Phenotypic Resistance	3 ^d (13%)	3 (6%)
Emergent PI-Resistance Substitutions and/or Phenotypic Resistance	2 ^e (9%)	9 (19%)
Total Subjects with Emergent RT/PR Substitutions to a Background Drug	7 (30%)	23 (48%)
MVC Resistance		1 (2%)

^aSubjects 351, **672**, 1067, **2568**, **2785** and **9402** (emergent substitutions L74L/M/I, Q95Q/L, T97A, E138A/T, V151V/I, R263K) (bolded subject IDs were also reported by the sponsor)

^bSubjects 260, 384, 419, 785, 946, 963, 977, 1077, 1146, 2214, 2426, 2427, 2457, 2472, 2688, 2734, 2769, 9013, 9088, 9479 and 9981 (substitutions at L74, E92, Q95, T97, G140, Y143, Q148, V151, N155, E157, G163)

^cSubjects 121 (K219E) and 2516 (V75L)

^dSubjects 1113, 2568, 2785 (121, 941, 2141, and 9174 had emergent NNRTI substitutions but had no NNRTI in background regimen)

^eSubjects 9402 and 9978

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Table 10. SAILING: DTG FDA-Defined Resistance Subjects with Post-Baseline Data

PID	Backgrd Drugs	Week of Failure Timept	Baseline PR/RT Subst	Emerging PR/RT Subst	Baseline INSTI Subst and BL Phenotype	Emerging INSTI Subst	Fold Change at Failure
121	ATV/r TDF	WK32	RT: T69T/N K70K/R A98A/G V118V/I Y181Y/C K219K/E L228L/H PR: M36I V82A	V118I Y181C K219E L228H D237D/N	V72I F181L ATV: 1.3 DTG: 1.0 TDF: 0.95		TDF: 0.9 DTG: 1.0
262	MVC TDF	WK16	PR: A71V V77I RT: V179D/E	No Post BL	DTG: 0.9 TDF: 1.28		DTG: 0.81 TDF: - -
292	DRV/r ddl	WK32	PR: L33V R57K I72V RT: M41L K65N S68S/G/R K70K/R K103N V108V/I Y181Y/C T215S K219K/R	RT: K82K/R Q197Q/E S251S/N	M50I V72I		
296	DRV/r TDF	WK84	PR: I15V M36I RT: L74I K103N M184V P225H			No Post BL	
351	ATV/R FTC TDF	WK4	RT: K103N V118I	No Post BL	G163E DTG: 0.88 TDF: 1.38	S17S/N V32V/I G70G/R L74L/M/I	DTG: 0.88 (1.0X from BL)
672	DRV/R TDF	WK16	PR: P15I/V M36I A71A/T RT: L100L/I K103K/N M184M/I/V	PR: P15V	DTG: 0.96	R263R/K	DTG: 1.12 (1.2X from BL)
941	ATV/R TDF	WK12	PR: M36I RT: M41L K43K/Q D67D/G K70K/E K101Q K103N M184V	RT: K101Q/P	L74I DTG:0.91 TDF: 0.81	K188K/R T206T/S A265A/V	DTG: 0.92

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			P225P/H				
1067	DRV/R TDF	WK16	PR: V77V/I RT: T69N K70K/R G196E	RT: E28E/A	G163E DTG: 0.85 TDF: 0.88	Q95Q/L	DTG: 0.84 (1.0X from BL)
1113	FPV/r TDF	WK12	PR: M36I RT: V60I K103N V179V/D M184M/I/V Y188Y/F/H/ L P225P/H	RT: R72R/K V106V/I R143R/K E203E/K H208H/Y	DTG:0.5 FPV: 0.91 TDF:0.53		FPV: 0.83
1977	ATV/r TDF	WK32	RT: K103K/N V108V/I M184M/V T215N/S/Y		V72I		
2141	DRV/R TDF	WK16	RT:L74L/I/V K101E/Q V106V/I M184V G190S	PR:E35E/D I72I/T RT:K104N	DTG:1.1 DRV:1.6 TDF:0.57		DTG: 1.0
2467	ATV/R LAM	WK8	PR: M36I L89M RT: L74V K101E V106V/I V108I Y181C M184V G190S K219K/E	NO POST BL	L74I DTG: 1.03 LAM: 83		DTG: 0.96
2516	LPV/R AZT	WK16	PR: V77I RT: K65K/R V75V/L K103N V108I M184V Q207E/G M230M/L	RT: K43K/E/Q V75L K287K/R	E138D DTG: 1.3 AZT: 0.27		DTG: 1.3 AZT: 0.18
2568	EFV TDF	WK24	PR: L10F M36I M46I I54V H69K A71V L76V V82A L89M RT: M41L S48S/T D67N K101E V118V/I M184V G196T Q207E L210W	RT:C162C/ S G190S Q197K	DTG: 0.92 EFV: 1.5 TDF-R: 3.4	V260I R263K	DTG: 1.93 (2.1X from BL) EFV-R: 136 TDF-R: 2.9

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			T215Y				
2591	LPV/r AZT	WK48	PR: I15I/V L89M RT: D67D/N S68S/N K70K/R A98A/G K101K/E V106V/M V179V/I M184M/V G190A/S K219K/E	PR: I15V RT: G190A	AZT: 5.1	A23A/V K258K/R	AZT: 0.89
2618	DRV/R TDF	WK16	PR: M36I R57K G68E RT: K103K/N M184M/V G190G/A		DTG: NO BL TDF: 0.79 DRV: 1.2	M154I (no BL IN)	DTG: 0.91 TDF: 1.0 DRV: 1.1
2785	EFV ABC	WK24	PR: V77V/I RT: V75V/L K103R V179I	RT: R83R/K K101K/E K103R/S D123D/N V179V/D/I/N G190A	L101I/V DTG: 0.94 ABC: 1.1 EFV: 0.7	L101I V151V/I	DTG: 0.92 (1.0X from BL) ABC: 1.2 EFV-R: 105
2812	LPV/R AZT	WK16	PR: M36I R57K RT: K65R S68N L74V K103N Y115F M184M/V		T97A G163R DTG: 0.49 LPV: 1.4 AZT: 0.5	NO POST BL	DTG:-- LPV: 1.8 AZT: 0.31
2920	DRV/R ABC	WK16	PR: M36I L89M RT: K65R S68S/G V90V/I V179I Y181C M184I Q207E K219K/E M230L	NO POST BL	DTG: 1.3 DRV: 0.62 ABC: 4.1	D270N D288QNME	DTG: 1.3
9046	LPV/R	WK8	PR: M36I RT: T69T/N L100I K103N M184V T215T/F/S/I P225P/H	H96L	G163A DTG: 0.8 LPV: 0.7		DTG: 0.8 LPV: 0.91
9068	LPV/r	WK12	PR: M36I V77I L89M	NO POST BL	L74I DTG: 0.9	R199K	DTG: 0.9

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					LPV: 0.9		
9072	LPV/r	WK32	PR: L10I M36I L89M RT: D67N A98S K103R V106M E138E/A V179D M184V K219K/R			V31V/I	DTG: 0.68
9080	EFV TDF	WK24	RT: K103N M184V P225H		DTG:0.85 EFV-R: 63 TDF: 0.7	E10E/D V31V/I C280C/R	DTG:0.8 EFV-R (BL): 88 TDF:0.7
9103	LPV/r	WK12	PR: M36I L89M RT: V90V/I K103N M184V	RT: I94I/L	L74I DTG: 0.6 LPV: 0.9	K188K/R V260V/E	DTG: 0.7 LPV: 0.6
9174	LPV/r	WK48	PR: M36I V77I V82V/I L89M RT: K104R V106M V179D M184V F227F/L M230M/L	RT: K103K/N	V31V/I	V31I	DTG: 0.94
9402	ATV/R TDF	WK16	PR: L10I I15V L33F M36I M46I I50V F53L V82A L89M RT: M41L D67E S68G V75M V118I M184V L210W T215Y	PR: V32V/I I50L	ATV: 4.1 TDF: 2.5 DTG:0.83 E138A G140S Q148H	L63L/I T97A E138T/A	DTG-R (148X) RAL-R ATV-R: 162x TDF-R: 1.6X
9978	DRV/R TDF	WK32	PR: I15V L33F M36I I50L G73G/S T74A V82I L89V L90M RT: K43K/R D67N T69T/N K70R K103Q M184V K219Q	PR: G73S RT: K43R	DRV: 3.1 TDF: 1.2	R20R/K	DTG: 1.1 TDF 0.9
9983	ATV/R	WK2	RT: T69T/N	NO POST	T97A	L45Q V77A	DTG:

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	TDF		K103N V108V/I M184V V189V/I	BL			0.9
9990	ATV/R TDF	WK24	PR: I15V M36I V77I RT: D67N V75I K103N V108I M184V G196E P243P/L	PR: N37N/S RT: M184M/I/V	ATV: 0.7 TDF: 0.8 M50M/I	M50M/I/R	DTG: 0.6

Bolded Subject numbers had INSTI emergent substitutions.

Table 11. ING111762 (SAILING): RAL FDA-Defined Resistance Subjects with Post-Baseline Data

PID	Backgrd Drugs	Week of Failure Timept	BL PSS	Emerging PR/RT Subst	Baseline INSTI Substitutions	Emerging INSTI Substitutions	Fold Change at Failure
004	DRV/R TDF	WK16	2			V79V/I K211K/T	
260	ABC TDF	WK16	2	RT: K70K/R V179D/N T215F M230M/L	L74I/M E138D Y143R	V79V/I E138E/D G140A Y143Y/C Q148Q/R E157E/Q	ABC: 2.4X RAL-R (BL) TDF-R: 1.4X DTG-R (18X)
294	fAPV TDF	WK24	2	V60V/I			
384	DRV/R TDF	WK48	2	NO POST BL		E92E/Q N155H	RAL-R DTG (2.3X)
419	FTC TDF	WK24	1	A71A/T	G163E	L74L/M T97T/A V151I N155H G163K	FTC-R RAL-R
492	ABC DRV/R	WK12	2	RT: L210S T215V	T97T/A	K240K/R	
587	ATV/R TDF	WK16	2				
588	DRV/R TDF	WK24	2			I217I/V K266K/R	
655	FTC TDF	WK8	2		G163S		
785	FTC TDF ETR LPV/r	WK40	2	PR: M36I M46L/V		G140S Q148H	RAL-R DTG-R (4.4X)
793	ATV/R LAM	WK16	2		G163E		
946	DRV/R TDF	WK32	2		K156N	N155N/H	
947	DRV ETR	WK8	1		G163E		ETR-R (BL)
963	TDF TPV/R	WK24	2	PR: M36I M46L/V		G140S Q148H	RAL-R TPV-R

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							DTG-R (4.1X)
976	fAPV TDF	WK12	2	H69H/R	G193G/R		
977	MVC AZT	WK 32	2			Y143Y/C N155N/H G163G/R F181F/L	RAL-R DTG (1.25X) MVC-R
1077	DRV/R MVC	WK40	2	G196G/E		N155N/H	RAL (1.2X)
1128	DRV/R TDF	WK16	1			A91A/T	
1146	FTC MVC	WK16	0			T97A Y143R D253E	RAL-R FTC-R (BL) DTG (1.3X)
1909	LPV/R TDF	WK16	2	L74L/I F227F/L			
1914	DRV/R TDF	WK40	1	T215T/A/I/V			TDF-R
1982	fAPV TDF	WK48	2				TDF-R
2201	DRV/R ETR	WK24	2	RT: M41M/L K101K/E M184M/V V179V/I Y181Y/C H208H/Y T215T/F/I/S K219K/E M230M/L	L74I		ETR-R
2214	FTC TDF	WK40	2	K103N V179E M184V P225H		E138E/Q Q148Q/R	FTC-R RAL-R (2.3X)
2360	DRV/R ETR	WK16	2	RT: E138E/K Y181Y/C			ETR-R
2425	LAM ABC	WK16	2		L74I		
2426	LAM ABC	WK48	2		L74I/L	L74I T97T/A N155H	RAL-R DTG (2X)
2427	LAM ABC	WK24	1	RT: E138E/K Y181Y/C	L74I	Q95Q/R N155H H171H/R	RAL-R LAM-R (BL) ABC-R (BL) DTG (2.1X)
2430	ABC D4T	WK4	2		L74I		
2457	LAM ABC	WK24	1	L74L/V V75V/I L210L/V	L74I	T97T/A Y143Y/N/R/S/ K/C N222N/T	LAM-R ABC-R RAL-R
2472	AZT LAM	WK16	1	RT: T215I	L74I	L63L/V V75V/I Y143Y/R/H/C Q148Q/R I257I/T	RAL-R LAM-R (BL) DTG (0.9X)
2495	DRV/R TDF	WK24	2	T69A V108I		NO POST BL IN	

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2513	LPV/R AZT	WK8	2	NO POST BL			
2518	LPV/R TDF	WK40	2	NO POST BL			
2571	LPV/R	WK16	1	RT: T69A		V150V/A	
2600	DRV/R ETV	WK48	1				
2632	ETV LPV/R	WK24	2	RT: Y181Y/C		NO POST BL IN	
2688	ATV/R TDF	WK24	2	RT: L74L/I K103K/E Y115F G190A		N155N/H	RAL (1.4X) DTG (0.9X)
2727	ATV/R LAM	WK16	2	I15V I72I/T V82I K101E Y181C			
2734	fAPV LAM	WK16	2		V151I		RAL-R (1.6X)
2765	ATV/R TDF	WK16	0	M46I I84V		NO POST BL IN	NO POST BL
2766	ATV/R TDF	WK16	2				
2769	ATV/R TDF	WK16	1	PR: M46I I84V		E92E/Q T97T/A V151V/I N155H	RAL-R ATV-R (BL) DTG-R (3.7X)
2835	ATV/R TDF	WK32	2		G163E	V260V/G	
2851	TDF AZT	WK16	2		L74I		
9013	LPV/R	WK60	1			G134G/D N155H I204I/V	RAL-R
9014	LPV/R	WK40	1			D278D/N	
9048	LPV/R	WK12	1	PR: L10D/F/V L33F K55K/R V77V/I	G163Q		
9071	LPV/R	WK12	1			I72V/I	
9088	LPV/R	WK24	1	PR: V77V/I	L74I	N155N/H	RAL-R DTG (1.4X)
9125	DRV/R MVC	WK24	2	V108VI		NO POST BL IN	
9415	LPV/R TDF	WK16	1	N37S M46I I54V V77I V82A		NO POST BL IN	LPV-R
9461	fAPV TDF	WK24	2	F53F/S		NO POST BL IN	TDF-R FPV-R
9479	LAM ABC	WK48	1		L74I	N155H A175A/V E198E/K K240K/T	RAL-R LAM-R
9981	ATV/R TDF	WK32	2	PR: M46I I54V V82A L89I RT: K103N	K173K/R	N155H A173K	RAL-R

Subjects 260, 384, 785, 963, 2426, 2427 and 2769 were cross-resistant to DTG (≥ 2 -fold).

4 CONCLUSION

Dolutegravir (DTG) in a fixed-dose combination with ABC/LAM is approvable with respect to virology for the treatment of HIV-1 in combination with other antiretrovirals in patients who are susceptible to each component of this fixed-dose combination.

In support of this indication, the sponsor submitted updated Week 96 results from the phase 3 treatment-naïve studies (SPRING-2 [ING113086] and SINGLE [ING114467]) and updated Week 48 data from the phase 3 treatment-experienced INSTI-naïve study (SAILING [ING111762]). The updated Week 96 and Week 48 results did not significantly change the conclusions from the clinical virology review of the original NDA.

5 Sponsor Proposed Package Insert

12.4 Microbiology

Mechanism of Action: Dolutegravir: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV 1 integrase and pre-processed substrate DNA resulted in IC₅₀ values of 2.7 nM and 12.6 nM.

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV TP), an analogue of deoxyguanosine 5' triphosphate (dGTP). (b) (4)

(b) (4) CBV TP inhibits the activity of HIV 1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. (b) (4)

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC TP). (b) (4)

(b) (4) The principal mode of action of 3TC TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue. (b) (4)

Antiviral Activity in Cell Culture: Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV 1 with mean concentration of drug necessary to effect viral replication by 50 percent (EC₅₀) values of 0.5 nM (0.21 ng/mL) to 2.1 nM (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC₅₀ of (b) (4) in a viral susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV 1 clinical isolates (b) (4)

(b) (4) Dolutegravir EC₅₀ values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Abacavir: The antiviral activity of abacavir against HIV 1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC₅₀ values ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV 1IIB and HIV 1BaL, respectively and was 0.26 ± 0.18 μM against 8 clinical isolates. The EC₅₀ values of abacavir (b) (4)

(b) (4)

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Lamivudine: The antiviral activity of lamivudine against HIV 1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 μ M (1 μ M = 0.23 mcg/mL). (b) (4)

[Redacted]

Antiviral Activity in Combination With Other Antiviral Agents:

[Redacted] (b) (4)

[Redacted] (b) (4)

Resistance in Cell Culture: Dolutegravir: Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV 1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Abacavir and Lamivudine: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT. (b) (4)

[Redacted]

combinations of three substitutions were required to confer more than an 8-fold (b) (4) in susceptibility.

[Redacted] (b) (4)

(b) (4)

Cross Resistance: Dolutegravir:

(b) (4)

Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Abacavir and Lamivudine: Cross resistance has been observed among NRTIs. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

6 FDA Proposed Package Insert

12.4 Microbiology

Mechanism of Action

Dolutegravir: Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV 1 integrase and pre-processed substrate DNA resulted in IC₅₀ values of 2.7 nM and 12.6 nM.

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate (CBV-TP), an analogue of deoxyguanosine 5' triphosphate (dGTP). CBV-TP inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by chain termination after its incorporation into viral DNA.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The

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principal mode of action of 3TC-TP is inhibition of RT via DNA chain termination after incorporation of the nucleotide analogue.

Antiviral Activity in Cell Culture

Dolutegravir: Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV 1 with mean concentration of drug necessary to effect viral replication by 50 percent (EC_{50}) values of 0.5 nM (0.21 ng/mL) to 2.1 nM (0.85 ng/mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with respective mean and median EC_{50} values of 0.52 and 0.54 nM (range: 0.41 to 0.60 nM) in a viral susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (n = 3 each for clades A-G and group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against three HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Abacavir: The antiviral activity of abacavir against HIV 1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC_{50} values ranged from 3.7 to 5.8 μ M (1 μ M = 0.28 mcg/mL) and 0.07 to 1.0 μ M against HIV-1IIB and HIV-1BaL, respectively, and was 0.26 ± 0.18 μ M against 8 clinical isolates. The EC_{50} values of abacavir 746 against different HIV-1 clades (A-G; n = 3 except n = 2 for clade B) ranged from 0.0015 to 1.05 μ M, and against HIV-2 isolates (n = 4), from 0.024 to 0.49 μ M.

Lamivudine: The antiviral activity of lamivudine against HIV 1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC_{50} values were in the range of 0.003 to 15 μ M (1 μ M = 0.23 mcg/mL). The EC_{50} values of lamivudine against different HIV-1 clades (A-G; n = 3 except n = 2 for clade B) ranged from 0.001 to 0.120 μ M, and against HIV-2 isolates (n = 4) from 0.003 to 0.120 μ M in PBMCs.

Antiviral Activity in Combination With Other Antiviral Agents: Neither dolutegravir, abacavir, nor lamivudine were antagonistic to all tested anti-HIV agents. See full prescribing information for ZIAGEN (abacavir), TIVICAY (dolutegravir), and EPIVIR (lamivudine).

Resistance in Cell Culture: *Dolutegravir:* Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV 1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold.

Abacavir and Lamivudine: HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT. The substitution at M184I or V causes high-level resistance to lamivudine and approximately two-fold decreased susceptibility to abacavir. Additional substitutions K65R, L74M, or Y115F conferred a 7- fold to 8-fold reductions in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reductions in susceptibility.

Resistance In Clinical Subjects: No subjects in the dolutegravir treatment arms of treatment-naïve trials SPRING-2 (dolutegravir + EPZICOM or dolutegravir + TRUVADA) and SINGLE (dolutegravir + EPZICOM) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 9) with HIV-1 RNA >400 copies/mL at failure or last visit through Week 96 and having resistance data). One subject in SINGLE with 275 copies/mL HIV-1 RNA in treatment-naïve trials SPRING-2 (dolutegravir + EPZICOM or dolutegravir + TRUVADA) and SINGLE (dolutegravir + EPZICOM) had a treatment-emergent INSTI-resistance substitution (E157Q/P) detected at Week 24, but no corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was isolated in the dolutegravir arm in the SINGLE trial.

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Cross Resistance: *Dolutegravir*. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a >2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Abacavir and Lamivudine: Cross resistance has been observed among NRTIs. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

6 APPENDIX

APPENDIX A. PIDs of Subjects with Emerging Substitutions/Resistance in SAILING

Emerging INSTI Substitutions in SAILING

DTG arm (n=6)

351, 672, 1067, 2568, 2785 and 9402

RAL arm (n=21)

260, 384, 419, 785, 946, 963, 977, 1077, 1146, 2214, 2426, 2427, 2457, 2472, 2688, 2734, 2769, 9013, 9088, 9479, 9981

Emerging NRTI Substitutions in SAILING

DTG arm (n=2)

121 (K219E), 2516 (V75L)

RAL arm (n=12)

260
492
1909
1914
2214
2427
2457
2472
2495
2571
2688
9461

Emerging NNRTI Substitutions in SAILING

DTG arm (n=3)

1113, 2568, 2785

RAL arm (n=3)

2201, 2360, 2632

Emerging PI Substitutions in SAILING

DTG arm (n=2)

9402, 9978

RAL arm (n=9)

785
963
2727
2765
2769
9048
9415
9461
9981

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/s/

LISA K NAEGER
08/06/2014

JULIAN J O REAR
08/06/2014

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 17 March 2014

TO: NDA 205551

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/NDMS

THROUGH: John Metcalfe, Ph.D.
Senior Review Microbiologist
CDER/OPS/NDMS

cc: Sohail Mosaddegh
CDER/OND/OAP/DAVP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for dolutegravir/abacavir sulfate/lamivudine (Proposed: TRIUMEQ) [Submission Date: 22 October 2013]

The microbial limits specification for dolutegravir/abacavir sulfate/lamivudine is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Dolutegravir/abacavir sulfate/lamivudine is a film-coated tablet for oral administration.

The manufacturing process involves (b) (4) and (b) (4) of components, as well as film coating of the (b) (4) tablets. The applicant describes a microbiological control strategy for drug product manufacturing, which (b) (4)

(b) (4) The drug substances (lamivudine, abacavir sulfate, and dolutegravir sodium) are manufactured using (b) (4) and result in final products with (b) (4) (b) (4), therefore are considered to be a low microbiological risk. The application contains microbial limits testing and (b) (4) from four batches (lamivudine and abacavir) or three batches (dolutegravir) demonstrating adequate microbial limits and (b) (4).

(b) (4)

MEMORANDUM

performed, with specifications of total aerobic microbial count (TAMC) not greater than (b) (4) CFU/g, total yeast and mold count (TYMC) not greater than (b) (4) CFU/g, and the absence of *Escherichia coli* per gram. Microbiological testing is performed according to methods described in USP <61> and USP <62>. Method verification testing was described in the application. (b) (4)

The application contains 12 months of stability data from three batches of drug product, and stability testing is ongoing. Microbial limits and (b) (4) are performed on batches held under long-term storage conditions (both 25°C/60% RH and 30°C/75% RH) at 0, 12, 24, 36, 48, and 60 months. All product tested to date has met acceptance criteria, which are the same as acceptance criteria for product release. The applicant does not propose microbial limits or (b) (4) as part of the post-approval stability protocol.

74-Day Letter Information Request

Your application provides a suitable approach and justification for microbial limits testing using a (b) (4) strategy. However, changes in drug product release specifications must be made by submitting a supplemental application for a post-approval manufacturing change. For your NDA, you should revise your list of release specifications to omit the footnote listed as Note #7, and plan to submit a supplemental application if you wish to remove the (b) (4)/microbial limits test from release specifications after 30 batches. For more information on post-approval changes, see FDA's Guidance for Industry: Changes to an Approved NDA or ANDA (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf>).

14 March 2014 Response

The applicant provided an updated list of specifications with the footnote removed.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol. The applicant provides suitable information on manufacturing process controls and product release testing to support the omission of microbiological testing for product stability.

END

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/s/

ERIKA A PFEILER
03/17/2014

JOHN W METCALFE
03/17/2014
I concur.

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 205551

Applicant: ViiV Healthcare

Stamp Date: 10/22/13

Drug Name: dolutegravir

NDA Type: Original

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	x		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	x		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	x		
4	On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	x		
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			na
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?			na
7	Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	x		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	x		standardized
9	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	x		
10	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	x		
11	Have all the study reports, published articles, and other references been included and cross-referenced in the	x		

File name: 5_Microbiology Filing Checklist for a NDA or Supplement 010908

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	annotated draft labeling or summary section of the submission?			
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

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

No review issues.

Lisa K. Naeger

12/17/13

Reviewing Microbiologist

Date

Jules O'Rear

12/17/13

Microbiology Team Leader

Date

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/s/

LISA K NAEGER
12/17/2013

JULIAN J O REAR
12/17/2013

PRODUCT QUALITY MICROBIOLOGY NON-STERILE DRUG PRODUCT FILING CHECKLIST

NDA Number: 205551 **Applicant:** ViiV Healthcare Company **Letter Date:** 22 OCT 2013
Drug Name: TRIUMEQ (proposed) **NDA Type:** 505(b)(1) **Stamp Date:** 22 OCT 2013
Dosage Form: Tablet **Reviewer:** Erika Pfeiler, Ph.D.

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		See Additional Comments.
4	Has the applicant submitted the results of analytical method verification studies?	X		
5	Has the applicant submitted preservative effectiveness studies (if applicable)?			N/A
6	Is this NDA fileable? If not, then describe why.	X		

Additional Comments:

(b) (4)

performed, with specifications of total aerobic microbial count (TAMC) not greater than (b) (4) CFU/g, total yeast and mold count (TYMC) not greater than (b) (4) CFU/g, and the absence of *Escherichia coli* per gram. This, along with microbiological process controls described in the application, is an adequate approach to release testing; however, the proposed specification table states that testing will only be performed on the first 30 batches of drug product, with no routine testing of this type to occur after production of 30 batches. An information request will be sent to the applicant to request revision of the release specifications.

Product Quality Microbiology Information Request:

Your application provides a suitable approach and justification for microbial limits testing using a (b) (4) strategy. However, changes in drug product release specifications must be made by

submitting a supplemental application for a post-approval manufacturing change. For your NDA, you should revise your list of release specifications to omit the footnote listed as Note #7, and plan to submit a supplemental application if you wish to remove the (b) (4)/microbial limits test from release specifications after 30 batches. For more information on post-approval changes, see FDA's Guidance for Industry: Changes to an Approved NDA or ANDA (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf>).

Erika Pfeiler, Ph.D. Date
Microbiologist

John Metcalfe, Ph.D. Date
Senior Review Microbiologist

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/s/

ERIKA A PFEILER
12/11/2013

JOHN W METCALFE
12/11/2013
I concur.