CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204790Orig1s000

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
ADDENDUM VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 07/10/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

NDA#: 204,790 **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

Initial Submission Dates:

Correspondence Date:	12/17/2012
CDER Receipt Date:	12/17/2012
Assigned Date:	12/17/2012
Review Complete Date:	05/17/2013
PDUFA Date:	08/17/2013

Amendments:

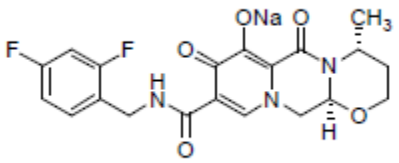
SDN	Date Submitted	Date Received	Date Assigned
007	02/22/2013	02/22/2013	02/25/2013
012	03/29/2013	03/29/2013	04/01/2013
026	05/06/2013	05/06/2013	05/06/2013
029	05/21/2013	05/21/2013	05/22/2013
031	06/03/2013	06/03/2013	06/03/2013
036	07/08/2013	07/09/2013	07/11/2013

Related/Supporting Documents: IND75382

Product Name(s)
Proprietary: TIVICAY
Non-Proprietary/USAN: dolutegravir
Code Name/Number: GSK1349572A

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

Molecular Weight: 441.36 g/mol (dolutegravir sodium)
Molecular Formula: $C_{20}H_{18}F_2N_3NaO_5$
Structural Formula:



Dolutegravir (DTG)

Dosage Form(s): tablet

Reference ID: 3339417

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
ADDENDUM VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 07/10/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

Route(s) of Administration: Oral
Indication(s): Integrase strand transfer inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients aged 12 years and older.

Dispensed: Rx

Abbreviations: ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BL, baseline; DRV, darunavir; DTG, dolutegravir; EC_{50}, effective concentration at 50%; EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; EVG, elvitegravir; FC, fold-change; FTC, emtricitabine; HSA, human serum albumin; IC_{50}, 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;

TABLE OF CONTENTS

Executive Summary*……....*Page 3

Correspondence with Sponsor*…….……....*Page 8

Final FDA-Negotiated Package Insert*……*Page 18

Appendices

Appendix A*…… *Page 22
Appendix B*…… *Page 23
Appendix C*……*Page 24
Appendix D*……*Page 28
Appendix E*……*Page 31
Appendix F*…….. *Page 34
Appendix G*……*Page 37

Reference ID: 3339417

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
ADDENDUM VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 07/10/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

EXECUTIVE SUMMARY

This addendum to the original NDA review of TIVICAY (dolutegravir; DTG) documents the labeling negotiations with the applicant and shows the final changes to the label.

The following modifications were made to the original review based on correspondence and negotiations with the sponsor. Correspondence with the sponsor regarding *Section 12.4 Microbiology* is documented.

ING111762 (SAILING)

Treatment-Experienced INSTI-Naïve Week 24 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.

Of the 33 subjects in the DTG FDA resistance analysis set, 18 had post-baseline resistance data; 15 (instead of 16) with INSTI post-baseline resistance data.

Table 25. ING111762 RESISTANCE ANALYSIS

	DTG 50 mg once daily (N=357)	**RAL 400 mg twice daily (N=362)**
PDVF FAILURES	76 (21%)	110 (30%)
FDA-Defined Resistance Analysis Set (>400 copies/mL or resistance data at failure)	33 (9%)	49 (14%)
With Post Baseline Data	18 (5%)	38 (10%)
INSTI Post BL Data	15	32
Emergent INSTI Resistance Substitutions and/or phenotypic resistance	5[a] (33%)	9[b] (28%)
RT/PR Post BL Data	13	34
Emergent NRTI-Resistance Substitutions	1 (8%) (V75L)	7 (21%)
Emergent NNRTI-Resistance Substitutions	4 (31%) NOTE: EFV	4 (12%)
Emergent PI-Resistance Substitutions	0	5 (15%)

[a]Subjects 351, 672, 1067, 2568, and 2785 (substitutions at L74, Q95, T97, E138, V151, G163, R263)
[b]Subjects 260, 419, (removed 785 and 977) , 963, 1146, 2427, added 2472, 2688, 2769 and 9088 (substitutions at L74, E92, T97, G140, Y143, Q148, V151, N155, G163)

Five subjects [Subjects 351, 672, 1067, 2568, and 2785] in the DTG arm had emergent INSTI substitutions (L74M and I, Q95Q/L, (removed T97A) V151V/I, and R263K) (Table 26). None of these subjects' isolates had emergent DTG or RAL phenotypic resistance.

One subject failure isolate (Subject 2516 on DTG, LPV/r and AZT) had a V75L resistance substitution emerge in RT from a mixture (V75V/L) at baseline (V75I is a multidrug resistant

Reference ID: 3339417

substitution IAS-USA 2013]. Four subjects taking a background NNRTI had emergent NNRTI resistance substitutions. Two of these subjects were taking EFV; Subject 2568 had a failure isolate with emergent G190S and 136-fold resistance to EFV and Subject 2785 had a failure isolate with emergent K101K/E and G190A and 105-fold resistance to EFV. Subject 1113 was taking FPV/r, but had emergent V106V/I and Subject 941 was taking ATV/r but had emergent K101Q/P from K101Q at baseline. Subject 9080 had EFV resistance (63-fold) at baseline but was assigned a DTG, EFV and TDF regimen and had 88-fold resistance to EFV at failure without resistance to DTG or TDF.

Table 26. ING111762 (SAILING): DTG FDA-Defined Resistance Subjects with Post-Baseline Data (n=15)

PID	Backgrd Drugs	Week of Failure Timept	Baseline PR/RT Subst	Emerging PR/RT Subst	Baseline INSTI Substitutions and BL Phenotype	Emerging INSTI Subst	Fold Change at Failure
262	MVC TDF	WK16	PR: A71V V77I RT: V179D/E	No Post BL	DTG: 0.9 TDF: 1.28		DTG: 0.81
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 P225P/H	RT: **K101Q/P**	L74I DTG:0.91 TDF: 0.81	K188K/R T206T/S A265A/V	DTG: 0.92
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	No post BL	FPV: 0.83
2141	DRV/R TDF	WK16	RT:L74L/I/V K101E/Q	PR:E35E/D I72I/T	DTG:1.1 DRV:1.6		DTG: 1.0

			V106V/I M184V G190S	RT:K104N	TDF:0.57		
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 T215Y	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
2618	DRV/R TDF	WK24	PR: M36I R57K G68E RT: K103K/N M184M/V G190G/A		DTG: NO BL TDF: 0.79 DRV: 1.2	M154I (no BL IN genotype or phenotype)	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		T97A G163R DTG: 0.49 LPV: 1.4	NO POST BL	DTG:-- LPV: 1.8 AZT:

Reference ID: 3339417

			S68N L74V K103N Y115F M184M/V		AZT: 0.5		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 D288QNM E	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 LPV: 0.9	R199K	DTG: 0.9
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
9402	ATV/R TDF	WK16	PR: L10I I15V L33F M36I M46I I50V F53L V82A L89M RT: M41L D67E S68G V75M V118I M184V L210W T215Y	NO POST BL	ATV: 4.1 TDF: 2.5 DTG:--	No IN data	DTG:--
9412	LPV/R TDF	WK24	PR: M36I L89M RT: K104K/R	NO POST BL	LPV: 1.6 TDF: 1.2	No IN data	DTG:--
9990	ATV/R TDF	WK24	PR: I15V M36I V77I RT: D67N V75I K103N	NO POST BL	ATV: 0.7 TDF: 0.8	No IN data	DTG:--

Reference ID: 3339417

			V108I M184V G196E P243P/L				

Bolded Subject numbers had INSTI emergent substitutions.

Of the 49 subjects in the RAL arm of the FDA resistance analysis set, 38 had post-baseline resistance data; 35 with INSTI post-baseline resistance data and 34 subjects with RT/PR post-baseline resistance data. Nine (instead of 10) subjects (29%) [Subjects 260, 419, (removed 789 and 977), 963, 1146, 2427, added 2472, 2688, 2769 and 9088] in the RAL arm had emergent INSTI substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E/Q and G163G/R) (Table 27). All 9 of these subjects had RAL phenotypic resistance, and of these, 5 (45%) isolates had DTG phenotypic resistance (≥2-fold change from reference in DTG susceptibility). In the RAL arm, 12% (4/34) had emergent NNRTI resistance substitutions, 18% (6/34) of subjects had failure isolates with emergent NRTI resistance substitutions, and 15% (5/34) had emergent PI resistance substitutions (Table 27).

Table 27. ING111762 (SAILING): RAL FDA-Defined Resistance Subjects with Post-Baseline Data and Emergent INSTI-Substitutions in Failures

PID	BKGRD DRUGS	FAILURE WEEK	BL PSS	EMERGING INSTI SUBSTITUTIONS	EMERGING RT/PI SUBSTITUTIONS	PHENO Fold-Change
260	ABC TDF	WK16	2	I60I/M, **L68L/V,** V79V/I, **G140A, Y143Y/C, Q148Q/R, E157E/Q**	RT: K70K/R M230M/L	RAL-R (BL) TDF-R **DTG-R (18X)**
419	FTC TDF	WK24	1	**L74L/M T97T/A V151I N155H G163K**	PR: A71A/T	RAL-R FTC-R (BL) DTG (1.89X)
492	ABC DRV/R	WK12	2	K240K/R	RT: L210S T215V	
785	FTCTDF	WK40	2	**G140S Q148H**		RAL-R **DTG-R (4.4X)**
947	DRV ETR	WK8	1			ETR-R (BL)
963	TDF TPV/R	WK24	2	**G140S Q148H**	PR: M36I M46L/V	RAL-R TPV-R **DTG-R (4.1X)**
977	MVC AZT	WK 32	2	**Y143Y/C N155N/H G163G/R F181F/L**		RAL-R DTG (1.25X)
1146	FTC MVC	WK16	0	**T97A Y143R** D253E		RAL-R FTC-R (BL) DTG (1.3X)
2201	DRV/R ETR	WK24	2		RT: M41M/L K101K/E M184M/V V179V/I Y181Y/C H208H/Y T215T/F/I/S	ETR-R

					K219K/E M230M/L	
2360	DRV/R ETR	WK16	2		RT: E138E/K Y181Y/C	ETR-R (BL)
2427	LAM ABC	WK24	1	**Q95Q/R N155H** H171H/R	RT: T215I	RAL-R LAM-R (BL) **DTG (2.1X)**
2472	AZT LAM	WK16	1	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		RT: T69A	
2571	LPV/R	WK16	1	V150V/A	RT: L74L/I K103K/E Y115F G190A	
2688	ATV/R TDF	WK24	2	**N155N/H**		RAL (1.4X) DTG (0.9X)
2765	ATV/R TDF	WK16	0		PR: M46I I84V	NO POST BL
2769	ATV/R TDF	WK16	1	**E92E/Q T97T/A** **V151V/I N155H**	PR: L10D/F/V L33F K55K/R	RAL-R ATV-R (BL) **DTG-R** **(3.7X)**
9048	LPV/R	WK12	1		PR: V77V/I	
9088	LPV/R	WK24	1	**N155N/H**		RAL-R DTG (1.4X)

Bolded Subject numbers had INSTI emergent substitutions.

CORRESPONDENCE 1

FDA VIROLOGY RESPONSE MAY 23, 2013

Emergent Substitutions in ING111762 (SAILING)

1. The FDA concludes substitutions L74M and I should be included as emergent substitutions in integrase. These substitutions when present at baseline are associated with decreased responses of 50-59% at Week 24 in the VIKING 3 study and also emerged in two subjects in VIKING3 (585 and 1206). We have revised text to more clearly state that these substitutions did not have detectable changes in DTG susceptibility.
2. Agree that Subject 0672 being a confirmed PDVF)
3. We conclude that changes at position Q95 have been associated with resistance to INSTI and that any substitution at this position including Q95E/Q should be reported.
4. Agree. that Subject 2568 being a confirmed PDVF)
5. We have resistance data from this subject at Week 16 at which time the subject was also failing treatment with a high viral load. The FDA concludes that this substitution should be reported as it emerged on failing treatment at an integrase position of interest.
6. We agree to remove substitution T97A.

INCLUSION/EXCLUSION OF SAILING RESISTANCE DATA:
The following DTG subjects had IN post-baseline resistance data in the Week 24 analysis:

FDA DTG RESISTANCE ANALYSIS SET WITH POST BASELINE IN DATA IN ING111762 (n=15) (we agree to removal of Subject 2618)
ING111762.0000262
ING111762.0000351
ING111762.0000672
ING111762.0000941
ING111762.0001067
ING111762.0002141
ING111762.0002467
ING111762.0002516
ING111762.0002568
ING111762.0002785
ING111762.0002920
ING111762.0009046
ING111762.0009068
ING111762.0009080
ING111762.0009103

The following RAL subjects had IN post-baseline resistance data in the Week 24 analysis:
FDA RAL RESISTANCE ANALYSIS SET WITH POST-BASELINE DATA IN ING111762 (n= 32)
ING111762.0000004
ING111762.0000260
ING111762.0000294
ING111762.0000419
ING111762.0000492
ING111762.0000587
ING111762.0000588
ING111762.0000655
ING111762.0000793
ING111762.0000947
ING111762.0000963
ING111762.0000976
ING111762.0001128
ING111762.0001146
ING111762.0001909
ING111762.0002201
ING111762.0002360
ING111762.0002425
ING111762.0002427
ING111762.0002430
ING111762.0002472
ING111762.0002513
ING111762.0002571
ING111762.0002688

Reference ID: 3339417

ING111762.0002727
ING111762.0002734
ING111762.0002766
ING111762.0002769
ING111762.0002851
ING111762.0009048
ING111762.0009071
ING111762.0009088

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT INSTI RESISTANCE SUBSTITUTIONS AND/OR PHENOTYPIC RESISTANCE (n=9)
Subjects 260, 419, 963, 1146, 2427, 2472, 2688, 2769 and 9088 (substitutions at L74, E92, T97, G140, Y143, Q148, V151, N155, G163)

We propose the following revised wording for the SAILING resistance information in section 12.4. We believe this revised wording addresses concerns about the DTG resistance substitutions.

The highlighted substitutions that emerged in the RAL arm may be included if the applicant would find that information beneficial for the comparison of DTG and RAL emergent substitutions.

Treatment-Experienced, Integrase Strand Transfer Inhibitor (INSTI)-Naive Subjects:
In [redacted] (b) (4) viruses from 5 of 15 [redacted] (b) (4) subjects with post-baseline resistance data had evidence of treatment-emergent integrase substitutions (L74M or I, Q95Q/L, V151V/I, and R263K) [redacted] (b) (4) none of these subjects' isolates had detectable phenotypic decreases in susceptibility to either dolutegravir or raltegravir. In the comparator raltegravir arm, 9 of 32 [redacted] (b) (4) subjects with post-baseline resistance data had evidence of emergent INSTI resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E/Q and G163G/R) and raltegravir phenotypic resistance.

VIKING-3
We maintain that the Week 24 baseline outcome analysis is most informative to physicians and clinicians because it shows the durability of DTG in an ARV regimen. The potency of DTG as functional monotherapy at Day 8 is conveyed in Section 14 by describing the primary efficacy endpoint results.

We have reviewed your response regarding the denominator for the Week 24 baseline outcome analysis. We do not agree with the use of the predetermined n=114 dataset with a planned cutoff date. The NDA submission included additional subjects' data which can and should be used to display the best representation of Week 24 response rates based on baseline genotypic and phenotypic criteria at this time. We do not believe there is bias in using all available data provided at NDA submission. In fact, we point out that of the 16 subjects you would like to exclude, 11 had Week 24 data and 9 were virologic successes. We agree to include Subject 10 (the rationale being the same for including Subject 15). We agree to exclude Subjects 1806 and 1964 because they were suppressed at early termination.

Reference ID: 3339417

We propose the following Subjects are included in the Week 24 analysis for both response by baseline genotypic and phenotypic analyses (n=124).

ING112574.0000001
ING112574.0000002
ING112574.0000003
ING112574.0000004
ING112574.0000007
ING112574.0000008
ING112574.0000010
ING112574.0000015
ING112574.0000021
ING112574.0000022
ING112574.0000024
ING112574.0000102
ING112574.0000103
ING112574.0000181
ING112574.0000182
ING112574.0000221
ING112574.0000222
ING112574.0000227
ING112574.0000228
ING112574.0000261
ING112574.0000301
ING112574.0000302
ING112574.0000343
ING112574.0000345
ING112574.0000381
ING112574.0000403
ING112574.0000462
ING112574.0000481
ING112574.0000483
ING112574.0000504
ING112574.0000507
ING112574.0000544
ING112574.0000545
ING112574.0000561
ING112574.0000562
ING112574.0000565
ING112574.0000566
ING112574.0000567
ING112574.0000569
ING112574.0000570
ING112574.0000582
ING112574.0000651
ING112574.0000663
ING112574.0000804
ING112574.0001001
ING112574.0001002
ING112574.0001004

Reference ID: 3339417

ING112574.0001006
ING112574.0001007
ING112574.0001008
ING112574.0001009
ING112574.0001011
ING112574.0001012
ING112574.0001013
ING112574.0001021
ING112574.0001026
ING112574.0001031
ING112574.0001036
ING112574.0001038
ING112574.0001041
ING112574.0001046
ING112574.0001048
ING112574.0001049
ING112574.0001051
ING112574.0001055
ING112574.0001056
ING112574.0001057
ING112574.0001061
ING112574.0001063
ING112574.0001066
ING112574.0001067
ING112574.0001090
ING112574.0001201
ING112574.0001202
ING112574.0001203
ING112574.0001205
ING112574.0001206
ING112574.0001208
ING112574.0001209
ING112574.0001210
ING112574.0001212
ING112574.0001213
ING112574.0001214
ING112574.0001215
ING112574.0001216
ING112574.0001217
ING112574.0001219
ING112574.0001221
ING112574.0001233
ING112574.0001234
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001263
ING112574.0001264
ING112574.0001271

ING112574.0001272
ING112574.0001273
ING112574.0001274
ING112574.0001401
ING112574.0001402
ING112574.0001403
ING112574.0001481
ING112574.0001601
ING112574.0001611
ING112574.0001612
ING112574.0001616
ING112574.0001802
ING112574.0001821
ING112574.0001841
ING112574.0001842
ING112574.0001843
ING112574.0001844
ING112574.0001861
ING112574.0001862
ING112574.0001901
ING112574.0001902
ING112574.0001961
ING112574.0001962
ING112574.0001982
ING112574.0001983
ING112574.0002001
ING112574.0002021
ING112574.0002063

Response to DAVP Labeling Comments of May 14 and May 24, 2013
NDA 204,790

Section 12.4 Microbiology

(b) (4)

Reference ID: 3339417

(b) (4)

- For the treatment-emergent INSTI substitutions observed for the SAILING study, we do not support the inclusion of the L74M or I substitution. Position 74 in IN is highly polymorphic; 13% of INI-naïve subjects have M or I at that position. Genotypic testing is standard practice prior to initiation of antiretroviral therapy; IN testing is increasingly provided in addition to standard RT/PRO sequencing. If L74M/I is included in the label as a treatment-emergent substitution, we are concerned that prescribers would interpret the presence of L74M/I in an INI-naïve subject as transmitted resistance, and would either not treat with DTG or treat with the wrong dose (ie, 50 mg twice daily as for INSTI resistance subjects); we see this as a risk regardless of language pointing out that this substitution alone is not associated with decreased phenotypic susceptibility in the label. The inclusion of L74M/I as a treatment-emergent substitution in the SAILING study in the USPI would also result in inclusion of this polymorphism broadly in DTG resistance algorithms, which we believe is not appropriate. Additional points are as follows:
  - Given that the L74M/I substitution is present in ~13% of isolates, we know that it is present in a large number of DTG phase 3 subjects at baseline. If it were indeed involved in resistance, we would expect to find far more subjects with emergent L74M or L74I substitutions and/or a high proportion of subjects who fail with L74M or L74I at baseline.
  - The L74M/I substitution was observed in only one subject in the INI-naïve studies; this was observed without other associated mutations in this subject, with only Day 1 HIV-1 RNA and Week 4 HIV-1 RNA measures, and without opportunity to meet any PDVF criteria.
  - We acknowledge the impact of L74M as a key secondary substitution in the setting of Q148 pathway mutations in the INI-resistant population (VIKING-3), but maintain that this is a different situation from treatment-emergent resistance in SAILING.
- From our VIKING 3 data set, Subject 585 had L74I/M present at Day 1 along with a substantial number of other RAL resistance mutations (L74I/M, T97T/A, E138E/K, G140G/A, S147S/G, Q148R, V151V/I/M); at PDVF the L74I was no longer present but L74M was present with G140A, Q148R. VIKING 3 Subject 1206 had no observed L74I or M or other prespecified resistance at Day 1, but at post baseline revealed a mixture at L74 (L74L/M) and substitutions at 4 other IN prespecified positions (T97T/A, E138E/K, G140S, Q148H). This reflects its well-characterized position as a RAL secondary resistance mutation.
- The FDA noted that "when present at baseline L74M and I are associated with decreased responses of 50% at Week 24 (n=125 subset) in the VIKING 3 study compared to the 63% overall response rate." We note that subjects with low response in this group do not have L74I or L74M alone, rather, they are present in the context of RAL resistance. The L74 substitutions are observed as secondary substitutions to RAL primary mutation upon extended therapy, and reflect the accumulation of substitutions which associate with higher DTG FCs.
  - The L74M substitution emerged in cell culture selection experiments, but only when the starting virus had RAL resistance substitutions (specifically, when the starting virus was a Q148H/G140S double mutant). This is consistent with its position as a

secondary resistance mutation rather than a primary DTG-associated resistance mutation.

- In conclusion, we believe that we have clearly described in the label the role that L74M plays in modulating resistance in subjects with baseline INI resistance (specifically, in subjects with Q148 pathway mutations at baseline). We do not believe it is appropriate, however, to suggest that L74M/I is a treatment-emergent substitution for subjects who do not have pre-existing resistance at baseline, and thus request that this substitution not be included for the SAILING population.

CORRESPONDENCE 2

FDA VIROLOGY RESPONSE: JUNE 6, 2013

Mechanism of Action: IC_{50} is used for biochemical assays.

(b) (4)

Treatment-Experienced, Integrase INSTI-Naive Subjects

- We have reviewed your response regarding the L74I/M substitution. The FDA concludes substitutions L74M and I should be included as emergent substitutions in integrase for this study. It is an important integrase substitution associated with resistance to INSTIs and emerged in cell culture selection experiments and in clinical trials.
- The sentence (b) (4) was removed because clinical team did not find it helpful (b) (4) Consideration will be given to including a similar statement for the treatment-naïve studies.

Integrase INSTI-experienced Subjects

After reviewing, consideration and discussion, we do not think the text provided (b) (4) provides any information that will be helpful to physicians treating patients with DTG. The Week 24 baseline outcome analysis is most informative to physicians and clinicians.

Response by Baseline Genotype: Additional rows have been added in Table 10 to further elucidate different response rates for baseline substitution patterns that were seen in VIKING-3. Footnotes have been added to clearly show which substitutions were included in each subgroup. The population N=124 was used for these analyses.

VERSION 2: JUNE 6, 2013

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an INSTI in Study ING112574 (VIKING-3)

Baseline Genotype	Response at Week 24

(b) (4)

Response by Baseline Phenotype: The population N=120 was used for these analyses because these were the subjects with available phenotypic data (note screening data was used in the absence of baseline data). After further analysis and consideration, a <3-fold change in DTG susceptibility at baseline was determined to most accurately show where response rates were better than the overall response rate based on the following results:

Baseline Dolutegravir Phenotype (Fold change from Reference)	Response at Week 24 (<50 copies/mL) Subset N=120
2 to 3	83% 5/6
3 to 4	33% 2/6

The results from fold change values between 3 and 4 support <3 and 3-<10 subgroups.

Cross-Resistance: We do not agree to add the (b) (4) section because this general information does not provide useful information for physicians (b) (4)

TABLE 10 NEGOTIATIONS

VERSION 2: JUNE 6, 2013

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an INSTI in Study ING112574 (VIKING-3)

Baseline Genotype	**Response at Week 24 (<50 copies/mL)**

(b) (4)

[redacted]

VERSION 3: JUNE 17, 2013

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an INSTI in Study ING112574 (VIKING-3)

(b) (4)

[redacted]

VERSION 4: July 1, 2013

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an INSTI in Study ING112574 (VIKING-3)

Baseline Genotype	Response at Week 24 (<50 copies/mL) Subset N=124
Overall Response	64% (79/124)
N155H without a Q148 substitution	80% (16/20)
Y143C/H/R without a Q148 substitution	56% (10/18)
Q148H/R + G140A/S without additional INSTI-resistance substitutions	56% (10/18)
Q148H/R + ≥2 INSTI-resistance substitutions[a,b]	18% (3/17)

[a]INSTI-resistance substitutions include L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R
[b]The most common pathway with Q148H/R+≥2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n=12)

FINAL FDA-NEGOTIATED PACKAGE INSERT

INDICATIONS AND USAGE

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients aged 12 years and older and weighing ≥at least 40 kg.

The following should be considered when initiating TIVICAY:

- Poor virologic response was observed in subjects treated with TIVICAY 50 mg twice daily with an INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions including L74I/M/, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R. *(See Microbiology 12.4).*

Table 1. Dosing Recommendations for TIVICAY in Adult Patients

Population	Recommended Dose
Treatment-naïve or treatment-experienced, INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced, INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
(b) (4)	50 mg twice daily

12.1 Mechanism of Action

Dolutegravir is an HIV antiviral agent *[see Microbiology (12.4)].*

12.4 Microbiology

Mechanism of Action:

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture:

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng/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 EC_{50} of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G and 3 group O) with EC_{50} values ranging

from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents:
The antiviral activity of dolutegravir was not antagonistic when combined with the integrase strand transfer inhibitor (INSTI) raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir or stavudine; the protease inhibitors (PIs) amprenavir or lopinavir; the CCR5 co-receptor antagonist maraviroc or the fusion inhibitor enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or with the antiviral, ribavirin.

Resistance
Cell Culture:
Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.
Treatment-Naïve Subjects:
No subjects in the dolutegravir 50 mg once daily treatment arms of treatment-naïve Studies ING113086 (SPRING-2) and ING114467 (SINGLE) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n=6 with HIV-1 RNA >400 copies/mL at failure or last visit through Week 48 and having resistance data). One additional subject in Study ING114467 with 275 copies/mL HIV-1 RNA had a treatment emergent INSTI-resistance substitution, (E157/P/Q), 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 either the SPRING-2 or SINGLE trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor (INSTI)-Naive Subjects:
In [redacted] (b) (4) viruses from 5 of 15 [redacted] (b) (4) subjects with post-baseline resistance data had evidence of treatment-emergent integrase substitutions (1 subject each with L74M/I, Q95Q/L, or V151V/I, and 2 subjects with R263K). However, none of these subjects' isolates had detectable phenotypic decreases in susceptibility to either dolutegravir or raltegravir. In the comparator raltegravir arm, 9of 32 [redacted] (b) (4) subjects with post-baseline resistance data had evidence of emergent INSTI resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148H/R, V151I, N155H, E157E/Q and G163G/R)and raltegravir phenotypic resistance.

Integrase Strand Transfer Inhibitor (INSTI)-Experienced Subjects:
[redacted] (b) (4) (VIKING-3) examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI (elvitegravir or raltegravir)-containing regimen.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed using a subset of subjects who had reached Week 24, as well as those who discontinued or rebounded before Week 24 (n=124) (See Table 10). The response rate at Week 24 for subjects with only historic evidence of INSTI-resistance at baseline was 75% (33/44). The response rate at Week 24 to dolutegravir-containing regimens was 36% (13/36) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI-resistance substitutions. Diminished virologic responses (25% [7/28]) were observed when ≥3 of the following INSTI-resistance substitutions were present at baseline; L74I/M, E138AD/K/T, G140A/S, Y143H/R, Q148H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an INSTI in (b) (4) (VIKING-3)

Baseline Genotype	Response at Week 24 (<50 copies/mL) Subset N=124
Overall Response	64% (79/124)
N155H without a Q148 substitution	80% (16/20)
Y143C/H/R without a Q148 substitution	56% (10/18)
Q148H/R + G140A/S without additional INSTI-resistance substitutions	56% (10/18)
Q148H/R + ≥2 INSTI-resistance substitutions[a,b]	18% (3/17)

[a]INSTI-resistance substitutions include L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R
[b]The most common pathway with Q148H/R+≥2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n=12)

Response by Baseline Phenotype
Response rates by baseline phenotype were analyzed using a subset of subjects who had reached Week 24 and had phenotypic data, as well as those who discontinued, or rebounded before Week 24 (n = 120) (See Table 11). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table 11. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Exposure to an INSTI in (b) (4) (VIKING-3)

Baseline Dolutegravir Phenotype (Fold change from Reference)	Response at Week 24 (<50 copies/mL) Subset N=120

Overall Response	63% (75/120)
<3-fold change	72% (63/87)
3 - <10-fold change	42% (10/24)
≥10-fold change	22% (2/9)

INSTI Treatment-Emergent Resistance
There were 40 subjects on the dolutegravir twice daily regimen in [redacted] (b) (4) with HIV-1 RNA >400 copies/mL at Week 24, the failure timepoint or the last timepoint on study who were included in the Week 24 resistance analysis set. In the Week 24 resistance analysis set, 45% (18/40) of the subjects had treatment emergent INSTI-resistance substitutions in their isolates. The most common treatment emergent INSTI- resistance substitution was T97A. Other frequently emergent integrase substitutions included E138K or A, G140S or A, and Q148H or R or K; substitutions at Q148 were detected in subjects with changes documented at or prior to enrollment in the trial. Substitutions L74M, E92Q, Y143H or C, S147G, V151A, M154I and N155H each emerged in 1 or 2 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 23-fold (range: 0.92 to 209) for isolates with emergent INSTI-resistance substitutions (n=18).

Resistance to background drugs in the dolutegravir twice daily regimen also emerged in 30% (12/40) of the subjects in the Week 24 resistance analysis set.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor (INSTI)-Resistant Mutant HIV-1 and HIV-2 Strains:
The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistancesubstitutions 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/Q148H 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.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains:
Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

APPENDICES

APPENDIX A: SPRING-2 STUDY ING113086

FDA DTG RESISTANCE SET (N=2)
ING113086.0003999
ING113086.0004335

FDA RAL RESISTANCE SET (N=8)
ING113086.0003073
ING113086.0003617
ING113086.0003864
ING113086.0004130
ING113086.0004314
ING113086.0004316
ING113086.0004424
ING113086.0004640

EMERGENT SUBSTITUTIONS IN RAL ARM OF STUDY ING113086
INSTI Emergent Substitutions (n=3)
Subjects 3617, 4316, and 4424

NRTI Emergent Substitutions (n=4)
Subjects 3173, 3294, 3617 and 4424

APPENDIX B. SINGLE STUDY ING114467

FDA DTG RESISTANCE ANALYSIS SET (>400 copies/ml or resistance data at failure) **(N=5)**
ING114467.0005233
ING114467.0005252
ING114467.0006860
ING114467.0006934
ING114467.0007912: Emergent INSTI-Resistance Substitution (E157Q/P)

FDA ATRIPLA RESISTANCE ANALYSIS SET (N=12)
ING114467.0005441
ING114467.0005506
ING114467.0005576
ING114467.0005692
ING114467.0005772
ING114467.0006033
ING114467.0006186
ING114467.0006639
ING114467.0006707
ING114467.0006772
ING114467.0006856
ING114467.0006886

EMERGENT SUBSTITUTIONS IN ATRIPLA ARM OF STUDY ING114467
Emergent NNRTI Substitutions (n=6)
Subjects 5506, 5576, 6033, 6707, 6856, 6886

Emergent NRTI Substitutions (n=1)
Subject 6707

Reference ID: 3339417

APPENDIX C. SAILING STUDY ING111762

FDA DTG RESISTANCE ANALYSIS SET in ING111762 (n=33)
ING111762.0000262
ING111762.0000283
ING111762.0000351
ING111762.0000420
ING111762.0000556
ING111762.0000573
ING111762.0000672
ING111762.0000941
ING111762.0000942
ING111762.0001067
ING111762.0001070
ING111762.0001113
ING111762.0002141
ING111762.0002418
ING111762.0002467
ING111762.0002500
ING111762.0002516
ING111762.0002568
ING111762.0002591
ING111762.0002618
ING111762.0002662
ING111762.0002785
ING111762.0002812
ING111762.0002920
ING111762.0009026
ING111762.0009046
ING111762.0009068
ING111762.0009080
ING111762.0009098
ING111762.0009103
ING111762.0009402
ING111762.0009412
ING111762.0009990

FDA DTG RESISTANCE ANALYSIS SET WITH POST BASELINE DATA IN ING111762 (n=18)
ING111762.0000262
ING111762.0000351
ING111762.0000672
ING111762.0000941
ING111762.0001067
ING111762.0001113
ING111762.0002141
ING111762.0002467
ING111762.0002516
ING111762.0002568

Reference ID: 3339417

Removed ING111762.0002618 - no baseline IN data
ING111762.0002785
ING111762.0002812
ING111762.0002920
ING111762.0009046
ING111762.0009068
ING111762.0009080
ING111762.0009103

FDA DTG RESISTANCE ANALYSIS SET WITH POST BASELINE INTEGRASE DATA IN ING111762 (n=15)
ING111762.0000262
ING111762.0000351
ING111762.0000672
ING111762.0000941
ING111762.0001067
ING111762.0002141
ING111762.0002467
ING111762.0002516
ING111762.0002568
ING111762.0002785
ING111762.0002920
ING111762.0009046
ING111762.0009068
ING111762.0009080
ING111762.0009103

SUBJECTS IN DTG ARM WITH TREATMENT EMERGENT INSTI RESISTANCE SUBSTITUTIONS AND/OR PHENOTYPIC RESISTANCE (n=5)
Subjects 351, 672, 1067, 2568, and 2785 (substitutions at L74, Q95, T97, E138, V151, G163, R263)

SUBJECT IN DTG ARM WITH TREATMENT EMERGENT NRTI RESISTANCE SUBSTITUTIONS (n=1)
Subject 2516

SUBJECTS IN DTG ARM WITH TREATMENT EMERGENT NNRTI RESISTANCE SUBSTITUTIONS (n=4)
Subjects 941, 1113, 2568 and 2785

FDA RAL RESISTANCE ANALYSIS SET IN ING111762 (n=49)
ING111762.0000004
ING111762.0000254
ING111762.0000260
ING111762.0000294
ING111762.0000419
ING111762.0000492

Reference ID: 3339417

ING111762.0000587
ING111762.0000588
ING111762.0000655
ING111762.0000742
Removed ING111762.0000785
ING111762.0000793
ING111762.0000947
ING111762.0000963
ING111762.0000976
Removed ING111762.0000977
ING111762.0001128
ING111762.0001146
ING111762.0001909
ING111762.0002201
Removed ING111762.0002214
ING111762.0002360
ING111762.0002371
ING111762.0002425
ING111762.0002427
ING111762.0002430
ING111762.0002457
ING111762.0002472
ING111762.0002489
ING111762.0002495
ING111762.0002513
ING111762.0002571
ING111762.0002632
ING111762.0002688
ING111762.0002727
ING111762.0002734
ING111762.0002765
ING111762.0002766
ING111762.0002769
ING111762.0002807
Removed ING111762.0002851
ING111762.0009048
ING111762.0009071
ING111762.0009088
ING111762.0009095
ING111762.0009125
ING111762.0009415
ING111762.0009461

FDA RAL RESISTANCE ANALYSIS SET WITH POST-BASELINE DATA IN ING111762 (n= 38)
ING111762.0000004
ING111762.0000260
ING111762.0000294
ING111762.0000419

ING111762.0000492
ING111762.0000587
ING111762.0000588
ING111762.0000655
Removed ING111762.0000793
ING111762.0000947
ING111762.0000963
ING111762.0000976
Removed ING111762.0000977
ING111762.0001128
ING111762.0001146
ING111762.0001909
ING111762.0002201
ING111762.0002360
ING111762.0002425
ING111762.0002427
ING111762.0002430
ING111762.0002472
ING111762.0002495
ING111762.0002513
ING111762.0002571
ING111762.0002632
ING111762.0002688
ING111762.0002727
ING111762.0002734
ING111762.0002765
ING111762.0002766
ING111762.0002769
ING111762.0002851
ING111762.0009048
ING111762.0009071
ING111762.0009088
ING111762.0009125

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT INSTI RESISTANCE SUBSTITUTIONS AND/OR PHENOTYPIC RESISTANCE (n=9)
Subjects 260, 419, removed 785 and 977, , 963, 1146, 2427, added 2472, 2688, 2769 and 9088 (substitutions at L74, E92, T97, G140, Y143, Q148, V151, N155, G163)

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT NRTI RESISTANCE SUBSTITUTIONS (n=6)
Subjects 260, 492, 2201, 2427, 2495, and 2571

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT NNRTI RESISTANCE SUBSTITUTIONS (n=4)
Subjects 260, 2201, 2360, and 2571

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT PI RESISTANCE SUBSTITUTIONS (n=5)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
ADDENDUM VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 07/10/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

Subjects 419, 963, 2765, 2769, and 9048

Reference ID: 3339417

APPENDIX D. VIKING-3 STUDY ING112574

DTG SUBJECTS IN DAY 8 FDA RESISTANCE ANALYSIS SET (<1 log_{10} change from baseline at Day 8 and ≥50 copies/mL) (N=32)

ING112574.0000008
ING112574.0000010
ING112574.0000015
ING112574.0000021
ING112574.0000181
ING112574.0000221
ING112574.0000231
ING112574.0000324
ING112574.0000408
ING112574.0000461
ING112574.0000504
ING112574.0000545
ING112574.0000585
ING112574.0001008
ING112574.0001048
ING112574.0001063
ING112574.0001067
ING112574.0001090
ING112574.0001203
ING112574.0001216
ING112574.0001264
ING112574.0001271
ING112574.0001274
ING112574.0001806
ING112574.0001842
ING112574.0001844
ING112574.0001865
ING112574.0001901
ING112574.0001964
ING112574.0002001
ING112574.0002042
ING112574.0002067

DTG SUBJECTS IN WEEK 24 FDA RESISTANCE ANALYSIS SET (>400 copies/mL at Failure or Week 24) (N=40)

ING112574.0000008
ING112574.0000010
ING112574.0000015
ING112574.0000041
ING112574.0000181
ING112574.0000221
ING112574.0000226
ING112574.0000227
ING112574.0000228

ING112574.0000461
ING112574.0000504
ING112574.0000566
ING112574.0000569
ING112574.0000585
ING112574.0000804
ING112574.0001008
ING112574.0001012
ING112574.0001056
ING112574.0001067
ING112574.0001089
ING112574.0001090
ING112574.0001201
ING112574.0001203
ING112574.0001206
ING112574.0001219
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001264
ING112574.0001274
ING112574.0001281
ING112574.0001401
ING112574.0001821
ING112574.0001842
ING112574.0001843
ING112574.0001844
ING112574.0001865
ING112574.0001901
ING112574.0002001
ING112574.0002021

DTG SUBJECTS IN WEEK 24 FDA RESISTANCE ANALYSIS SET (>400 copies/mL at Failure or Week 24) WITH POST-DAY 8 RESISTANCE DATA (N=22)

ING112574.0000008
ING112574.0000227
ING112574.0000504
ING112574.0000566
ING112574.0001008
ING112574.0001012
ING112574.0001056
ING112574.0001206
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001274
ING112574.0001821
ING112574.0001843
ING112574.0001901

ING112574.0002021

DTG SUBJECTS WITH TREATMENT EMERGENT INSTI SUBSTITUTIONS AT DAY 8 (n=6)
ING112574.0000010
ING112574.0000015
ING112574.0000221
ING112574.0000231
ING112574.0000585
ING112574.0001281

DTG SUBJECTS WITH TREATMENT EMERGENT INSTI SUBSTITUTIONS IN WEEK 24 FDA RESISTANCE ANALYSIS SET (n=18)
ING112574.0000008
ING112574.0000041
ING112574.0000227
ING112574.0000461
ING112574.0000504
ING112574.0000566
ING112574.0000569
ING112574.0001008
ING112574.0001012
ING112574.0001203
ING112574.0001206
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001821
ING112574.0001843
ING112574.0001901
ING112574.0002021

APPENDIX E. WEEK 24 BASELINE OUTCOME SET (N=125)

ING112574.0000001
ING112574.0000002
ING112574.0000003
ING112574.0000004
ING112574.0000007
ING112574.0000008
ING112574.0000010
ING112574.0000015
ING112574.0000021
ING112574.0000022
ING112574.0000024
ING112574.0000102
ING112574.0000103
ING112574.0000181
ING112574.0000182
ING112574.0000221
ING112574.0000222
ING112574.0000227
ING112574.0000228
ING112574.0000261
ING112574.0000301
ING112574.0000302
ING112574.0000343
ING112574.0000345
ING112574.0000381
ING112574.0000403
ING112574.0000462
ING112574.0000481
ING112574.0000483
ING112574.0000504
ING112574.0000507
ING112574.0000544
ING112574.0000545
ING112574.0000561
ING112574.0000562
ING112574.0000565
ING112574.0000566
ING112574.0000567
ING112574.0000569
ING112574.0000570
ING112574.0000582
ING112574.0000651
ING112574.0000663
ING112574.0000804
ING112574.0001001
ING112574.0001002
ING112574.0001004
ING112574.0001006

ING112574.0001007
ING112574.0001008
ING112574.0001009
ING112574.0001011
ING112574.0001012
ING112574.0001013
ING112574.0001021
ING112574.0001026
ING112574.0001031
ING112574.0001036
ING112574.0001038
ING112574.0001041
ING112574.0001046
ING112574.0001048
ING112574.0001049
ING112574.0001051
ING112574.0001055
ING112574.0001056
ING112574.0001057
ING112574.0001061
ING112574.0001063
ING112574.0001066
ING112574.0001067
ING112574.0001090
ING112574.0001201
ING112574.0001202
ING112574.0001203
ING112574.0001205
ING112574.0001206
ING112574.0001208
ING112574.0001209
ING112574.0001210
ING112574.0001212
ING112574.0001213
ING112574.0001214
ING112574.0001215
ING112574.0001216
ING112574.0001217
ING112574.0001219
ING112574.0001221
ING112574.0001233
ING112574.0001234
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001263
ING112574.0001264
ING112574.0001271
ING112574.0001272

ING112574.0001273
ING112574.0001274
ING112574.0001401
ING112574.0001402
ING112574.0001403
ING112574.0001481
ING112574.0001601
ING112574.0001611
ING112574.0001612
ING112574.0001616
ING112574.0001802
ING112574.0001806
ING112574.0001821
ING112574.0001841
ING112574.0001842
ING112574.0001843
ING112574.0001844
ING112574.0001861
ING112574.0001862
ING112574.0001901
ING112574.0001902
ING112574.0001961
ING112574.0001962
ING112574.0001964
ING112574.0001982
ING112574.0001983
ING112574.0002001
ING112574.0002021
ING112574.0002063

APPENDIX F.

N155H without Q148 SUBSET (n=20)

USUBJID	EFFICW24	INN155
ING112574.0000003	Y	N/H
ING112574.0000021	Y	H
ING112574.0000022	Y	H
ING112574.0000182	Y	H
ING112574.0000222	Y	H
ING112574.0000302	Y	H
ING112574.0000343	N	N/H
ING112574.0000403	Y	H
ING112574.0000483	N	H
ING112574.0000561	Y	H
ING112574.0000562	Y	H
ING112574.0001008	N	H
ING112574.0001038	Y	H
ING112574.0001055	Y	H
ING112574.0001061	Y	H
ING112574.0001263	Y	N/H
ING112574.0001802	Y	H
ING112574.0001821	N	H
ING112574.0001841	Y	H
ING112574.0001982	Y	H

Y143 without Q148 SUBSET (n=18)

USUBJID	EFFICW24	INY143
ING112574.0000002	Y	R
ING112574.0000103	N	R
ING112574.0000261	Y	R
ING112574.0000343	N	Y/C/H/R
ING112574.0000345	Y	R
ING112574.0000544	N	R
ING112574.0000565	N	R
ING112574.0000567	Y	C
ING112574.0000570	Y	C
ING112574.0000582	Y	R
ING112574.0000804	N	R
ING112574.0001007	Y	R
ING112574.0001021	N	R
ING112574.0001031	Y	R
ING112574.0001066	Y	C
ING112574.0001090	N	R
ING112574.0001219	N	R
ING112574.0001983	Y	C

Q148H/R + G140A/S without additional INSTI Resistance Substitutions (n=18)

USUBJID	EFFICW24
ING112574.0000004	Y
ING112574.0000007	Y
ING112574.0000008	N
ING112574.0000221	N
ING112574.0000462	Y
ING112574.0000507	Y
ING112574.0000545	Y
ING112574.0000651	Y
ING112574.0001004	N
ING112574.0001009	Y
ING112574.0001203	N
ING112574.0001208	Y
ING112574.0001216	Y
ING112574.0001233	Y
ING112574.0001242	N
ING112574.0001616	N
ING112574.0001844	N
ING112574.0002021	N

Q148H/R + ≥2 INSTI-resistance substitutions SUBSET (n=17)

INL074	INE138	ING140	INY143	INQ148	INE157	ING163	ING193	EFFICW24	USUBJID
		G/S		Q/H		S		N	ING112574.0000569
		S		H	Q			N	ING112574.0001843
		S		H/N		Q		Y	ING112574.0001862
	A	A		R			E	N	ING112574.0000227
	A	S		H				N	ING112574.0001067
	A	S		H				N	ING112574.0001842
	A	S		H				Y	ING112574.0001234
	E/A	G/S		Q/H			E	N	ING112574.0001264
	E/A	S	H	H				Y	ING112574.0001049
	E/A/K/T	S		H				N	ING112574.0000015
	K	S		H				N	ING112574.0000181
	K	S	R	H	Q	E	E	N	ING112574.0001901
	T	S		H				N	ING112574.0000566
	T	S		H		G/E		N	ING112574.0001012
I		S		H		S		N	ING112574.0000504
I	E/K	G/C		Q/R				N	ING112574.0002063
L/I/M				Q/R				N	ING112574.0000010

≥3 INSTI-resistance substitutions SUBSET (n=28)

INL074	INE138	ING140	INY143	INQ148	INE157	ING163	ING193	EFFICW24	USUBJID
		G/S		Q/H		S		N	ING112574.0000569
		S		H			E	N	ING112574.0002001
		S		H	Q			N	ING112574.0001843
		S		H/N		Q		Y	ING112574.0001862
	A	A		R			E	N	ING112574.0000227
	A	S		H				N	ING112574.0001067
	A	S		H				N	ING112574.0001842
	A	S		H				Y	ING112574.0001234
	D				E/Q	K		Y	ING112574.0001802
	D				Q		E	Y	ING112574.0000003
	E/A	G/S		Q/H			E	N	ING112574.0001264
	E/A	S	H	H				Y	ING112574.0001049
	E/A/K/T	S		H				N	ING112574.0000015
	E/D				Q	K		N	ING112574.0001008
	K		R		Q		R	N	ING112574.0000804
	K	S		H				N	ING112574.0000181
	K	S	R	H	Q	E	E	N	ING112574.0001901
	T	S		H				N	ING112574.0000566
	T	S		H		G/E		N	ING112574.0001012
I					Q	K		N	ING112574.0001821
I		S		H		S		N	ING112574.0000504
I	E/A/K/T		R		E/Q			N	ING112574.0001090
I	E/K	G/C		Q/R				N	ING112574.0002063
I/M			R		E/Q			Y	ING112574.0000345
I/M			R		Q			N	ING112574.0000103
M			R			R		N	ING112574.0001021
M			R		Q	G/R		N	ING112574.0000544
M	D		R					Y	ING112574.0000582

APPENDIX G. Week 24 Outcome and Baseline INSTI Resistance-Associated Substitutions

INL074	INE138	ING140	INY143	INQ148	INE157	ING163	ING193	EFFICW24	N Rows
								N	8
								Y	38
						E		Y	3
						G/R		Y	1
						Q		N	1
						R		Y	2
					Q			N	1
					Q			Y	1
					Q		G/E	Y	1
			C					Y	3
			G					Y	1
			R					N	1
			R					Y	1
			Y/C/H/R					N	1
		A		R				Y	2
		G/S						N	1
		G/S		H				N	1
		G/S		Q/H		S		N	1
		S		H				N	7
		S		H				Y	8
		S		H			E	N	1
		S		H	Q			N	1
		S		H/N		Q		Y	1
	A							Y	1
	A	A		R			E	N	1
	A	S		H				N	2
	A	S		H				Y	1
	D				E/Q	K		Y	1
	D				Q		E	Y	1
	E/A	G/S		Q/H			E	N	1
	E/A	S	H	H				Y	1
	E/A/K/T	S		H				N	1
	E/D							Y	1
	E/D					K		Y	1
	E/D				Q	K		N	1

Reference ID: 3339417

	K		R		Q		R	N	1
	K	S		H				N	1
	K	S	R	H	Q	E	E	N	1
INL074	INE138	ING140	INY143	INQ148	INE157	ING163	ING193	EFFICW24	N Rows
	T	S		H				N	1
	T	S		H		G/E		N	1
I								Y	1
I					Q	K		N	1
I			C					Y	1
I			R					N	1
I		S		H		S		N	1
I	E/A/K/T		R		E/Q			N	1
I	E/K	G/C		Q/R				N	1
I/M								Y	1
I/M			R		E/Q			Y	1
I/M			R		Q			N	1
L/I/M				Q/R				N	1
L/M								Y	1
L/Q								Y	1
M								N	1
M			R					Y	3
M			R			R		N	1
M			R		Q	G/R		N	1
M	D		R					Y	1

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

/s/

LISA K NAEGER
07/11/2013

JULIAN J O REAR
07/11/2013

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 05/14/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

NDA#: 204,790 **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

Initial Submission Dates:

Correspondence Date:	12/17/2012
CDER Receipt Date:	12/17/2012
Assigned Date:	12/17/2012
Review Complete Date:	05/17/2013
PDUFA Date:	08/17/2013

Amendments:

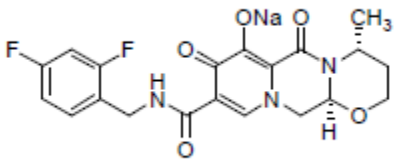
SDN	Date Submitted	Date Received	Date Assigned
007	02/22/2013	02/22/2013	02/25/2013
012	03/29/2013	03/29/2013	04/01/2013
026	05/06/2013	05/06/2013	05/06/2013

Related/Supporting Documents: IND75382

Product Name(s)
Proprietary: TIVICAY
Non-Proprietary/USAN: dolutegravir
Code Name/Number: GSK1349572A

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

Molecular Weight: 441.36 g/mol (dolutegravir sodium)
Molecular Formula: $C_{20}H_{18}F_2N_3NaO_5$
Structural Formula:



Dolutegravir (DTG)

Dosage Form(s): tablet
Route(s) of Administration: Oral

Reference ID: 3310743

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 05/14/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

Indication(s): Integrase strand transfer inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients aged 12 years and older.

Dispensed: Rx

Abbreviations: ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BL, baseline; DRV, darunavir; DTG, dolutegravir; EC_{50}, effective concentration at 50%; EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; EVG, elvitegravir; FC, fold-change; FTC, emtricitabine; HSA, human serum albumin; IC_{50}, 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;

TABLE OF CONTENTS

Executive Summary……..... *Page 3*
1 *Recommendations*
1.1 *Recommendations on Approvability*……..... *Page 8*
1.2 *Recommendation on Phase 4 Commitments*…….. *Page 8*
2 *Summary of Virology Assessments*……
2.1 *Non-Clinical Virology*…… *Page 8*
2.2 *Clinical Virology* ……*Page 10*
3 *Administrative signatures*……..... *Page 15*
4 *OND Virology Review*……
4.1 *Important Milestones in Development*…….. *Page 16*
4.2 *Methodology*……..*Page 16*
4.3 *Prior FDA Reviews*……...*Page 17*
4.4 *State of antivirals used for the indication sought*……..... *Page 18*
4.5 *Non-Clinical Virology* …… *Page 19*
4.6 *Clinical Studies*……*Page 29*
4.7 *Clinical Virology*……....*Page 35*
5 *Conclusion*…… *Page 77*

6 *Package Insert*
Applicant Proposed…….....*Page 78*
FDA Proposed …….....*Page 81*

7 *Appendices*
Appendix A…….....*Page 85*
Appendix B……..……..*Page 86*
Appendix C……*Page 87*
Appendix D……*Page 91*
Appendix E……*Page 94*

Reference ID: 3310743

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 204790 **SDN**: 000 **DATE REVIEWED:** 05/14/2013
Virology Reviewer: Lisa K. Naeger, Ph.D.

EXECUTIVE SUMMARY

This NDA for dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), is approvable with respect to virology for the treatment of HIV-1 in combination with other antiretrovirals. DTG should be administered as 50 mg once daily for treatment-naïve and treatment-experience INSTI-naïve adults and children age 12 and older weighing at least 40 kg. DTG should be administered 50 mg twice daily for INSTI-experienced adults and patients taking the anti-HIV-1 drugs fosamprenavir/ritonavir, efavirenz (EFV) or tipranavir/ritonavir.

(b) (4)

Dolutegravir (DTG) inhibits HIV integrase (IN) by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. The EC_{50} values of DTG against HIV-1 reference strains ranged from 0.5 nM to 2.1 nM in PBMCs and MT-4 cells. DTG had activity against a diverse panel of clade B isolates, group M clades A, C, D, E, F, G and group O isolates with EC_{50} values ranging from 0.02 nM to 2.1 nM. DTG also had sub-nanomolar activity against HIV-2 clinical isolates in PBMC assays. The effect of 100% human serum was extrapolated as 75-fold based on cell culture antiviral assay results in the presence of different concentrations of human serum. The antiviral activity of DTG was not antagonistic with representatives of each class of anti-HIV drugs and the antiviral drugs ribavirin and adefovir.

DTG-resistant viruses were selected in cell culture starting from wild-type HIV-1 strains and had 3- to 4-fold reductions in DTG susceptibility for the passaged resistant virus populations. Substitutions in IN that emerged in passaged resistant virus included E92Q, G118R, S153Y, T and F, G193E and R263K. Passage of mutant viruses with the Q148R or H substitutions selected for additional substitutions in IN including L74M, E92Q, T97A, E138K, G140S, M154I, and N155H.

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 in the FDA resistance analysis. 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 6 subjects' isolates in the Atripla (EFV/tenofovir disoproxil fumarate/emtricitabine) arm of Study ING114467 had emergent EFV resistance substitutions with one of these also having emergent NRTI resistance substitutions.

Reference ID: 3310743

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 9% of subjects (33/357) in the DTG arm compared to 14% (49/362) of subjects in the RAL arm who were eligible for resistance analysis.

Thirty-one percent (5/16) 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, V151V/I, and R263K) similar to 29% (10/35) in the RAL arm with emergent INSTI 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, none of the subjects' isolates with emergent INSTI resistance substitutions had phenotypic changes in susceptibility to either DTG or RAL. Overall, emergent resistance to drugs in the background regimen was lower in the DTG arm compared to the RAL arm. One subject (1/13; 8%) in the DTG arm had emergent NRTI-resistance substitutions compared to 6 subjects (6/34; 18%) in the RAL arm. No subject's isolates on a PI-containing regimen had emergent PI resistance substitutions in the DTG arm of this study compared to 15% (5/34) in the RAL arm. However, 4 subjects (4/13; 31%) in the DTG arm taking a background NNRTI had emergent NNRTI resistance substitutions [2 subjects were taking efavirenz (EFV)] compared to 4 subjects (4/34; 12%) with emergent NNRTI resistance substitutions in the RAL arm. This information provides further supportive evidence that the BID DTG regimen rather than the QD DTG regimen should be administered for subjects taking DTG with EFV.

The 10 subjects' isolates in the RAL arm with emergent INSTI resistance substitutions all had RAL phenotypic resistance and of these 5 isolates (45%) had DTG phenotypic resistance (≥2-fold-change from reference in DTG susceptibility).

INSTI-Experienced Study 112574

The patient population in ING112574 (VIKING-3) was highly treatment-experienced with 82% of the subjects resistant to at least one NRTI, 73% resistant to at least one NNRTI and 72% resistant to at least one PI. There were also 13% of the subjects resistant to enfuvirtide (ENF) and 12% not susceptible to maraviroc (MVC) with CXCR4-utilizing virus at Baseline. Most of the subjects (90%) had an overall susceptibility score (OSS) of 0 or 1 at Baseline. Sixty-four percent of the subjects had phenotypic resistance to RAL at Baseline with a >1.5-fold change in RAL susceptibility. Most of the subjects had prior exposure to RAL (179/183; 98%) with only 5 subjects having prior exposure to elvitegravir (EVG) (note one subject had prior exposure to both RAL and EVG).

Of the 182 subjects with Baseline data, 30% harbored virus with a substitution in IN at Q148 at Baseline. Of these subjects' isolates, 18% had Q148 substitutions with 1 INSTI resistance substitution and 12% had Q148 substitutions with 2 or more INSTI resistance substitutions. Almost all (97%; 31/32) of the Q148+1 group had the Q148+G140 substitution combination and most (67%; 14/21) of the Q148+≥2 group had the combination of Q148+G140+E138 substitutions. Importantly, 33% of the study population had no primary INSTI substitutions at baseline. The subjects with no primary INSTI substitutions at baseline had historical genotypic evidence of INSTI substitutions, phenotypic evidence of RAL or EVG resistance, or genotypic evidence of INSTI

Reference ID: 3310743

substitutions at screening. Most of the subjects with historical evidence had historical genotypic evidence of Q148H or N155H substitutions.

Response by Baseline Genotype and Phenotype
Response at both Day 8 and Week 24 was analyzed by baseline genotype and phenotype. Subjects had lower response rates at both Day 8 and Week 24 when their baseline viral isolates had a substitution at position Q148. After functional DTG monotherapy at Day 8, subjects in the INSTI substitution category Q148+1 and Q148+≥2 secondary substitutions had lower response rates of 69% (22/32) and 50% (10/20), respectively, compared to the overall response rate of 82% [response defined as >1.0 $\log_{10}$ copies/mL decrease or <50 copies/mL] (Table 1). Other INSTI baseline substitutions that contributed to a decreased response on functional DTG monotherapy at Day 8 were E138A/K/T, G140S, S147G, Q148H or R and G193E/R.

At Week 24, subjects in the Q148+≥2 category had very low response rates of 7% (1/14) compared to the overall response rate of 63% (79/125) subjects achieving <50 copies/mL (Table 1). In particular Q148+E138 had low response rates; these subjects' isolates had at least 3 INSTI substitutions with 13 of 14 isolates having substitutions at Q148, G140, and E138. Subjects with isolates containing Q148, G140 and E138 had low response rates of 15% (2/13) at Week 24. Subjects in the Q148+1 INSTI substitution category had response rates of 57% (12/21) of subjects achieving <50 copies/mL. Overall, INSTI baseline substitutions that contributed to a decreased response to DTG at Week 24 were L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, Q148H or R, E157Q, G163E/K/R/Q/S/T/N and G193E/R. These substitutions were often in combination with Q148H or R substitutions.

Response rates were greater than the overall response at both Day 8 and Week 24 for subjects with no primary INSTI substitutions detected at baseline and likewise for subjects with no Q148 substitutions at baseline (Table 1). It should be noted that due to the small number of subjects in this study that had reached Week 24 at the time of NDA submission, the numbers in some of the subgroups are small making it difficult to make definitive conclusions from the limited data.

Table 1. Summary of INSTI Substitutions that Decrease Response

Baseline Genotype (excluded Subjects with only Screening data and no BL data)	Response at Day 8 (≥1 Log_{10} Change from Baseline or <50 copies/mL) (N=182*)	Response at Week 24 (<50 copies/mL) Subset N=125
Overall Response	82% (150/182)	63% (79/125)
Q148H or R	60% (32/53)	35% (13/37)
Q148+1	69% (22/32)	57% (12/21)
Q148+≥2	50% (10/20)	7% (1/14)
Q148+G140+E138	47% (7/15)	15% (2/13)
≥2 primary INSTI substitutions	75% (6/8)	50% (3/6)
No Q148 Substitution	89% (115/128)	75% (66/88)

Primary INSTI Not Detected	95% (57/60)	75% (33/44)

*Subject 2063 had no Day 8 visit and was not included in the Day 8 analysis

Based on an analysis of response by incremental subgroups of baseline DTG phenotype (fold-change), response rates at Day 8 began to decline when baseline DTG phenotypes were >4-fold, whereas at Week 24, response rates started to decrease when DTG baseline phenotypes were >2-fold. Increments of <2, 2-<10 and ≥10-fold in DTG baseline phenotype elucidate differential response rates both at Day 8 and Week 24 and should provide physicians with valuable clinical response information based on baseline DTG phenotype (Table 2). At Week 24, subjects with baseline DTG phenotype <2-fold had response rates greater than the overall response. Subjects with a baseline DTG phenotype ≥2 but <10-fold had decreased response rates of 48% compared to the overall response rate of 63%. These results indicate that in subjects with baseline DTG phenotypes >2, careful consideration should be given to having a good supportive background regimen to maintain the durability of DTG. The most dramatic reduction in response rates, 18%, was seen for subjects with baseline DTG phenotypes of ≥10-fold. These subjects may not be the best candidates for a DTG-containing regimen. Almost all of the subjects (10/11) with a 10-fold or greater baseline DTG phenotype harbored Q148 +≥2 INSTI-resistance substitutions. Nine of these subjects did not achieve <50 copies/mL HIV-1 at Week 24 on DTG treatment.

Table 2. Response by Baseline DTG Phenotype (Fold-Change from reference in DTG Susceptibility)

Baseline DTG Phenotype (Fold-change from Reference)	**Response at at Day 8 (≥1 Log_{10} Change from Baseline or <50 copies/mL) (N=182)**	**Response at Week 24 (<50 copies/mL) Subset N=125**
Overall	82% (150/182)	63% (79/125)
<2	92% (104/113)	71% (55/77)
2 - <10	76% (31/41)	48% (14/29)
≥10	33% (5/15)	18% (2/11)

Response by Other Baseline Factors
Analysis of response at Day 8 and Week 24 by overall susceptibility score (OSS) did not show an obvious effect on response by the overall susceptibility to background drugs. Response was also analyzed by the anchor drug in the background regimen with both the failing Baseline regimen and new optimized Week 4 regimen. Response rates were the highest (80%) when ritonavir boosted darunavir (DRV/r) was used in the background regimen either at Baseline or Week 4 and lowest (50%) when ENF was used in the Baseline or Week 4 background regimen. If RAL was a background drug in the failing regimen at Screening or Baseline, response rates were 62 and 63%, respectively.

Treatment-Emergent INSTI Substitutions
On functional DTG monotherapy, 6 subjects had treatment-emergent INSTI resistance substitutions (L74M, T97T/A, G140A, G148R, M154I and E157E/Q) at Day 8. Five of these subjects' isolates had Q148R or H substitutions or mixtures plus at least one other

INSTI substitution (e.g., G140S or A) at baseline. The baseline DTG phenotype of these 5 subjects' isolates ranged from 0.7- to 34-fold and the fold-change in DTG susceptibility from baseline at Day 8 ranged from 1.1- to 32-fold.

In the FDA resistance analysis at Week 24, 18 subjects had treatment-emergent INSTI resistance substitutions post-Day 8 on the DTG BID regimen. The most common treatment-emergent INSTI substitution was T97A, which emerged in 45% of subjects' isolates on DTG treatment. Other frequently emergent substitutions, which emerged in 10-20% of subjects' isolates, included E138K or A, G140S or A, Y143H or C, Q148H or R or K and M154I. Substitutions L74M, V75M, E92Q, S147G, V151A, and N155H each emerged in 1 or 2 subjects' isolates (<10% of subjects' isolates). The baseline median DTG fold-change from reference was 4-fold for isolates with emergent INSTI resistance substitutions (n=18). At failure, the median DTG fold-change from reference was 23-fold (range of 0.92 to 209) and the median fold-change from baseline was 7-fold for these isolates. Four subjects with emergent Q148 substitutions had a median 36-fold change from baseline in DTG susceptibility, which highlights the significant impact on DTG susceptibility of emergent substitutions at this position. The emergence of T97A and E138 substitutions in the presence of G140S and Q148H (either present at baseline or emergent) resulted in >25-fold decreases in DTG susceptibility from baseline.

Resistance to background drugs in the DTG BID regimen was also analyzed. NNRTI resistance substitutions emerged in 3 subjects' isolates (14%), NRTI resistance substitutions emerged in 5 subjects' isolates (23%), and PI resistance substitutions emerged in 4 subjects' isolates (18%). In addition, 7 subjects' isolates (32%) had emergent phenotypic resistance to ENF. Many of these subjects' isolates were resistant to most of the background drugs in their regimen at baseline. With the new regimens starting at Day 8, half of the subjects' isolates with post-Day 8 resistance data had an OSS=1 and the other half had an OSS of ≥2.

Cross-Resistance

Considering the available cell culture and clinical data, the presence of substitutions at Q148 plus 2 or more other INSTI substitutions (such as L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, E157Q, G163E/K/R/Q/S/T/N, or G193E/R) are likely to decrease the efficacy of DTG.

In the treatment-naïve studies (IND113086 and 114467), none of the FDA DTG resistant analysis subjects with post-baseline resistance data were resistant to RAL.

In the treatment-experienced INSTI-naïve study (ING111762), none (n=18) of the FDA DTG resistant analysis subjects with post-baseline resistance data were resistant to RAL. Additionally, none of the subjects' isolates in the DTG arm with emergent INSTI resistance substitutions (n=5) had phenotypic changes in susceptibility to either DTG or RAL. The 11 subjects' isolates in the RAL arm with emergent INSTI resistance substitutions all had RAL phenotypic resistance and of these 5 isolates (45%) had DTG phenotypic resistance (≥2-fold change from reference in DTG susceptibility).

In the VIKING-3 study (ING112574), all the subjects' isolates of Week 24 FDA resistance subset with emergent INSTI resistance substitutions were cross-resistant to

Reference ID: 3310743

RAL. The study was designed to enroll only INSTI-experienced subjects, so it is not unexpected that DTG failures in this study would be resistant to RAL.

1. RECOMMENDATIONS

1.1. Recommendation and Conclusion on Approvability

This NDA for dolutegravir (DTG; TIVICAY), an integrase strand transfer inhibitor (INSTI), is approvable with respect to virology for the treatment of HIV-1 in combination with other antiretrovirals. DTG should be administered as 50 mg once daily for treatment-naïve and treatment-experience integrase strand transfer inhibitor-naïve adults and children age 12 and older weighing at least 40 kg. DTG should be administered 50 mg twice daily for integrase strand transfer-experienced adults and patients taking the anti-HIV drugs fosamprenavir/ritonavir, efavirenz (EFV) or tipranavir/ritonavir.

Indications and Usage

(b) (4)

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

Please provide the complete efficacy and resistance data from VIKING-3 and VIKING-4 and submit in format appropriate for uploading into JReview.

2. SUMMARY OF OND VIROLOGY ASSESSMENTS

2.1 Non-Clinical Virology

Mechanism of Action
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 IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture
DTG EC_{50} values were 0.51 nM and 0.53 nM against HIV-1 strain BaL or HIV-1 strain NL432, respectively, in PBMCs. MT-4 cells infected with HIV-1 strain IIIB and incubated with dolutegravir for 4 or 5 days resulted in EC_{50} values of 0.71 nM and 2.1 nM.

Dolutegravir exhibits antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from the clinical isolates. Dolutegravir demonstrates antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G and 3 group O) the with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values ranged from 0.09 nM to 0.61 nM when tested against 3 HIV-2 clinical isolates in PBMC assays.

(b) (4)

Antiviral Activity in Combination with Other Antiviral Agents
The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI raltegravir, NNRTIs efavirenz or nevirapine; the NRTIs abacavir or stavudine; the PIs amprenavir or lopinavir; the fusion inhibitor enfuvirtide; or the CCR5 co-receptor antagonist maraviroc. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor adefovir or with the antiviral ribavirin.

Cell Culture Resistance
DTG-resistant viruses were selected in cell culture starting from wild-type HIV-1 strain IIIB and had a 4-fold maximum fold decrease in susceptibility for the passaged resistant virus populations with substitutions S153F and S153Y in integrase. Passage of the wild-type HIV-1 strain NL432 in the presence of dolutegravir selected for E92Q (passage population virus fold change = 3.1) and G193E (passage population virus fold-change = 3.2) substitutions. Additional passage of wild-type clade B, C, and A/G viruses in the presence of dolutegravir selected for R263K, G118R, and S153T. Passage of mutant viruses with the Q148R or H substitutions selected for additional substitutions in integrase including L74M, E92Q, T97A, E138K, G140S, M154I, and N155H.

The susceptibility of DTG was tested against 60 integrase inhibitor-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 integrase inhibitor-resistant site-directed mutant HIV-2 viruses. Single INSTI substitutions T66K, I151L and S153Y conferred a >2-fold decrease in DTG susceptibility (range 2.3- to 3.6-fold). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148H and substitutions at E138/G140/Q148 showed a >2-fold decrease in DTG susceptibility (range 2.5 to 21). In HIV-2 mutants, substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in DTG susceptibility and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in DTG susceptibility, respectively.

2.2 Clinical Virology

TREATMENT-NAIVE STUDIES
Study ING113086
In Study ING113086 where once daily DTG was compared to RAL 400 mg twice daily both administered with fixed-dose dual NRTI therapy, the resistance dataset for Study

Reference ID: 3310743

ING113086 had 22 subjects in the DTG arm and 30 subjects in the RAL arm. The majority of subjects in the Study ING113086 resistance dataset had low-level viremia at the failure timepoint: 68% (15/22) of subjects in the DTG arm and 77% (23/30) in the RAL arm had HIV-1 RNA viral loads ≥50 copies and ≤400 copies/mL at the failure timepoint. For the FDA virologic failure analysis, in order to take into account blipping, the virologic failure "rebound" criteria were modified to "confirmed >400 copies/mL after confirmed suppression to <50 copies/mL" or evidence of emergent resistance. Based on these criteria, there were 2 FDA-defined virologic failures in the DTG arm (Subjects 3999 and 4335) and 8 virologic failures in the RAL arm (Subjects 3073, 3617, 3864, 4130, 4314, 4316, 4424, and 4640).

The 2 FDA-defined DTG virologic failure subjects had emergent substitutions in IN without a change in phenotype. Subject isolate 3999 had an emergent A21T substitution and Subject 4335 isolate had an emergent M50M/V mixture and an L74I substitution at baseline. In the comparator RAL arm, 3 subjects had emergent INSTI resistance substitutions in their viral isolates with 2 also having emergent NRTI substitutions associated with the background NRTIs. Two additional RAL subjects' isolates had emergent NRTI subsititutions.

Study ING114467
In the submitted resistance dataset for Study ING114467 (SINGLE), there were 19 subjects in the DTG arm and 20 subjects in the Atripla arm. In the DTG treatment arm, 17 subjects (4%) met the definition of protocol defined virologic failure (PDVF) and 17 (4%) subjects in the Atripla treatment group met the definition of PDVF. 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: 79% (15/19) of subjects in the DTG arm and 60% (12/20) in the Atripla arm. Based on the FDA criteria for resistance analysis at Week 48, there were 5 subjects (1.2%) in the DTG arm and 12 subjects (3%) in the Atripla arm with >400 copies/mL HIV-1 RNA at the failure timepoint or with resistance data at failure.

Of the 5 subjects in the FDA DTG resistance analysis, one subject's isolate, 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). Two subjects' isolates had emergent substitutions in RT; Subject 6934's isolates had an emergent W88W/R substitution but no phenotypic resistance to ABC or LAM and Subject 7912's isolate had an emergent Q91Q/R substitution and the E138A substitution changed from E138G, but again there was no phenotypic resistance to ABC or LAM.

In the comparator Atripla arm, 6 subjects' isolates had emergent EFV resistance substitutions of which 4 had corresponding EFV phenotypic resistance. One of these subjects' isolates also had emergent mixtures of NRTI resistance substitutions with no change in TDF or FTC susceptibility.

TREATMENT-EXPERIENCED INSTI-NAÏVE STUDY
Study ING111762
Study ING111726 (SAILING) compared DTG 50 mg once daily to RAL 400 mg twice daily, 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

Reference ID: 3310743

not have been active) in treatment-experienced INSTI-naïve subjects at Week 24. At Week 24, 79% of subjects receiving DTG and 70% of subjects receiving RAL achieved the Week 24 endpoint of plasma HIV-1 RNA <50 copies/mL in the FDA Snapshot algorithm. Response rates for subjects taking DTG were better than for subjects taking RAL whether they had ≤2 susceptible drugs in their background regimen. Approximately 80% of subjects in this study had DRV/r as one of their background drugs. For subjects taking DRV/r, response rates in the DTG arm were similar for subjects regardless if their HIV-1 had major PI substitutions (82% without vs. 83% with). Subjects not taking DRV/r as one of their background drugs also had better response rates in the DTG arm (79%) than subjects in the RAL arm (69%).

In the DTG treatment arm of Study ING111762, 76 subjects (21%) met the definition of protocol defined virologic failure (PDVF) and 110 (30%) subjects in the RAL treatment group met the definition of PDVF. Based on the FDA criteria for resistance analysis, there were 33 subjects (9%) in the DTG arm and 49 subjects (14%) in the RAL arm with >400 copies/mL HIV-1 RNA at the failure timepoint or with resistance data at failure. Of the 33 subjects in the FDA DTG resistance analysis set, 18 had post-baseline resistance data; 16 with INSTI post-baseline resistance data and 13 subjects with RT/PR post-baseline resistance data.

Five subjects' isolates (31%) in the DTG arm had emergent INSTI resistance substitutions (L74M and I, Q95Q/L, T97A, V151V/I, and R263K) compared to 10 (29%) in the RAL arm who had emergent INSTI resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E/Q and G163G/R). Four subjects (4/13; 31%) in the DTG arm taking a background NNRTI had emergent NNRTI resistance substitutions [2 subjects were taking EFV] compared to 4 subjects (4/23; 12%) with emergent NNRTI substitutions in the RAL arm.

One subject's failure isolate (8%) in the DTG arm on AZT had a V75L resistance substitution emerge in RT from a mixture (V75V/L) at baseline. V75I is a multidrug resistant substitution (IAS-USA 2013). No subject's isolates on a PI-containing regimen had emergent PI resistance substitutions in the DTG arm of this study. In the RAL arm, 6 subjects' isolates (18%) had emergent NRTI substitutions and 5 subjects' isolates (15%) had emergent PI resistance substitutions.

The 10 subjects' isolates in the RAL arm with emergent INSTI resistance substitutions all had RAL phenotypic resistance, and of these, 5 isolates (45%) had DTG phenotypic resistance (≥2-fold change from reference in DTG susceptibility).

INSTI-EXPERIENCED STUDY

Study ING112574

DTG efficacy with an optimized background ART was also assessed in an INSTI-experienced subject population at Week 24. The patient population in ING112574 (VIKING-3) was highly treatment-experienced with 73% resistance to at least one NNRTI, 82% of the subjects resistant to at least one NRTI, and 72% resistant to at least one PI. There were also 13% of the subjects resistant to ENF and 12% not susceptible to MVC with CXCR4-tropic virus at baseline. Most of the subjects' isolates (90%) had an OSS of 0 or 1.

Reference ID: 3310743

INSTI resistance substitution inclusion criteria for this study included substitutions T66I, A or K, E92Q or V, Y143C or R or H, Q148H or K or R and N155H. Sixty-four percent of the subjects' isolates had phenotypic resistance to RAL with a >1.5-fold change in RAL susceptibility. Most of the subjects' isolates had prior exposure to RAL (179/183; 98%) with only 5 subjects (Subjects 242, 403, 463, 1841 and 1962) having prior exposure to EVG (note one subject's isolate had prior exposure to both RAL and EVG).

Of the 182 subjects with baseline data, 30% harbored virus with a substitution at Q148 at Baseline. Of these subjects' isolates, 18% had Q148 substitutions with 1 INSTI resistance substitution and 12% had Q148 substitutions with 2 or more INSTI resistance substitutions. Almost all of the Q148+1 group had the Q148+G140 substitution combination and most of the Q148+≥2 group had the combination of Q148+G140+E138 substitutions. At baseline, 11% of subjects' isolates had the L74M substitution, 16% had the T97A substitution, 15% had Y143 substitutions and 18% had the N155H substitution. The T66A or K and E92Q substitutions were each detected in 2 subjects' isolates at baseline with other INSTI primary substitutions. Four percent of the subjects' baseline isolates had 2 or more primary INSTI resistance substitutions.

Importantly, 33% of this study population had no primary INSTI resistance substitutions at baseline. These subjects' isolates with no primary INSTI substitutions at baseline had historical genotypic evidence of INSTI resistance substitutions, phenotypic evidence of RAL or EVG resistance, or genotypic evidence of INSTI resistance substitutions at screening. Most of the subjects with historical evidence had historical genotypic evidence of Q148H or N155H substitutions.

Response by Baseline Factors
Analysis of response at Day 8 and Week 24 by overall susceptibility score (OSS) did not show an obvious effect of OSS on response. Response was analyzed by the anchor drug in the background regimen with both the failing Baseline regimen and new optimized Week 4 regimen. Response rates were the highest (80%) when DRV/r was used in the background regimen either at Baseline or Week 4 and lowest (50%) when ENF was used in the Baseline or Week 4 background regimen. If RAL was a background drug in the failing regimen at Screening or Baseline, response rates were 62 and 63%, respectively.

Response by Baseline Genotype and Phenotype
Response at both Day 8 and Week 24 was analyzed by baseline genotype and phenotype. Subjects had lower response rates at both Day 8 and Week 24 when their baseline viral isolates had a Q148 substitution. At Day 8, subjects in the INSTI substitution category Q148+1 and Q148+≥2 secondary substitutions had 69% and 50%, respectively, achieving a >1.0 $\log_{10}$ copies/mL decrease or <50 copies/mL compared to the overall response rate of 82%. Other INSTI baseline substitutions that contributed to a decreased response to DTG at Day 8 were E138A/K/T, G140S, S147G, Q148H or R and G193E/R.

At Week 24, subjects in the Q148+1 category had response rates of 57% achieving <50 copies/mL and in the Q148+≥2 category had very low response rates of 7% (1/14) achieving <50 copies/mL compared to the overall response rate of 63%. In particular

Reference ID: 3310743

Q148+E138 had low response rates of 14%; all of these subjects' isolates had at least 3 INSTI resistance substitutions with substitutions at Q148+G140+E138. INSTI baseline substitutions that contributed to a decreased response to DTG at Week 24 were L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, Q148H or R, E157Q, G163E/K/R/Q/S/T/N and G193E/R. These substitutions were often in combination with Q148H or R substitutions and the response rates at Week 24 were decreased. Response rates for subjects with no primary INSTI resistance substitutions detected in baseline isolates had greater than the overall response at both Day 8 and Week 24.

Based on an analysis of response by incremental subgroups of baseline DTG phenotype (fold-change), subgroups of <2, 2-<10 and ≥10 in DTG baseline phenotype elucidate differential response rates both at Day 8 and Week 24 and should provide physicians with valuable clinical response information based on baseline DTG phenotype. At Day 8, subjects with baseline DTG phenotype of <2 had response rates of 92%, greater than the overall response. At Week 24 in the n=125 subset, subjects with baseline DTG phenotype <2 had response rates greater than the overall response. Subjects with baseline DTG phenotype of ≥2 but <10 had decreased response rates of 48% compared to the overall response rate of 63% at Week 24. The most dramatic reduction in response rates was seen for subjects with baseline DTG phenotypes of ≥10 with response rates of 18% at Week 24.

Treatment-Emergent Resistance

At Day 8 after functional DTG monotherapy, 6 subjects had treatment-emergent INSTI resistance substitutions (L74M, T97T/A G140A and G148R, M154I and E157E/Q). Five of these subjects' isolates had Q148R or H substitutions or mixtures plus at least one other INSTI substitution (e.g., G140S or A) at baseline. The baseline DTG phenotype of these 5 subjects' isolates ranged from 0.7- to 34-fold and the fold change in DTG susceptibility from baseline at Day 8 ranged from 1.1- to 32-fold.

In the FDA resistance analysis at Week 24, 18 subjects' isolates had treatment-emergent INSTI resistance substitutions post Day 8 on the DTG BID regimen. The most common treatment-emergent INSTI substitution was T97A, which emerged in 45% of subjects' isolates on DTG treatment. Other frequently emergent substitutions, which emerged in 10-20% of subjects' isolates, included E138K or A, G140S or A, Y143H or C, Q148H or R or K or M154I. Substitutions L74M, V75M, E92Q, S147G, V151A, and N155H each emerged in 1 or 2 subjects' isolates (<10% of subjects' isolates).

At Baseline, the Week 24 FDA resistance subset (n=40) (>400 copies/mL at Week 24, failure or last timepoint (interim)) had a median fold-change from reference of 4-fold (range 0.45 to 37) in DTG susceptibility compared to median fold-change of 1.2-fold (range 0.47 to 20) for the Week 24 responders (n=79). Of the isolates in the FDA resistance failure subset with emergent INSTI resistance substitutions (n=18), the baseline median DTG fold-change from reference was 4.4-fold. At failure with emergent INSTI resistance substitutions, the median DTG fold-change from reference was 23-fold (range of 0.92 to 209) and the median fold-change from baseline was 7-fold. Four subjects' isolates with emergent Q148 substitutions had a median 36-fold change from baseline and 100-fold change from reference in DTG susceptibility. The emergence of T97A and E138 substitutions in the presence of G140S and Q148H (either present at

Reference ID: 3310743

baseline or emergent) resulted in significant decreases in DTG susceptibility from baseline (>25-fold change) and >70-fold change from reference.

Resistance to background drugs in the regimen was also analyzed. NNRTI resistance substitutions emerged in 3 subjects' isolates, NRTI substitutions emerged in 5 subjects' isolates, and PI resistance emerged in 4 subjects' isolates. In addition, 7 subjects' isolates had emergent phenotypic resistance to ENF. Many of these subjects were resistant to most of the background drugs in their regimen at baseline. With the new regimens starting at Day 8, 50% (11/22) of subjects with post-Day 8 resistance data had an OSS=1, 41% (9/22) Q148Hof subjects had an OSS=2 and 9% (2/22) had an OSS >2.

Effect of Duration of INSTI Use and Time from End of INSTI Use on Response
We examined whether the duration of prior INSTI use (RAL or EVG) or Time for INSTI use affected response rates to DTG at Day 8 or Week 24. Subjects who had ≤6 months duration of prior INSTI use had lower response rates than subjects who had >6 months or >24 months duration of prior INSTI use. These results might indicate that subjects who failed on an INSTI regimen in <6 months (perhaps because of an inadequate regimen, compliance issues or PK issues) had more INSTI resistance than subjects who were on an INSTI regimen longer than 6 months. In support of this suggestion, the three subjects with ≤6 months prior INSTI duration use who responded at Week 24 had no primary INSTI substitutions but historical N155H, whereas the six subjects who failed at Week 24 had historical or screening Q148+1 or ≥2 INSTI substitutions.

Subjects with a shorter time (<50 days) from end of prior RAL or EVG use to start of DTG had lower response rates than subjects who had discontinued from a RAL or EVG regimen for 2 months - >12 months prior to starting DTG. This result may reflect the presence of more INSTI resistance substitutions if subjects were failing on a RAL or EVG regimen just prior to the start of DTG. A short time from switching from RAL or EVG to DTG appeared to contribute to lower response rates even if subjects had been on the INSTI for >24 months. Subjects who had durations of INSTI use of ≤6 months and short time from INSTI End Date (<50 days) to DTG start had low response rates of 56% at Day 8 and 0% at Week 24. However, it appears likely that the low response rates can be explained by the presence of baseline INSTI substitutions, particularly Q148H+G140S. In this Week 24 group of failures, all had INSTI substitutions at baseline.

CROSS-RESISTANCE
Considering the available cell culture and clinical data, the presence of substitutions at Q148 plus 2 or more other INSTI substitutions (such as L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, E157Q, G163E/K/R/Q/S/T/N, or G193E/R) are likely to decrease the efficacy of DTG.

In the treatment-naïve studies (IND113086 and 114467), none of the FDA DTG resistant analysis subjects with post-baseline resistance data were resistant to RAL.

In the treatment-experienced INSTI-naïve study (ING111762), none (n=18) of the FDA DTG resistant analysis subjects with post-baseline resistance data had virus resistant to RAL. Additionally, none of the subjects' isolates in the DTG arm with emergent INSTI

Reference ID: 3310743

substitutions (n=5) had phenotypic changes in susceptibility to either DTG or RAL. The 11 subjects' isolates in the RAL arm with emergent INSTI substitutions all had RAL phenotypic resistance, and of these, 5 isolates (45%) had DTG phenotypic resistance (≥2-fold change from reference in DTG susceptibility).

In the VIKING-3 study (112574), all the isolates of Week 24 FDA resistance subset with INSTI substitution emergence were cross-resistant to RAL.

3. ADMINISTRATIVE

3.1. Reviewer's Signature

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

3.2. Concurrence

HFD-530/Micro TL _____Date _____

Reference ID: 3310743

4. OFFICE OF NEW DRUGS VIROLOGY REVIEW

4.1 Important Milestones in Product Development

The sponsor planned to submit resistance data only from the Phase 2b/3 studies in ART-experienced subjects. During the pre-NDA meeting, we clarified to the sponsor that baseline and failure genotypic and phenotypic resistance data from both the treatment-naïve and treatment-experienced treatment failures should be included with the NDA. In addition, baseline genotypic and phenotypic data for all subjects in the treatment-experienced studies should be included. They agreed to submit data in resistance datasets according to our specified template.

We further clarified that all positions in the RT, PR and IN sequence should be included rather than just the major substitutions sites.

In the VIKING-3 study, approximately 30% of the subjects had no primary INSTI resistance substitutions detected at Baseline in their isolates. The Sponsor proposed to describe responses to DTG in labeling by baseline IN genotype for the INSTI-resistant patient population. Given that VIKING-3 is a small study with 114 subjects in the ITT population and 35 protocol-defined virologic failures of which 31 had genotypic/phenotypic data, we discussed that it will be difficult to make broad interpretations of the data when subdividing these small numbers further by baseline substitutions. Therefore, we clarified that it will be a review issue to determine if a sufficient number of subjects had clinically relevant RAL and EVG resistance substitutions to support labeling of DTG to treat a broad population of INSTI-resistant viruses and to describe DTG response by baseline integrase genotype. Additionally, we asked the sponsor to submit the historical genotypic and phenotypic data in the resistance dataset

The sponsor also agreed to submit a study report on the prevalence of polymorphisms at common INSTI resistance-associated sites in Clade B isolates with the NDA.

4.2 Methodology

Genotypic and phenotypic analyses were carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense and GenoSure testing methods for RT, or with their GeneSeq Integrase and PhenoSense Integrase assays. Only viral genotype was analyzed at screening and this was done through Quest Diagnostics. In most cases, HIV-1 subtype (clade) was determined using the screening sample.

Subjects experiencing confirmed virologic failure (confirmed HIV-1 RNA ≥50 copies/mL throughout the study and/or confirmed HIV-1 RNA ≥200 copies/mL at or after Week 48) had plasma samples tested for HIV-1 RT genotype and phenotype and HIV-1 integrase genotype and phenotype from both Baseline samples and from samples collected at the time of suspected virologic failure.

OSS was determined by Screening Monogram resistance test Net Assessment results. Net Assessment is an assessment of antiviral activity of background ARTs using both genotypic and phenotypic test results interpreted through a proprietary algorithm (from

Reference ID: 3310743

Monogram Biosciences) and provides the overall susceptibility of the drug (Note: partially sensitive and resistant calls are considered not fully active in this analysis). For determining overall susceptibility of background ARTs (OSS), a binary scoring system (0= not fully active, 1= fully active) for each antiretroviral agent was used. OSS was calculated as the sum of the net assessment scores of ARTs comprising the subject's Day 8 ORB and categorized as 0, 1, 2, or >2. *The cutoffs for the PhenoSense GT assay are shown below*.

PhenoSense GT Susceptibility Cutoffs for Determining Net Resistance Assessment

Drug	Cutoffs (Lower – Upper)
NRTIs	
Abacavir	**4.5 – 6.5**
Didanosine	**1.3 – 2.2**
Emtricitabine	3.5
Lamivudine	**3.5**
Stavudine	**1.7**
Tenofovir	**1.4 - 4**
Zidovudine	1.9
NNRTIs	
Delavirdine	6.2
Efavirenz	3
Etravirine	**2.9 – 10**
Nevirapine	4.5
Rilpivirine	2
PIs	
Atazanavir	**2.2**
Atazanavir/R	**5.2**
Darunavir	**10-90**
Fosamprenavir	**4 – 11**
Indinavir	10
Lopinavir	**9 - 55**
Nelfinavir	3.6
Ritonavir	2.5
Saquinavir	**2.3 – 12**
Tipranavir	**2 - 8**

Lower and Upper Clinical Cutoff in bold; not bolded = biological cutoff

4.3 Prior FDA Virology Reviews

Prior IND75382 reviews were done by Clinical Virology Reviewer Dr. Sung Rhee, Ph.D. Since January 2012, Dr. Lisa K. Naeger, Ph.D., Sr. Clinical Virology Reviewer, has reviewed this IND and NDA submissions.

4.4 State of antivirals used for the indication (s) sought*:*

Since highly-active antiviretroviral therapy (HAART) regimens have been introduced, the number of AIDS cases has decreased dramatically; however, HAART does not clear

Reference ID: 3310743

HIV-1 from subjects and even though the number of serum HIV-1 RNA copies is reduced to undetectable levels, HIV-1 re-emerges quickly after discontinuation of HAART. Therefore, with the currently available regimens, it is likely that HIV-infected subjects will require antiretroviral therapy throughout their lives.

There are currently twenty-six FDA-approved anti-HIV-1 drugs including including INSTIs (elvitegravir and raltegravir), NNRTIs (delavirdine, efavirenz, etravirine, nevirapine, rilpivirine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranivir), the fusion inhibitor enfuvirtide, and the CCR5 coreceptor antagonist maraviroc. Maraviroc inhibits the interaction between the viral envelope glycoprotein gp120 and the human CCR5 receptor membrane protein and inhibits entry of the virus into the cell. Enfuvirtide is a gp41 fusion inhibitor preventing the joining of the viral and cellular membranes necessary for virus entry. NRTIs mimic nucleosides and target HIV-1 RT by competing with natural deoxynucleoside triphosphates for binding to RT and by incorporating into newly synthesized viral DNA resulting in chain-termination. NNRTIs inhibit HIV-1 RT by binding near the catalytic site of RT and acting as noncompetitive inhibitors. Integrase catalyzes the integration of linear viral DNA into host cell DNA forming the provirus. PIs work at the late stage of viral replication to prevent virus production from infected cells. They block the HIV-1 protease enzyme, which is necessary for the production of mature virions, resulting in defective particles which are unable to infect new cells.

Unfortunately, HIV-1 develops resistance to antiretroviral drugs over time usually from the accumulation of multiple substitutions. HAART regimens are also associated with acute toxicities such as diarrhea, kidney stones, rash, CNS toxicities and hepatotoxicity. Long-term toxicities from antiretroviral therapies include mitochondrial toxicities associated with NRTIs (lactic acidosis, myopathy, neuropathy, pancreatitis), and disorders of lipid metabolism (dyslipidemia) and glucose metabolism (lipodystophy, hypercholesterolemia, hypertriglyceridemia) associated with PIs. These tolerability issues make compliance to therapy more challenging. Compliance is an important determinant of successful virologic suppression for subjects on HAART. Regimens that are well-tolerated and easy to administer with a few pills once daily are likely to aid in subject compliance and improve clinical outcomes. There is a need for new anti-HIV drugs that are well-tolerated and easy to use with new modes of action and low likelihood of viral resistance development. Additionally, drugs that are effective against viruses resistant to all currently approved drugs are needed for the heavily treatment-experienced population. In particular, drugs effective against INSTI-resistant virus are needed to add to the options for treatment of EVG- and RAL-experienced virologic failures.

4.5 Non-Clinical Virology

MECHANISM OF ACTION

Dolutegravir inhibits HIV-1 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.

The mechanism of action of DTG on HIV-1 replication was evaluated by assessing HIV DNA synthesis, integration, and formation of 2 LTR containing circular DNA by quantitative PCR in infected cells. MT-4 cells were acutely infected with HIV-1 infectious molecular clone NL-432 in the presence or absence of inhibitors. Raltegravir (RAL) was used as a reference integrase strand transfer inhibitor (INSTI) and efavirenz (EFV) was used as a standard non-nucleoside reverse transcriptase inhibitor (NNRTI) in this assay. Neither DTG nor RAL affected the amount of late RT products, while EFV decreased it in dose-dependent manner. The EC_{50} value for EFV determined by total PCR is 4.8 nM. In contrast, both DTG and RAL inhibited integration of HIV linear unintegrated DNA in a dose-dependent manner. The EC_{50} values determined by Alu PCR are 0.72 and 2.4 nM for DTG and RAL, respectively. Both DTG and RAL increased the amount of 2 LTR containing circular DNA, while efavirenz decreased it. A dose dependent decrease in integrated HIV-1 DNA (Alu PCR) and an increase of 2 LTR containing circular DNA was observed with DTG treatment indicating that the antiviral activity is a direct consequence of its effect on viral integration.

Strand transfer biochemical assays using purified recombinant HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM in the GlaxoSmithKline analysis and 12.6 nM in the Shionogi and Co., Ltd analysis.

Additionally, passage studies with DTG selected substitutions within the integrase enzyme (See Resistance Development in Cell Culture section below). These substitutions conferred decreased susceptibility to DTG type in site-direct mutant HIV viruses compared to wild-type. Altogether, these data are consistent with DTG directly targeting the HIV-1 integrase in cells.

Evaluation of DTG Dissociation from Wild Type and Integrase Strand Transfer Inhibitor (INSTI)-Resistant Integrase-DNA Complexes

The dissociation of DTG, EVG, and RAL and from wild-type and mutant IN proteins complexed with DNA was investigated. Viral long terminal repeat DNA duplexes were prepared and attached via the 5′-biotin linker on the plus strand to streptavidin-coated scintillation proximity assay (SPA) imaging beads. IN-DNA-bead complexes were formed by incubating with wild-type or mutant IN protein with DNA-bead complex at 37°C. INSTI binding was initiated by mixing IN-DNA-bead complex or DNA-bead complex (control wells) and [^{3}H]-labeled DTG, ELV, or RAL in 96-well microtiter plates overnight to obtain maximum binding. DTG demonstrated slower dissociation from all IN-DNA complexes tested, including those with single and double residue INSTI substitutions, compared to EVG and RAL.

The dissociation rate of [^{3}H]-labeled INSTIs was determined against a panel of recombinant integrase proteins. The panel included wild-type and signature EVG- and RAL-resistant substitutions (E92Q, G140S, Y143C, Y143H, Y143R, Q148H, Q148K, Q148R, N155H, E92Q/N155H, E138K/Q148R, G140S/Q148H). For wild-type integrase, the half-life ($t_{1/2}$) of dissociation for DTG was approximately 71 hours, compared to the half-life of 2.7 hours for EVG and 8.8 hours for RAL. Faster dissociation (shorter half-lifes) of DTG were observed for mutants E92Q (17 hours), Y143C/H/R (42-60 hours), Q148H/K/R (5.2-11 hours) and N155H (9.6 hours) integrase

mutants compared to wild-type (71 hours). The addition of a second substitution (E92Q, E138K, G140S) to either a Q148 or N155 mutant resulted in faster dissociation of DTG with a decrease in the half-life of 3-4 hours compared to the single mutant. The addition of multiple RAL secondary substitutions to IN with Q148H generally resulted in faster DTG dissociation. Dissociative half-lives of 2 hours and 1 hour were obtained for DTG with IN-DNA complexes containing the E138K/G140S/ Q148H/ M154I and V75I/E138K/G140S/Q148H/M154I substitutions, respectively. Half-lives of 0.3-0.6 hours were observed for combination mutants E92Q/G140S/Q148H and G140S/Q148H/N155H. However, the dissociative half-life for DTG was greater than 10 hours (10.3 to 15.5 hours) for IN-DNA complexes containing the IN substitutions from DTG passage studies G118R, G118R/E138K, P145S, or R263K.

ANTIVIRAL ACTIVITY

DTG demonstrated antiviral activity with EC_{50} values ranging from 0.51 to 2.2 nM against BaL HIV-1 in PBMCs, HIV-1IIIB in MT4 cells and pseudotyped HIV-1 in CIP4 cells (Table 3; Module 2.7.2.4 Special Studies, page 14).

Table 3. Antiviral Activity of DTG against HIV-1 in PBMC, MT4, or CIP4 cells

Cell lines	Virus	DTG Geometric mean IC50 (nM)	95% CI	N
PBMC	Ba-L	0.51	0.34-0.77	12
PBMC	NL432	0.53	SD = 0.21	5
MT4	HIV-1^{IIIB}	0.71	0.40-1.3	9
MT4	HIV-1^{IIIB}	2.1	SD = 0.82	3
CIP4	PHIV vector	2.2	0.96-5.2	2

DTG demonstrated equivalent activity (mean EC_{50} values 1.3 - 2.1 nM) against 2 NNRTI-resistant (K103N, Y188L) and 3 nucleoside inhibitor (NRTI)-resistant (M184V; D67N/K70R/T215Y; V75I/F77L/F116Y/Q151M) isolates compared with the wild-type strain (EC_{50} value = 1.4 nM) in a HeLa-CD4 assay. DTG also demonstrated comparable antiviral activity in an MT4 assay against 2 protease inhibitor (PI)-resistant HIV-1 mutant clones (M46I/I47V/I50V; L24I/M46I/L63P/A71V/ G73S/V82T) with mean EC_{50} values of 0.4 nM compared with the EC_{50} value = 0.88 nM for the wild-type strain.

Susceptibility of Multiple Clade B Clinical Isolates of HIV-1

The susceptibility of 13 clinically diverse HIV-1 clade B isolates to DTG was tested with the Monogram Bioscience's PhenoSense assay. The mean EC_{50} value for viral replication of the clinical isolate based viruses was 0.52 nM (range 0.41 to 0.60 nM) (Table 4; Module 2.7.2.4 Special Studies, page 17).

Table 4. Activity of DTG against a Panel of HIV-1 Clinical Isolates

Virus	IC_{50} (nM)
ASJM 108	0.54
ASM 34	0.54
ASM 42	0.59
NIH 57	0.60
NIH 660	0.41
NIH 657	0.54
NIH 714	0.54
NIH 727	0.50
CV 110	0.49
CV 154	0.49
CV 163	0.55
CV 243	0.43
CV 281	0.49
HIV-1 IIIB	0.46
HXB2	0.65
NL4-3	0.60
Isolate mean	0.52
Isolate Median	0.54
Isolate standard deviation	0.06
Isolate range	0.41 - 0.60
Laboratory virus mean	0.57
Laboratory virus median	0.60
Laboratory virus standard deviation	0.10
Laboratory virus range	0.46 - 0.65

The antiviral activity of DTG was tested against a panel of HIV-1 isolates (3 in each group of M clades A, B, C, D, E, F and G, and 3 group O isolates) and 3 HIV-2 isolates, in PBMC assays. DTG had activity against all HIV-1 (geometric mean EC_{50} of 0.20 nM with a range of 0.02 to 2.14 nM) and HIV-2 (geometric mean EC_{50} of 0.18 nM with a range of 0.09 to 0.61 nM) isolates tested. In cell-based monocyte-derived macrophage assays using 4 clade B isolates, the geometric mean EC_{50} value was 0.87 nM and values ranged from 0.37 to 1.98 nM. The mean antiviral activity of DTG against different HIV-1 subtypes and HIV-1 in PBMCs is summarized in Table 5 (Module 2.7.2.4 Special Studies, page 19).

Table 5. Mean Activity of DTG against HIV-1 Subtypes and HIV-2 in PBMCs and Subtype B Isolates in Macrophages

Virus	Mean IC_{50} (nM)
Subtype A	0.26
Subtype B	0.62
Subtype C	0.23
Subtype D	0.23
Subtype E	0.22
Subtype F	0.25
Subtype G	0.36
Group O	0.87
HIV-2	0.29
Subtype B in Macrophages	1.07

Antiviral Activity against Non-HIV Viruses

DTG was evaluated for antiviral activity against a panel of 19 non-retrovirus isolates. No significant antiviral activity was seen against this panel containing bovine viral diarrhea virus (BVDV) (EC_{50} value = 66 μM), dengue virus (EC_{50} value = 69.5 μM), measles (EC_{50} value = 30.3 μM), hepatitis C virus replicon (HCV) (EC_{50} value = 11.2 μM), varicella zoster virus (VZV) (EC_{50} value = 88.1μM) in addition to other viruses (Table 6; Module 2.7.2.4 Special Studies, page 20). The applicant also noted DTG caused a mild cytotoxic effect at the high test concentration.

Table 6. Activity of DTG against a Range of Viruses in Cytoprotection Assays

Virus	High Concentration (μM)	IC50 (μM)	TC50 (μM)
Adenovirus	100	>100	>100
Bovine Viral Diarrhea Virus	100	66	>100
Dengue Virus (serotype 2)	100	69.5	>100
Yellow Fever Virus	100	>100	>100
HSV-1	100	>100	>100
HSV-2	100	>100	>100
Influenza A	100	>100	64.9
Influenza B	100	>100	75.7
Human Parainfluenza	100	>100	>100
Measles Virus (Morilli virus)	100	30.3	>100
Respiratory Syncytial Virus	100	>100	>100
Coxsackie A Virus	100	>100	97.6
Coxsackie B Virus	100	>100	>100
Enterovirus	100	>100	>100
Polio Virus	100	>100	>100
Rhinovirus	100	>100	>100
HCV	100	11.2	96.7
HCMV	100	>100	>100
VZV	100	88.1	>100

HCV was assessed in an HCV replicon assay.
Human cytomegalovirus (HCMV) and varicella zoster virus (VZV) were assessed in a plaque reduction assay.

ANTIVIRAL ACTIVITY OF DTG IN THE PRESENCE OF HUMAN SERUM PROTEINS

The effect of human serum albumin (HSA) (20 or 40 mg/mL), α1-acid glycoprotein (AAG) (2 mg/mL) (Table 7; Module 2.7.2.4 Special Studies, page 14) and human serum (extrapolated up to 100%) on the antiviral activity of DTG was evaluated in PHIV or MT-4 assay systems. HSA was the predominant DTG binding component compared with AAG. In the presence of 40 mg/mL HSA, the EC_{50} value of DTG in MT4 cells against HIV-1 IIIB decreased 12-fold. The maximum fold shift in EC_{50} value observed with MT-4 assays extrapolated to 100% human serum was a mean consensus 75-fold for DTG with an extrapolated EC_{50} value of 38 nM for PBMCs in 100% serum.

Table 7. The Effect of Serum Proteins on Antiviral Activity of DTG in HIV-1 IIIB-Infected MT4 Cells

Serum Protein	Geometric Mean IC50	95% Confidence Interval	Potency Shift	N
40 mg/mL HSA	18 nM	16 – 21 nM	12-fold	10
2 mg/mL AAG	3 nM	2.6 – 3.5 nM	2-fold	4

CYTOTOXICITY

Cytotoxicity assays with DTG were conducted in parallel with the antiviral assays. Overall, the cytotoxicity measured in these assays provided a therapeutic index from >350-fold to 6,800-fold indicating that the observed antiviral activity of DTG was not due to cytotoxicity.

In addition, cytotoxicity assays were conducted in proliferating human leukemic and lymphomic cell lines and PHA stimulated and unstimulated human PBMCs from the same donors, with resulting cell cytotoxicity CC_{50} values for DTG in proliferating IM-9, U-937, MT-4 and Molt-4 cells of 4.8, 7.0, 14 and 15 μM, respectively. In stimulated and unstimulated PBMCs, CC_{50} values were 52 μM and 189 μM, respectively (Table 8; Module 2.7.2.4 Special Studies, page 16). When compared to the antiviral activity of DTG EC_{50} value of 0.51 nM in PBMCs, the therapeutic index for antiviral activity was >9,400.

Table 8. Cytotoxicity Assay Results in PBLs and B and T Cells

Cell lines	DTG CC50 (μM)	95% CI	Flavopiridol CC50 (μM)	95% CI
IM-9 (n=4)	4.8	3.0-7.7	0.019	0.012-0.030
U-937 (n=4)	7.0	4.8-10	0.035	0.024-0.050
MT-4 (n=4)	14	7.0-29	0.13	0.062-0.26
Molt-4 (n=4)	15	12-19	0.16	0.13-0.21
Stimulated PBLs (n=8)	52	36-76	0.36	0.25-0.53
Unstimulated PBLs (n=8)	189	58-620	0.29	0.15-0.56

ANTIVIRAL ACTIVITY OF DTG IN COMBINATION WITH OTHER ANTIRETROVIRALS

DTG was tested for antiviral activity in combination with currently approved antiviral drugs. The anti-HIV-1 activity in cell culture of DTG was studied in checkerboard format in combination with representative anti-HIV drugs (stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide (T20), and raltegravir (RAL)) and the anti-HBV drug (adefovir; PMEA) in MT-4 cells with HIV-1 strain IIIB (Table 9; Module 2.7.2.4 Special Studies, page 15), and in combination with the anti-HIV drug maraviroc in Magi-CCR5 cell line with HIV-1 strain BaL. All anti-HIV drugs were additive or synergistic with DTG, and adefovir (PMEA) had no apparent effect on DTG activity. The anti-HIV activity of DTG was also measured in the presence of fixed concentrations of ribavirin. The anti-HIV activity of DTG was not antagonized in the presence of ribavirin concentrations up to 5.06 μM. The combination of ribavirin and d4T was used as an antagonistic control and ribavirin antagonized the anti-HIV activity of d4T.

Table 9. Inhibition of HIV-1IIIB by DTG in Combination with Other Marketed Anti-HIV Agents in MT-4 cells

Compound	Deviation from Additivity			Interaction with DTG
	Average	S.E.	p-value	
DTG	0.031	0.151	0.423	Additive
D4T	-0.473	0.083	0.001	Synergy
ABC	-0.605	0.150	0.002	Synergy
EFV	-0.356	0.102	0.005	Synergy
NVP	-0.246	0.087	0.015	Synergy
LPV	-0.310	0.082	0.005	Synergy
APV	-0.332	0.085	0.003	Synergy
T-20	-0.245	0.110	0.034	Synergy
PMEA	-0.179	0.168	0.168	Additive
RAL	-0.05	0.16	0.39	Additive

RESISTANCE DEVELOPMENT IN CELL CULTURE

Virus cultures were derived by co-culturing MT-2 cells with Molt-4 cells persistently infected with HIV-1 strain IIIB. This strain has ~40% T124A polymorphism in the integrase (IN) in viral stocks used for passage (Kobayashi, 2011). The culture media from the co-cultures including resuspended co-cultured cells was used for initiating passage of resistant variants. Every 3 or 4 days the cells were examined for apparent cytopathic effects and supernatants were used to infect new MT-2 cells in the presence of increasing DTG concentrations (up to 5-fold). Infected cell DNA was prepared and HIV proviral DNA sequence was determined.

At selected intervals (14, 28, 42, 56, 70, 84, 98 and 112 days), susceptibility to DTG was measured using the supernatant from passaged cells in assays using HeLa-CD4 cells carrying a reporter β-galactosidase gene. Passaged viruses with a 4.1-fold maximum resistance to DTG were observed during the 112 day passage, with substitutions at the

conserved IN positions S153F and S153Y. These data are consistent with DTG directly targeting the HIV-1 integrase in cells.

Wild-type HIV-1 NL432 and molecular clones with single amino acid substitutions (E92Q, Q148H, Q148K, Q148R, and N155H) within the IN open reading frame were passaged sequentially under increasing concentration of DTG for up to 56 days. Passaged virus populations were analyzed for genotypic changes on Days 14, 28, 42 and 56, and for phenotypic fold-change on Day 56 samples.

Passage of the wild-type HIV-1 NL432 in the presence of 6.4 nM DTG selected for E92Q (fold-change =3.1) and G193E (fold-change =3.2) substitutions in the IN region on Day 56. Passage of the Q148K mutant selected E138K/Q148K (fold-change = 47 to 190) on Day 14 and was present throughout the remaining passages up to 32 nM DTG with no additional substitutions selected up to Day 56. Passage of the Q148R mutant selected E138K/Q148R and G140S/Q148R (fold-change =16) on Days 14 and 28, respectively, in the presence of 6.4 nM DTG. Further passage at ≤32 nM DTG selected E138K/G140S/Q148R (fold-change =13). Substitutions T97A/G140S/Q148H (fold-change =44) and V75I/E138K/G140S/Q148H/M154I (fold-change =46) were selected on Day 56 in the presence of 32 nM DTG. Passage of the E92Q or N155H mutant viruses in the presence of DTG did not lead to additional substitutions. Passage of site-directed mutant viruses with polymorphic substitutions L101I, L101I/T124A, and RAL resistance substitutions Y143C and Y143R in the presence of DTG did not lead to additional substitutions in these experiments.

Passage of G140S/Q148H at 6.4 nM DTG selected the addition of N155H at Day 28 (fold-change = 85 to >120) and E92Q (fold-change >120), and of E92Q/E138K by Day 56 (fold-change >120). Passage at 32 nM DTG selected for addition of F139S at day 28 (fold-change not determined), L74M at Day 42 (fold-change = 15 to 95), or L74M/T123S/V113L (fold-change >120).

Additionally, serial passage experiments were performed with DTG using healthy donor primary human cord blood mononuclear cells (CBMCs) infected with various subtype B, C, and A/G viruses. After 20 weeks, the R263K substitution was observed in all 5 subtype B selections and 1 of 2 subtype A/G selections. The R263K substitution was detected alone or in combination with other substitutions that varied among virus strains. During the selections, neither L101I nor T124A appeared. However, the S153Y substitution was observed in combination with R263K for one subtype B virus and S153S/T was detected in one subtype C virus. Importantly, the only subtype B or A/G virus that did not bear the R263K substitution carried the G118R substitution, which was characterized as a resistance substitution to MK-2048, another second generation integrase inhibitor. The G118R substitution was observed in one subtype C virus.

CROSS-RESISTANCE

Site-Directed Mutants

The susceptibilities of DTG and RAL were compared using 60 RAL resistant site-directed HIV-1 mutants and 6 site-directed HIV-2 mutants. Twenty-eight HIV-1 viruses with single substitutions (Table 10; Module 2.7.2.4 Special Studies, page 27) and 32

Reference ID: 3310743

HIV-1 viruses with two or more substitutions (Table 11; Module 2.7.2.4 Special Studies, page 28) were produced from wild-type virus NL-432 using site-directed mutagenesis. Susceptibility to DTG and other INSTI was tested in a HeLa-CD4 cell assay carrying a reporter β-galactosidase gene driven by an HIV-1 LTR. DTG showed >2-fold change in susceptibility against mutant viruses with single substitutions T66K, I151L and S153Y (Table 10). DTG showed >2-fold change in susceptibility against mutant viruses with multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148H and combinations of substitutions at E138/G140/ Q148 (Table 11).

Overall, for these site-directed mutants, RAL showed a fold-change of >2 for 44 of 60 (73%), a fold-change of ≥10 for 32 of 60 (53%). Of the 46 mutant viruses with data for EVG, 39 of 46 (85%) showed a fold-change of >2 and a fold-change of ≥10 for 30 of 46 (65%).

Table 10. Fold Change (FC) of DTG and RAL against INSTI-Resistance Single Site-Directed Mutant Viruses by HeLa-CD4 Assay

virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
Wild type (NL432)	1.0 (IC50=2.1 nM, SD=0.36)	1.0 (IC50=6.1 nM, SD=0.89)	-
Wild type (NL432)	1.0 (IC50=2.0 nM, SD=0.34)	1.0 (IC50=8.6 nM, SD=1.3)	1.0 (IC50=1.3 nM, SD=0.24)
T66A	0.26 (0.01)	0.61 (0.09)	-
T66I	0.26 (0.09)	0.51 (0.10	8 (1.7)
T66K	2.3 (0.35)	9.6 (1.3)	84 (29)
E92I	1.5 (0.19)	2.1 (0.62)	-
E92Q	1.6 (0.12)	3.5 (1.4)	19 (8.1)
E92V	1.3 (0.20)	1.4 (0.18)	-
G118R	10 (4.7)	7.2 (1.5)	-
G118S	1.1 (0.21)	1.2 (0.30)	-
F121Y	0.81 (0.12)	6.1 (1.3)	36 (23)
T124A	0.95 (0.19)	0.82 (0.08)	1.2 (0.29)
E138K	0.97(0.029)	1.0 (0.30)	0.93 (0.12)
G140S	0.86 (0.30)	1.1 (0.22)	2.7 (0.63)
Y143C	0.95 (0.26	3.2 (0.57)	1.5 (0.46)
Y143R	1.4 (0.29)	16 (3.9)	1.8 (0.16)
Y143H	0.89 (0.11)	1.8 (0.38)	1.5 (0.047)
P145S	0.49 (0.08)	0.87 (0.20)	>345
Q146R	1.6 (0.17)	1.2 (0.26)	2.8 (0.72)
Q148H	0.97 (0.67)	13 (5.0)	7.3 (2.3)
Q148K	1.1 (0.19)	83 (6.6)	>1726
Q148R	1.2 (0.21)	47 (9.3)	244 (91)
+I151L	3.6 (3.6)	8.4 (4.7)	-
S153F	1.6 (0.20)	1.3 (0.14)	2.8 (0.93)
S153Y	2.5 (1.1)	1.3 (0.19)	2.3 (0.49)
M154I	0.93 (0.27)	0.82 (0.18)	1.1 (0.18)
N155H	0.99 (0.094)	8.4 (1.8)	25 (7.8)
N155S	1.4 (0.36)	6.2 (1.9)	68 (2.6)
N155T	1.9 (0.32)	5.2 (2.0)	-
G193E	1.3 (0.25)	1.3 (0.35)	1.3 (0.40)

Table 11. Fold Change (FC) of DTG and RAL against INSTI-Resistance Multiple Mutant Viruses by HeLa-CD4 Assay

virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
Wild type (NL432)	1.0 (IC50=2.1 nM, SD=0.36)	1.0 (IC50=6.1 nM, SD=0.89)	-
Wild type (NL432)	1.0 (IC50=2.0 nM, SD=0.34)	1.0 (IC50=8.6 nM, SD=1.3	1.0 (IC50=1.3 nM, SD=0.24)
T66I, I74M	0.35 (0.08)	2.0 (0.81)	-
T66I, E92Q	1.2 (0.19)	18 (3.6)	185 (103)
T66K, L74M	3.5 (0.94)	40 (13)	117 (33)
V72I, F121Y, T125K	1.3 (0.54)	13 (7.1)	-
V72I, F121Y, T125K, I151V	1.2 (0.32)	7.0 (2.8)	-
L74M, N155H	0.91 (0.17)	28 (12)	42 (8.6)
V75I, E138K, G140S, Q148H, M154I	21 (6.6)	>660	2600 (450)
E92Q, N155H	2.5 (1.2)	>130	320 (39)
T97A, N155H	1.1 (0.46)	26 (7.9)	37 (6.9)
T97A, G140S, Q148H	13 (2.1)	>660	3900 (630)
L101I, S153F	2.0 (0.11)	1.3 (0.54)	2.6 (0.23)
L101I, T124A, S153F	1.9 (0.24)	1.4 (0.14)	2.0 (0.40)
F121Y, T125K	0.98 (0.35)	11 (0.49)	-
E138K, Q148H	0.89 (0.24)	17 (5.9)	6.7 (1.5)
E138K, Q148K	19 (8.0)	330 (75)	-
E138K, Q148R	4.0 (1.1)	110 (37)	461 (229)
E138A, Q148R	2.6 (0.47)	110	260 (12)
E138K, G140S, Q148H	4.5 (1.1)	500 (210)	1600 (370)
E138K, G140S, Q148R	8.3 (1.1)	>660	190 (43)
E138K, G140S, Q148H, M154I	8.4 (1.5)	>660	2400 (670)
E138A, S147G, Q148R	1.9 (0.89)	27 (3.7)	130 (8.8)
G140C, Q148R	4.9 (1.8)	200 (42)	-
G140S, Q148H	2.6 (1.4)	>130	>890
G140S, Q148K	1.5 (0.10	3.7 (1.3)	94 (53)
G140S, Q148R	8.4 (4.0)	200 (5.3)	-
G140S, Q148H, M154I	7.0 (0.98)	>660	3000 (780)
G140S, Q148R, V201I	10 (3.0)	>660	420 (80)
Y143H, N155H	1.7 (0.27)	38	16 (4.6)
Q148R, N155H	10 (1.4)	>140	390
N155H, G163R	1.1 (0.18)	17 (5.9)	35 (12)
N155H, G163K	1.4 (0.40)	23 (7.2)	35 (4.4)
N155H, D232N	1.4 (0.25	20 (3.9)	36 (7.1)

Six site-directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with RAL who showed virologic failure. DTG susceptibility was <2-fold against 2 HIV-2 mutant virus with substitutions S163D and G140A/Q148R (Table 12; Module 2.7.2.4 Special Studies, page 30). DTG susceptibility was approximately 4-fold for HIV-2 mutants expressing A153G/N155H/S163G and E92Q/T97A/N155H/S163D. DTG showed decreased susceptibility against HIV-2 mutants expressing E92Q/N155H (8.5-fold) and G140S/Q148R (17-fold) (Table 12). EVG and RAL showed reduced activity against 4 of the 5 mutants with full susceptibility against the S163D mutant only. DTG, EVG and RAL all had similar activity against site-directed HIV-2 mutant virus expressing S163D, which was comparable to wild-type. For the 4 resistant HIV-2

Reference ID: 3310743

mutant viruses, EVG and RAL had susceptibility fold-changes ranging from 22 to 640 and 6.4 to 420, respectively (Table 12).

Table 12. Fold-Resistance (FR) of DTG against Raltegravir-Resistant HIV-2 viruses

Compound	DTG	RAL	EVG	AZT
Viruses	Mean FC (SD)			
Wild type (ROD)	1.0	1.0	1.0	1.0
S163D	0.87 (0.070)	0.86 (0.093)	1.1 (0.40)	1.2 (0.26)
E92Q, N155H	8.5 (0.57)	110 (24)	340 (49)	2.8 (0.67)
G140A, Q148R	0.60 (0.35)	6.4 (0.38)	110 (5.7)	0.21 (0.087)
G140S, Q148R	17 (1.5)	420 (100)	640 (190)	0.43 (0.11)
A153G, N155H, S163G	3.8 (0.12)	16 (2.6)	22 (3.2)	4.5 (0.99)
E92Q, T97A, N155H, S163D	3.9 (0.35)	57 (8.0)	200 (82)	0.43 (0.049)

Clinical Samples

Thirty-nine clinical isolate samples with genotypic and phenotypic resistance to RAL (median >81-fold change) were examined for susceptibility to DTG using the Monogram Biosciences PhenoSense assay. The median fold-change to DTG for these isolates containing changes at G140S+Q148H = 3.8, at G140S+Q148R = 13, at T97A+Y143R = 1.0 and at N155H = 1.4 (Table 13; Module 2.7.2.4 Special Studies, page 32).

Table 13. Summary Fold-Change to DTG and RAL for Clinical Isolates in Subjects Failing RAL Therapy

Genotype	n	DTG FC		RAL FC	
		Median	Range	Median	Range
N155H	5	1.37	1.22 to 1.45	19.0	14.0 to 36.0
G140S, Q148H	7	3.75	2.05 to 15.0	>87	58.0 to >87
G140s, Q148R	2	13.3	7.57 to 19.0	>87	>87 to >87
T97A, Y143R	2	1.05	1.04 to 1.06	>81	>81 to >81

Seven hundred and five clinical isolates from RAL-experienced patients in Monogram Bioscience's isolate library Jan 2010 through Mar 2012 were analyzed for susceptibility to DTG using the Monogram Biosciences PhenoSense assay. The 705 isolates were selected based upon a RAL fold-change >1.5, and had diverse RAL-associated IN resistance patterns and proportions. The proportion of isolates within the different INSTI substitution categories in these samples was 13% in the Q148+≥2 substitution category, 26% in the Q148+1 substitution category, 14% in the Y143 substitution category, 29% in the N155 substitution category, 6% in the ≥2 Primary INSTI substitutions category, and 12% of the isolates were in the Primary not detected category (Table 14).

Overall, 662 (94%) of the 705 RAL resistant isolates had a DTG fold-change of ≤10, and 13 (2%) had a DTG fold-change of >25. The two Q148 categories Q148+1 and Q148+≥2 INSTI substitutions consisted of 184 and 92 isolates, respectively, and contain the majority (41 of 43) of the isolates which had a DTG fold-change >10. Of the 705 isolates, 332 (47%) had RAL fold-change > MAX measurable and were found within all categories, while 3 of 705 isolates all within the Q148+≥2 category had DTG fold-change

> MAX measurable. The tested isolates had a broad range of phenotypic fold-change within the ranges for the Q148+1 and Q148+≥2 categories.

Table 14. Proportion of Samples for INSTI Substitution Categories

	Proportion % (n)	Mean DTG FC	Range DTG FC	Mean RAL FC
All	**N = 705**	**1.76**	**0.19 - 58**	**89**
Q148+≥2	**13% (92)**	**5.98**	**1.5 - 58**	**116**
Q148+1	**26% (184)**	**4.84**	**0.49 - 44**	**116**
Y143	**13.9% (98)**	**1.24**	**0.45 - 2.2**	**100**
N155	**28.9% (204)**	**1.5**	**0.75 - 6.8**	**25**
≥2 Primary	**6% (42)**	**1.81**	**0.91 - 37**	**79**
Primary Not Detected	**12.1% (85)**	**0.88**	**0.19 - 4.3**	**4**

INSTI substitutions list, primary resistance substitutions are bolded**: Q148H, Q148K, Q148R, Y143C, Y143H, Y143R, N155H**, H51Y, G118R, S147G, S153F, S153Y, G193E, R263K, L74I, L74M, T97A, **E92Q, E92V,** E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R.

Characterization of DTG resistance in the Raltegravir-Resistant Clinical Isolate Population

To better understand the extent and evolving characteristics of DTG resistance in broad clinical practice for subjects experiencing virologic failure on RAL, queries into RAL resistant pathway frequencies was carried out on 1079 patient samples with an aim to detecting genotypic changes over time, and the proportion of isolates with potential increased DTG fold change resistance.

Interestingly, the prevalence of Q148H and G140A/C/S decreased 10-13% over the period of Aug 2008-Dec 2009 (n=273) and the period of Jan 2010-Feb 2012 (n=806), whereas other INSTI substitutions such as L74I/M, E92Q/V, E138A/K/T, Y143C/H/R, and G163K/R had little change in prevalence over the time period. INSTI substitutions T97A, V151I, N155H increased 4%, 2% and 3%, respectively, in prevalence over the time period. In the subset of isolates in the Q148+≥2 category, the majority of subjects' isolates had Q148+G140+E138 substitutions (n=46) followed by G140+L74 (n=14) and then Q148+G140+E138+L74 (n=2).

4.6 Clinical Studies

PHASE II SPECIAL STUDIES

Minority Species Analysis Using Ultradeep Sequencing and Clonal Sequencing

Plasma samples from subjects in Study ING112961 representing different times on RAL therapy (days on RAL and days off RAL) were selected for ultradeep pyrosequencing (UDPS) at both Screening and Day 1. A total of 40 viruses (16 Screen, 24 Day 1) were analyzed by UDPS. UDPS identified additional INSTI-associated resistance substitutions (L74M or I, T97A, E138A or T, G140S, Q148R, V151I, N155H, G163K, G193E) in quasispecies at screen or Day 1 in 14 of the 40 (35%) subjects tested (Table 15; Module 2.7.2.4 Special Studies, page 42). The frequency of these INSTI-associated resistance substitutions detected by UDPS was generally below 5%, but ranged from 1% to 57%. No novel INSTI resistance substitutions were detected.

Table 15. UDPS Summary INSTI-Associated Resistance Substitutions Detected in Screen or Day 1 Virus but Not Detected by Population Genotyping

Subject	Visit Type	Viral RNA	Time On RAL	Time Off RAL	Screen/Day1 Population Genotyping INI-Associated Resistance Mutations	Screen/Day1 UDPS Summary INI-Associated Resistance Mutations not Detected by Population Genotyping (Frequency ≥1%)
1110[b]	Screen	35361	333	146	none	none
1140	Screen	41467	29	351	none	none
1150	Screen	7765	177	688	none	none
1130[b]	Day 1	1781	700	0	G140S, Q148H	none
1141	Day 1	26776	827	0	L74L/M/I, E138D, V151V/I, N155H, G163R	L74M (10.07%), V151I (21.02%)
1171	Day 1	815	674	0	G140S, Q148H	none
1610	Day 1	48736	1176	0	V151I, N155H	none
1611	Day 1	13350	802	0	L74M, E92A, Y143R	none
1612	Day 1	52935	816	287	L74I, T97A, Y143R	none
1621	Day 1	57497	1254	0	L74M, T97A, E138A, Y143R	none
1622	Day 1	7385	810	20	L74L/M, T97A, E138K/T/Q/P, Y143R	none
1630	Day 1	7434	944	0	L74I, G140S, Q148H	none
1640	Day 1	173080	103	0	L74M, T97A, Y143R	none
1662	Day 1	5587	1078	169	E92Q	N155H (22.30%), T97A (1.76%), G193E (2.38%)
1680	Day 1	240221	743	0	G140S, Y143H, Q148H	L74I (2.63%), L74M (1.0%), E138A (6.32%)
1681	Day 1	9771	754	0	G140S, Q148H	none
1703	Day 1	10255	731	71	E138A, G140S, Y143H, Q148H	none
1811	Day 1	45907	1078	96	none	G140S (4.52%), Q148 (4.4%)
2000[c]	Screen	42263	1178	0	NA[a]	E92Q (8.28%)
2100	Screen	234337	762	41	NA	none
2101	Screen	2971	728	67	G163E	G163K (23.78%)
2102	Screen	2261	1076	0	none	T97A (1.76%), N155H (33.24%), G193E (2.38%)
2103	Screen	16278	147	579	none	T97A (7.29%),
2104	Screen	160576	818	55	none	none
2122	Screen	14151	363	572	NA	none
2201	Screen	75422	174	103	none	none
2202	Day 1	18621	1901	0	E138E/K, G140G/S, Q148Q/H	none
2310	Day 1	68652	1174	0	G140S, Q148H	none
2340	Day 1	60256	1505	0	T97A, V151I, N155H	none
2360	Screen	1291	490	561	none	L74I (15.22%)
2369	Screen	4508	984	287	none	none
2410	Day 1	12841	836	0	L74L/M, E138E/K, Y143R	L74M (2.56%), Q148R (3.60%), T97A (56.6%)
2415	Day 1	147851	941	312	L74L/M, T97T/A, Y143Y/C	none
2430	Day 1	28875	310	664	E138A, Q148H	E138T (3.98%)
2432	Day 1	51505	NA	NA	G140S, Y143Y/H/R/C, Q148H	G163R (2.47%)
2460	Day 1	12378	316	0	G140S, Q148H	none
2461	Screen	210935	930	0	E138E/D, V151I	G193E (1.11%)
2462	Day 1	16306	868	0	G140S, Q148H	none
2464	Screen	16522	1123	0	none	none
2480	Screen	75938	247	3	L74M, E92Q, T97A	none

a. NA- Data not available
b. Subjects enrolled in Cohort I are Day 1 and numbered in the 1000 range
c. Subjects enrolled in Cohort II are Day 1 and numbered in the 2000 range

Clonal analyses were also performed on virus from subjects experiencing virologic failure by week 24 at both the Day 1 and protocol defined virologic failure (PDVF) time

points. The percentage of additional substitutions (T66A, T97A, Y143H or C, N155H, G193E) detected by clonal sequencing at failure ranged from 0.5% to 17% (Table 16; Module 2.7.2.4 Special Studies, page 44).

Table 16. Summary of INSTI-Associated Resistance Substitutions Detected and Frequency at Day 1 and VF by Clonal Analyses but Not by Population Genotyping

Subject	IN Mutational Group	Virologic Failure Visit	INI-Associated Resistance Mutations			
			Day 1 Population	Day 1 Additional Mutations detected by Clonal[a]	VF Population	VF Additional Mutations detected by Clonal[a]
1680[d]	Mixture	Day 11	G140S, Y143H, Q148H	L74M (3.2%) L74I (2.4%) E138A (96.8%)	L74I/M, T124A[b], E138E/A, G140S, Q148H	Y143H (17.2%)
1630	Q148+2	Day 11	L74I, G140S, Q148H	T97A (0.8%)	L74I, T124A, G140S, Q148H	NA[c]
1624	Q148+2	Day 11	E138K/T, G140S, Q148H	T97A (27.4%), Y143C (0.5%),	E138K, G140S, Q148H	T97A (2.0%)
1625	Q148+2	Day 11	L74I, G140S, Q148R,G163R	T66I (3.9%), T97A (0.7%)	L74I , G140S, Q148R, G163R	None[f]
1681	Q148+1	Day 11	G140S,Q148H	T97A (0.7%)	G140S, Q148H	None
1703	Mixture	Day 11	E138A,G140S, Y143H, Q148H	R263K (0.5%)	E138A, G140S, Y143H, Q148H	G193E (0.6%)
1811	Other	Week 8	None	T97A (0.6%), G140S (1.8%), Y143H (0.6%), Q148H (1.8%)	L74L/M/I, T97A, G140S, Q148H	N155H (5.4%)
1610	N155	Week 12	V151I, N155H	T97A (0.4%), G193E (0.4%)	V151V/I, N155H	Y143H (0.9%)
1623	Y143	Week 12	L74I, T97T/A, E138E/K.Y143R	T66A (0.6%), L74V (4.0%), E138A (65.2%).	L74I, T97A, E138K, Y143R	NA
1700	Y143	Week 16	L74L/M, Y143R	E138K (1.2%)	Y143R	T97A (0.5%)
1621	Y143	Week 24	L74M, T97A, E138A, Y143R	G140S (0.3%), Q148H (0.3%)	L74M, T97A, E138A, Y143R, N155H	Y143C (0.9%)
1640	Y143	Week 24	L74M, T97A, Y143R	Y143C (0.7%)	L74M, T97A, Y143R, N155H	None
2310[e]	Q148+1	Week 16	G140S, Q148H	None	T97T/A,E138E/K, G140S, Q148H, N155H	T66A (0.8%)
2340	N155H	Day 11	T97A, V151I, N155H	None	T97A, V151I, N155H	NA
2462	Q148+1	Week 8	G140S, Q148H	None	E92E/V, E138E/K, G140S, Q148H, N155H	None

a. INI-associated resistance mutations not detected by population genotyping (frequency)
b. T124A is a well characterized polymorphism that has no impact on integrase resistance
c. NA – Amplicon could not be generated
d. Subjects enrolled in Cohort I are numbered in the 1000 range
e. Subjects enrolled in Cohort II are numbered in the 2000 range
f. None- no mutations detected

In addition to showing the frequency of substitutions, clonal analyses also determined the frequency of primary and/or secondary INSTI-associated substitutions residing on a subset of genomes. The clonal analyses showed that the INSTI-associated resistance substitutions detected by population genotyping accumulate and reside on a subset of genomes.

Overall, UDPS and clonal genetic analyses of subjects with PDVF did not identify any new substitutions within the viral integrase gene that are associated with resistance to DTG. UDPS identified additional INSTI-associated resistance substitutions in minority quasispecies at screen or Day 1 in 35% of subjects tested but generally at low frequencies. Clonal analyses on paired Day 1 and PDVF virus provided additional information that the INSTI-associated resistance substitutions that emerged at PDVF were added to pre-existing Day 1 INSTI-associated resistance substitution profiles and that this accumulation of INSTI-associated resistance substitutions likely contributed to failure on a DTG regimen.

Integrase Polymorphism Effects on DTG Resistance and Clinical Response

A total of 2997 integrase sequences were identified and aligned from INSTI-naïve sequences obtained from LANL and SRD. The major genomic subtypes represented in this data set included B (55%), CRF02_AG (13%), C (13%), and CRF01_AE (6%). The analysis revealed a high degree of conservation across the 288 amino acid residues. The majority of positions (59% were found to vary by <1% at the amino acid level (i.e. >99% conservation). These highly conserved positions spanned long regions across the integrase protein. A total of 34 positions met the criteria for a polymorphic site (>10% amino acid diversity) and were distributed across integrase (Vavro, 2012).

To characterize the impact on DTG susceptibility of polymorphisms seen in the integrase enzyme, a panel of site-directed molecular clones (SDMs) was constructed from pNL-432 with single, double, and triple mutants (Vavro, 2012). This panel comprised INSTI substitutions identified during passage in cell culture with DTG as well as integrase polymorphic sites. Baseline viruses from a study in INSTI-naive, HIV-infected patients were evaluated for DTG and RAL susceptibility and differences in HIV-1 RNA decline with DTG monotherapy were evaluated. Fold change susceptibility to DTG and RAL was measured using HeLa CD4 cells.

The SDMs with polymorphic amino acid changes T124A and L101I had DTG fold-change values below the assay cutoff for reduced susceptibility. The fold-change for SDMs ranged from 0.91 for the L101I/T124A double substitution to 2.5 for the non-polymorphic substitution S153Y, which arose during cell culture passage of DTG (Table 17; Module 2.7.2.4 Special Studies, page 47).The mean fold-change for L101I was 1.4 for DTG and 1.2 for RAL, each of which is within the assay's variability. The addition of polymorphisms L101I and T124A to the S153F substitution had fold-change within 2-fold. DTG trough concentrations are 19-fold above the protein-adjusted EC_{90} value of 152 nM that was observed at the once daily, 50 mg dose, which is above the maximum fold-change for these SDMs.

Table 17. DTG Drug Susceptibility for Site-Directed Mutants with Polymorphisms and Substitutions observed during DTG Passage

Amino acid substitution in NL-432	Where observed	DTG FC, mean	RAL FC, mean
L101I	Polymorphism/Passage	1.40	1.20
T124A	Polymorphism/Passage	0.95	0.82
L101I/T124A	Polymorphism	0.91	0.77
S153F	Passage	1.60	1.30
S153Y	Passage	2.50	1.30
L101I/S153F	Polymorphism/Passage	2.00	1.30
L101I/T124A/S153F	Polymorphism/Passage	1.90	1.40
E92Q	Passage	1.60	3.50
G193E	Passage	1.30	1.30

a. Assay variability of 2-fold changes

In the phase IIa dose-ranging study of DTG monotherapy, HIV-infected subjects were randomized to receive DTG (2, 10, or 15 mg) as a monotherapy or placebo every 24 hours for 10 days. Integrase genotypes and phenotypes were determined at Day 1 by Monogram Biosciences. All genotypes at polymorphic positions 101 and 124 had similar EC_{50} values and overlapping variance ranges for DTG and RAL. The average fold-change to DTG was 0.79, and the average fold-change to RAL was 0.89. No polymorphism showed an average shift in susceptibility >2-fold to either DTG or RAL, and no median fold-change observed was greater than the fold-change assay variability.

Two additional analyses for the phase IIa dose-ranging study evaluated polymorphism effects. Dose-adjusted differences in viral load response at Day 11 were compared across the 34 polymorphic positions. The differences in change from baseline in $\log_{10}$ HIV-1 RNA at day 11 after adjusting for the effect of dose in a linear model at polymorphic substitutions positions were consistent with random variation about a mean of zero and a small variance (<0.3 $\log_{10}$ copies/mL). This result indicated no apparent difference in viral load decline with any polymorphism. In addition, the effect of substitutions at each position was tested using a multivariate linear model that adjusted for dose and the presence or absence of substitutions at each position. The distribution of P values ranged from 0.035 to 0.99, a pattern consistent with no position examined having an effect on day 11 response to DTG. Baseline clinical samples taken from participants in the phase IIa study showed no differences in HIV-1 RNA decline with any polymorphism, including sites 101 and 124.

PHASE III STUDIES

STUDIES IN INSTI-NAÏVE SUBJECTS

Pivotal efficacy studies ING113086 (SPRING-2), ING114467 (SINGLE), and ING111762 (SAILING) are Phase III, international, multicenter, parallel-group randomized, double-blind, active-controlled, double-dummy studies conducted in antiretroviral (ART)-naïve (ING113086 and ING114467) and ART-experienced (INSTI-naïve) subjects (ING111762). Supportive study ING112276 (SPRING-1) is a Phase IIb international, multicenter, parallel group randomized partially blinded active controlled dose-ranging study conducted in ART-naïve subjects.

ING113086 (SPRING-2): A Phase III study of the safety and efficacy of DTG 50 mg once daily compared to RAL400 mg twice daily both administered with fixed-dose dual NRTI therapy over 96 weeks in 822 HIV-1 infected ARV-naive adult subjects; 48 week results.

Both treatment arms, 88% of DTG subjects and 85% of RAL subjects, achieved the primary endpoint of <50 copies/mL plasma HIV-1 RNA at Week 48 based on the outcomes of the FDA "snapshot" algorithm. PDVF was defined strictly as two consecutive HIV-1 RNA values ≥50 copies/mL HIV-1 RNA from Week 24 onwards. This study demonstrated DTG is non-inferior to RAL at Week 48, because the lower end of the 95% CI for the treatment difference (-2.2%) is greater than -10%.

Virologic non-responders by the FDA "snapshot" algorithm through Week 48 were more common in the RAL treatment group compared to the DTG treatment group (RAL 8%, DTG 5%). In both treatment groups, 7% of subjects were considered virologic non-responders because of lack of virologic data at Week 48.

ING114467 (SINGLE): A Phase III randomized, double-blind, active-controlled, multicenter, non-inferiority study conducted in 833 HIV-1 infected, antiretroviral-naive subjects comparing DTG 50 mg plus ABC/LAM fixed dose combination (FDC) therapy compared to fixed-dose EFV/TDF/FTC (Atripla) both administered once daily over 96 weeks.

Both treatment arms achieved the primary endpoint at Week 48 based on outcomes of the Snapshot algorithm with 88% of DTG+ABC/3TC subjects and 81% of Atripla subjects having <50 copies/mL plasma HIV-1 RNA at Week 48. The lower end of the 95% CI for the treatment difference from the primary analysis (+2.5%) is above 0% and hence superiority of DTG+ABC/3TC is concluded. Virologic response rate differences between DTG+ABC/3TC and Atripla were primarily driven by discontinuations due to AEs or deaths (DTG+ABC/3TC 2% (9/414), versus Atripla 10% (40/419)). A total of 6% virologic nonresponders were observed in the Atripla treatment group compared with the 5% in the DTG+ABC/3TC treatment group.

STUDIES IN TREATMENT-EXPERIENCED INSTI-NAÏVE SUBJECTS

ING111762 (SAILING): A Phase III, randomized, double-blind, active-controlled, multicenter, non-inferiority study. Subjects (n=715) were randomized 1:1 to receive 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. The study was conducted in INSTI-naïve subjects, whose virus had documented genotypic or phenotypic resistance to at least one member of each of at least two ART drug classes (NNRTI, N[t]RTI, PI, fusion inhibitor (T20), or CCR5 coreceptor-antagonist (maraviroc)). Randomization was stratified by screening plasma HIV-1 RNA ≤50,000 copies/mL versus >50,000 copies/mL, number of fully active drugs in background regimen (2 vs <2) and DRV/r use without primary PI resistance: subjects who use DRV/r in their background regimen and whose Screening genotype shows no primary PI substitutions, versus (capped at 170 subjects), or subjects who either do not use DRV/r

Reference ID: 3310743

or whose Screening genotype shows primary PI substitutions. When historic resistance results were utilized to determine study eligibility, primary PI substitutions may have been identified using historic genotypes.

At Week 24, 79% of subjects receiving DTG and 70% of subjects receiving RAL achieved the Week 24 endpoint of plasma HIV-1 RNA <50 copies/mL the FDA Snapshot algorithm.

STUDIES IN ELVITEGRAVIR- OR RALTEGRAVIR-RESISTANT SUBJECTS
Pivotal efficacy study ING112574 (VIKING-3) is an international, multicenter, open-label, single-arm, Phase III study to demonstrate the antiviral activity and safety of DTG in HIV-1-infected adult subjects with resistance to the INSTIs elvitegravir or raltegravir. Supportive study ING112961 (VIKING) is a Phase IIb international, multicenter, open-label single-arm sequential cohort pilot study in ART-experienced (INSTI-resistant) subjects.

ING112574 (VIKING-3): A Phase III study of DTG 50 mg BID with optimized background ART to treat HIV-1 infected adults with prior ART use and prior or current virologic failure on an INSTI-containing regimen associated with emergence of INSTI-resistant virus.

ING112574, is a single arm, open-label study with a 7-day functional monotherapy period to evaluate DTG 50 mg BID in INSTI-resistant subjects. The enrolled subjects all experienced virological failure on a EVG- or RAL-containing regimen and either have evidence at Screening of genotypic and/or phenotypic resistance to those INSTIs or documented evidence of resistance from prior EVG or RAL failure. Efficacy was assessed at Day 8 by change from Baseline in plasma HIV-1 RNA and at Week 24 by proportion of subjects with <50 copies/mL HIV-1 RNA. These two primary efficacy objectives provide a characterization of the antiviral activity of DTG alone and the durability of a DTG regimen at Week 24 with at least one other active regimen in the background therapy. The mean reduction in HIV-1 RNA at Day 8 in the ITT population was 1.43 $\log_{10}$ copies/mL, which was statistically different from 0. At Day 8, 82% of the subjects achieved a decrease in excess of 1.0 $\log_{10}$ copies/mL or <50 copies/mL. In an assessment of all subjects who had the opportunity to reach Week 24 before the data cut-off, 63% of the Week 24 ITT population (N=114) achieved viral suppression to <50 copies/mL based on the snapshot algorithm. The lack of virologic suppression to <50 copies/mL was the primary reason for virologic failure with 32% (37/114) of subject experiencing virologic failure and 4% (5/114) discontinuing due to an adverse event.

4.7 Clinical Virology

PHASE III STUDIES

INSTI substitutions that were specifically analyzed by the applicant are shown below. The bolded substitutions have been shown to confer resistance to EVG and RAL. The other listed substitutions were detected during clinical studies of INSTI and from cell culture selections experiments with DTG.

Amino Acids in HIV Integrase for Analysis	H51Y, **T66A**, **T66I**, **T66K**, L68V, L68I, L74I, L74M, L74R4, **E92Q**, **E92V**, Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, **Y143C, Y143H, Y143R**, P145S, S147G, **Q148H, Q148K, Q148R**, V151I, V151L, S153F, S153Y, **N155H**, E157Q, G163R, G163K, G193E, R263K

IN substitutions listed above in bold were defined from http://hivdb6.stanford.edu with a score of >45
All other mutations were detected during INI clinical investigation or during in vitro studies with DTG.

ING113086 (SPRING-2)

Treatment-Naïve 48 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=20) met the definition of PDVF while 7% of (n=28) subjects in the RAL treatment group met the definition of PDVF (Table 18).

In the submitted resistance dataset for Study ING113086, there were 22 subjects in the DTG arm and 30 subjects in the RAL arm. The majority of subjects in the Study ING113086 resistance dataset had low-level viremia at the failure timepoint: 68% (15/22) of subjects in the DTG arm and 77% (23/30) in the RAL arm had HIV-1 RNA viral loads ≥50 copies and ≤400 copies/mL at the failure timepoint (Table 18). There were 6 subjects in the DTG arm and 7 subjects in the RAL arm with >400 copies/mL at the failure timepoint.

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. Based on these criteria, there were 2 FDA-defined virologic failures in the DTG arm (Subjects 3999 and 4335) and 8 virologic failures in the RAL arm (Subjects 3073, 3617, 3864, 4130, 4314, 4316, 4424, and 4640) (Table 19). 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.

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 was included in the FDA virologic failure analysis because of an emergent substitution (M50M/V) in IN at Week 24 (Table 20).

Table 18. Virologic Failures

	DTG 50 mg QD N=411	**RAL 400 mg BID N=411**
Subjects in Resistance Dataset	22	30*
HIV-1 RNA at failure timepoint		
<50 copies/mL	1	
≥50 to ≤400 copies/mL	15 (68%)	23 (77%)
>400 copies/mL	6	7
PDVF Subjects	20 (5%)	28* (7%)
FDA-Defined Failures	2 (0.5%)	8* (2%)

*Subjects 3864 and 4640 in the RAL arm are included in the FDA-Defined Failures, but not in sponsor's PDVF. Subject 4424 was <400 copies/mL at Week 24 but had an emergent substitution at Week 24.

Table 19. Study ING113086

	DTG 50 mg QD	**RAL 400 mg BID**
FDA-Defined Failures	2	8
INSTI BL and Failure Genotype Results in FDA-Defined Failures	2	5
Subjects with Emergent IN Substitutions in FDA-Defined Failures	2 (A21T from mixture, and M50V/M)	3
Subjects with Phenotypic Resistance at Failure in FDA-Defined Failures	0	1
RT/PR BL and Failure Genotype Results in FDA-Defined Failures	1[a]	8[b]
Subjects* with Emergent NRTI Substitutions	0	4
Subjects* with Emergent PI Substitutions	0	0
Subjects* with Emergent INSTI Substitutions	2	3

*Overall, not just in FDA-Defined Failures
[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

Subjects predominantly had HIV-1 subtype B, with A1 being the next most common. In other subjects, a variety of subtypes were seen in small numbers, including AG, BF, C, F1, and G.

Table 20. 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)			
4316	RAL LAM/ ABC	Week 24		No BL; V37I M50I I60V T122I V113I **E157Q** K160Q A205S K211R V234L N254S S255G	Q102K		0.82 RAL
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
4640	RAL LAM/ ABC	Week 24		--	None	None	FTC 1.6 LAM 1.38

3173#	RAL TDF/ FTC	Week 24 (52 copies/mL)			**M184M/I**		FTC 1.13
3294#	RAL TDF/ FTC	Week 24 (192 copies/mL)			**A62A/V**		TDF 1.2

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

Five subjects in the RAL treatment arm had treatment-emergent resistance substitutions in their viral isolates (Table 20). Three subjects' isolates had emergent INSTI resistance substitutions; two of whcih had both INSTI and NRTI emergent resistance substitutions. Two additional subjects' isolates had emergent NRTI resistance substitutions.

- Subject 3617 isolates had treatment-emergent INSTI resistance substitutions T97T/A, E138E/D, V151V/I, and N155H at Week 24. The Week 24 virus had a 34-fold change to RAL compared to 1.15 at baseline and 2.02-fold change to DTG compared to 1.48 at Baseline. The Week 24 virus also had treatment-emergent NRTI substitutions A62A/V, K65K/R, K70K/E, and M184V with accompanying 1.44-fold change to TDF and maximal fold change to FTC.
- Subject 4424 isolates had INSTI resistance substitutions L74I and G193V emerge on treatment at Week 24 from mixtures at baseline. There was no corresponding phenotypic change to RAL or DTG. The NRTI substitution M184M/V also emerged in this subject's isolate resulting in phenotypic resistance to FTC and LAM.
- Subject isolate 4316 had a treatment-emergent INSTI resistance E157Q substitution but no change in RAL susceptibility (0.8 fold change).
- Two subjects isolates had NRTI substitutions emerge on RAL treatment with no corresponding change in phenotype: Subject 3173 had M184M/I and Subject 3294 had A62A/V, but these subjects were not included in the FDA resistance analysis set, because viral loads were <400 copies/mL.

Two subjects in the DTG treatment arm had emergent substitutions in IN without a change in phenotype (Subject isolate 3999 had an emergent A21T substitution and Subject 4335 isolate had an emergent M50M/V mixture and an L74I substitution at baseline) (Table 20).

Some subjects' isolates from the sponsor PDVF analysis had INSTI substitutions (H51Q, L74I, G163Q, or G193E) at baseline (Table 21). However, none of these subjects were considered virologic failures in the FDA analysis because the viral load at failure was below 400 copies/mL. Most of these subjects did not have a post-baseline genotype sample and even those with a post-baseline sample did not have additional emergent INSTI substitutions.

Table 21. INSTI Substitutions at Baseline in Study ING113086

PID	ARM	Baseline IN Genotype	Failure/Viral Load	Baseline Phenotype	Post BL IN Genotype
4003	DTG	V151I	Week 48 = 131 copies/mL	0.81	--
4119	DTG	L74I G163E	Week 32 = 57 copies/mL	0.65	L74I G163E
4290	DTG	L74I	Week 24 = 54 copies/mL	0.79	--
4387	DTG	L74I	Week 24 = 59 copies/mL	1.04	--
4391	DTG	L74I	Week 32 = 103 copies/mL	0.92	--
4559	DTG	G193E	Week 48 = 131 copies/mL	0.76	
3270	RAL	G163Q	Week 24 = 83 copies/mL	0.8	G163Q
4021	RAL	G193E	Week 32 = 195 copies/mL	1.37	--
4135	RAL	H51Q	Week 32 = 84 copies/mL	0.84	--
4308	RAL	L74I	Week 40 = 150 copies/mL	1.14	L74I
4343	RAL	L74I	Week 24 = 89 copies/mL	1.04	L74I

ING114467 (SINGLE)

Treatment-Naïve 48 Week Results: DTG 50 mg once daily plus ABC/LAM fixed dose combination (FDC) compared to fixed-dose dual EFV/TDF/FTC (Atripla)

In the submitted resistance dataset for Study ING114467, there were 19 subjects in the DTG arm and 20 subjects in the Atripla arm. In the DTG treatment arm, 17 subjects (4%) met the definition of PDVF and 17 (4%) subjects in the Atripla treatment group met the definition of PDVF (Table 22). 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: 79% (15/19) of subjects in the DTG arm and 60% (12/20) in the Atripla arm (Table 22). Based on the FDA criteria for virologic failure analysis at Week 48, there were 5 subjects (1.2%) in the DTG arm and 12 subjects (3%) in the Atripla arm with >400 copies/mL HIV RNA at the failure timepoint or resistance data at failure.

Subjects 5233, 5252, 6860, 6934, 7912 in the DTG arm were analyzed in the FDA resistance analysis. One subject, 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). Two subjects had emergent substitutions in RT (Table 23). Subject 6934 had an emergent W88W/R substitution but no phenotypic resistance to ABC or LAM. Subject 7912 had an emergent Q91Q/R substitution and the

E138A substitution changed from E138G, but again there was no phenotypic resistance to ABC or LAM.

In the comparator Atripla arm, 6 subjects had emergent EFV resistance substitutions of which 4 had corresponding EFV phenotypic resistance (Table 23). One of these subjects also had emergent mixtures of NRTI resistance substitutions with no change in TDF or FTC susceptibility.

Table 22. Study ING114467 RESISTANCE ANALYSIS

	DTG/ABC/LAM N=414	**ATRIPLA N=419**
Subjects in Resistance Dataset	19	20
Subjects with PDVF (sponsor)	17 (4%)	17 (4%)
HIV-1 RNA at failure timepoint/resistance analysis timepoint		
<50 copies/mL	6	6
≥50 to ≤400 copies/mL	9	6
>400 copies/mL	4	8
FDA-Resistance Analysis Set (>400 copies/ml or resistance data at failure)	5[a] (1.2%)	12 (2.9%)
Subjects with Post BL IN	7	
Subjects with Emergent INSTI-Resistance Substitutions	1[b] (14%)	--
Subjects with Post BL RT	9	10
Subjects with Emergent NNRTI-Resistance Substitutions	--	6 (60%)
Subjects with Emergent NRTI – Resistance Substitutions	0	1 (10%)
Subjects with Phenotypic Resistance at Failure	0	4 (40%)

[a] Subjects 5233, 5252, 6860, 6934, 7912
[b]Subject 7912 (E157Q/P)

Table 23. 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 Substitutions and BL Phenotype**	**Emerging INSTI Subst**	**Phenotypic Fold Change at Failure**
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
6707	Atripla	WK24		**K65K/R** **D67D/G** **G190G/E** Q197Q/R			TDF 0.7 FTC 1.3
6856	Atripla	WK24	**K103R**	**V179V/D** **G190G/A** L264L/S			EFV-R 20X
6886	Atripla	WK48		**V90V/I** **K103N** C162S A272P			EFV-R 18X
5233	DTG	WK24 FU	S68G			A128A/V	DTG 1.0
5252	DTG	WK24 FU			V72V/I G163G/E G193G/E	V72I P90P/S	DTG 1.2
6860	DTG	WK48			--	--	--
6934	DTG	WK24		W88W/R	V72I G193E	--	--
7912	DTG	WK24	E138G	Q91Q/R E138A	V72I L74L/V E157Q	**E157Q/P** K173K/E K266K/R	DTG 1.1

ING111762 (SAILING)

Treatment-Experienced INSTI-Naïve Week 24 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 24, 79% (n=281) of subjects receiving DTG and 70% (n=252) of subjects receiving RAL achieved the Week 24 endpoint of plasma HIV-1 RNA <50 copies/mL the FDA Snapshot algorithm (Table 24). Analysis of response by phenotypic susceptibility score (PSS) determined that 80% (n=198) of subjects with PSS=2 in the DTG arm responded compared to 69% (n=185) in the RAL arm. Of subjects with PSS<2, 77% (n=83) responded in the DTG arm compared to 71% (n=67) in the RAL arm. Therefore, response rates for subjects taking DTG were better than for subjects taking RAL whether they had ≤2 susceptible drugs in their background regimen. Most subjects (~80%) had DRV/r as one of their background drugs. For subjects taking DRV/r, response rates in the DTG arm were similar for subjects regardless if their HIV had major PI substitutions (82% without vs. 83% with) (Table 24). Subjects not taking DRV/r as one of their background drugs had better response rates in the DTG arm (79%) than subjects in the RAL arm (69%) (Table 24).

Table 24. ING111762 (N=719) Week 24 HIV-1 RNA Response

	DTG 50 mg once daily (N=357)	RAL 400 mg twice daily (N=362)
RESPONDERS	281 (79%)	252 (70%)
Response by		
PSS = 2	80% (198/249)	69% (185/268)
PSS < 2	77% (83/108)	71% (67/94)
Used DRV/r	83% (123/149)	79% (124/156)
Without major PI substitutions	82% (60/73)	80% (66/82)
With major PI substitutions	83% (63/76)	79% (60/76)
No DRV/r Use	79% (275/349)	69% (246/355)

In the DTG treatment arm of Study ING111762, 21% of subjects (n=76) met the definition of PDVF and 30% (n=110) subjects in the RAL treatment group met the definition of PDVF (Table 25). Based on the FDA criteria for resistance analysis (>400 copies/mL HIV-1 RNA at the failure timepoint or Week 24 or with resistance data at failure), there were 33 subjects (9%) in the DTG arm and 49 subjects (14%) in the RAL arm. Of the 33 subjects in the DTG FDA resistance analysis set, 18 had post-baseline resistance data; 16 with INSTI post-baseline resistance data and 13 subjects with RT/PR post-baseline resistance data.

Table 25. ING111762 RESISTANCE ANALYSIS

	DTG 50 mg once daily (N=357)	RAL 400 mg twice daily (N=362)
PDVF FAILURES	76 (21%)	110 (30%)
FDA-Defined Resistance Analysis Set (>400 copies/mL or resistance data at failure)	33 (9%)	49 (14%)
With Post Baseline Data	18 (5%)	38 (10%)
INSTI Post BL Data	16	35
Emergent INSTI Resistance Substitutions and/or phenotypic resistance	5[a] (31%)	10[b] (29%)
RT/PR Post BL Data	13	34
Emergent NRTI-Resistance Substitutions	1 (8%) (V75L)	7 (21%)
Emergent NNRTI-Resistance Substitutions	4 (31%) NOTE: EFV	4 (12%)
Emergent PI -Resistance Substitutions	0	5 (15%)

[a] Subjects 351, 672, 1067, 2568, and 2785 (substitutions at L74, Q95, T97, E138, V151, G163, R263)
[b]Subjects 260, 419, 785, 963, 977, 1146, 2427, 2688, 2769 and 9088 (substitutions at L74, E92, T97, G140, Y143, Q148, V151, N155, G163)

Five subjects (31%) [Subjects 351, 672, 1067, 2568, and 2785] in the DTG arm had emergent INSTI substitutions (L74M and I, Q95Q/L, T97A, V151V/I, and R263K) (Table 26). None of these subjects' isolates had emergent DTG or RAL phenotypic resistance.

One subject failure isolate (Subject 2516 on DTG, LPV/r and AZT) had a V75L resistance substitution emerge in RT from a mixture (V75V/L) at baseline (V75I is a multidrug resistant substitution IAS-USA 2013]. Four subjects taking a background NNRTI had emergent NNRTI resistance substitutions. Two of these subjects were taking EFV; Subject 2568 had a failure isolate with emergent G190S and 136-fold resistance to EFV and Subject 2785 had a failure isolate with emergent K101K/E and G190A and 105-fold resistance to EFV. Subject 1113 was taking FPV/r, but had emergent V106V/I and Subject 941 was taking ATV/r but had emergent K101Q/P from K101Q at baseline. Subject 9080 had EFV resistance (63-fold) at baseline but was assigned a DTG, EFV and TDF regimen and had 88-fold resistance to EFV at failure without resistance to DTG or TDF.

Table 26. ING111762 (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 Substitutions and BL Phenotype	Emerging INSTI Subst	Fold Change at Failure
262	MVC TDF	WK16	PR: A71V V77I RT: V179D/E	No Post BL	DTG: 0.9 TDF: 1.28		DTG: 0.81 TDF: - -
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 P225P/H	RT: **K101Q/P**	L74I DTG:0.91 TDF: 0.81	K188K/R T206T/S A265A/V	DTG: 0.92
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/	RT: R72R/K **V106V/I** R143R/K E203E/K H208H/Y	DTG:0.5 FPV: 0.91 TDF:0.53		FPV: 0.83

			L P225P/H				
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 T215Y	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
2618	DRV/R TDF	WK24	PR: M36I R57K G68E RT: K103K/N M184M/V G190G/A		DTG: NO BL TDF: 0.79 DRV: 1.2	M154I (no BL IN genotype or phenotype)	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 D288QNM E	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 LPV: 0.9	R199K	DTG: 0.9
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
9402	ATV/R TDF	WK16	PR: L10I I15V L33F M36I M46I I50V F53L V82A L89M RT: M41L D67E S68G V75M V118I M184V L210W T215Y	NO POST BL	ATV: 4.1 TDF: 2.5 DTG:--	--	DTG:--
9412	LPV/R TDF	WK24	PR: M36I L89M RT: K104K/R	NO POST BL	LPV: 1.6 TDF: 1.2	--	DTG:--
9990	ATV/R	WK24	PR: I15V	NO POST	ATV: 0.7	--	DTG:--

	TDF		M36I V77I RT: D67N V75I K103N V108I M184V G196E P243P/L	BL	TDF: 0.8		

Bolded Subject numbers had INSTI emergent substitutions.

Of the 49 subjects in the RAL arm of the FDA resistance analysis set, 38 had post-baseline resistance data; 35 with INSTI post-baseline resistance data and 34 subjects with RT/PR post-baseline resistance data. Ten subjects (29%) [Subjects 260, 419, 785, 963, 977, 1146, 2427, 2688, 2769 and 9088] in the RAL arm had emergent INSTI substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E/Q and G163G/R) (Table 27). All 10 of these subjects had RAL phenotypic resistance, and of these, 5 (45%) isolates had DTG phenotypic resistance (≥2-fold change from reference in DTG susceptibility). In the RAL arm, 12% (4/34) had emergent NNRTI resistance substitutions, 18% (6/34) of subjects had failure isolates with emergent NRTI resistance substitutions, and 15% (5/34) had emergent PI resistance substitutions (Table 27).

Table 27. ING111762 (SAILING): RAL FDA-Defined Resistance Subjects with Post-Baseline Data and Emergent INSTI-Substitutions in Failures

PID	BKGRD DRUGS	FAILURE WEEK	BL PSS	EMERGING INSTI SUBSTITUTIONS	EMERGING RT/PI SUBSTITUTIONS	PHENO Fold-Change
260	ABC TDF	WK16	2	I60I/M, **L68L/V,** V79V/I, **G140A, Y143Y/C, Q148Q/R, E157E/Q**	RT: K70K/R M230M/L	RAL-R (BL) TDF-R **DTG-R (18X)**
419	FTC TDF	WK24	1	**L74L/M T97T/A V151I N155H G163K**	PR: A71A/T	RAL-R FTC-R (BL) DTG (1.89X)
492	ABC DRV/R	WK12	2	K240K/R	RT: L210S T215V	
785	FTCTDF	WK40	2	**G140S Q148H**		RAL-R **DTG-R (4.4X)**
947	DRV ETR	WK8	1			ETR-R (BL)
963	TDF TPV/R	WK24	2	**G140S Q148H**	PR: M36I M46L/V	RAL-R TPV-R **DTG-R (4.1X)**
977	MVC AZT	WK 32	2	**Y143Y/C N155N/H G163G/R F181F/L**		RAL-R DTG (1.25X)
1146	FTC MVC	WK16	0	**T97A Y143R** D253E		RAL-R FTC-R (BL) DTG (1.3X)
2201	DRV/R ETR	WK24	2		RT: M41M/L K101K/E M184M/V	ETR-R

					V179V/I Y181Y/C H208H/Y T215T/F/I/S K219K/E M230M/L	
2360	DRV/R ETR	WK16	2		RT: E138E/K Y181Y/C	ETR-R (BL)
2427	LAM ABC	WK24	1	**Q95Q/R N155H** H171H/R	RT: T215I	RAL-R LAM-R (BL) **DTG (2.1X)**
2472	AZT LAM	WK16	1	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		RT: T69A	
2571	LPV/R	WK16	1	V150V/A	RT: L74L/I K103K/E Y115F G190A	
2688	ATV/R TDF	WK24	2	**N155N/H**		RAL (1.4X) DTG (0.9X)
2765	ATV/R TDF	WK16	0		PR: M46I I84V	NO POST BL
2769	ATV/R TDF	WK16	1	**E92E/Q T97T/A V151V/I N155H**	PR: L10D/F/V L33F K55K/R	RAL-R ATV-R (BL) **DTG-R (3.7X)**
9048	LPV/R	WK12	1		PR: V77V/I	
9088	LPV/R	WK24	1	**N155N/H**		RAL-R DTG (1.4X)

Bolded Subject numbers had INSTI emergent substitutions.

There is the potential for a drug-drug interaction between DTG and EFV resulting in reduced DTG drug exposure. Analysis of response in subjects on EFV+DTG vs EFV+RAL showed more subjects failed with DTG+EFV and had EFV resistance emergence compared to RAL+EFV (Table 28). The numbers are small, but this analysis supports that a DTG 50 mg BID should be recommended when used in a regimen with EFV.

Table 28. Subjects on EFV with DTG or RAL in SAILING

	DTG 50 mg once daily (N=13)	**RAL 400 mg twice daily (N=12)**
Responders	62% (8/13)	92% (11/12)
Failures	5	1
No post baseline	2	1
EFV-R at Baseline	1 (Subject 9080)	
EFV-R Emergence	2*	

***EFV-R emergence: Subject 2568 and 2785**

Reference ID: 3310743

ING112574 (VIKING-3)

INSTI-Experienced Week 24 Results: DTG 50 mg BID with optimized background ART to treat HIV-1 infected adults with prior ART use and prior or current virologic failure on an INSTI-containing regimen associated with emergence of INSTI-resistant virus.

BASELINE RESISTANCE

The patient population in ING112574 (VIKING-3) was highly treatment-experienced with 73% (n=133) resistance to at least one NNRTI, 82% (n=149) of the subjects resistant to at least one NRTI, and 72% (n=131) resistant to at one PI (Table 29). There were also 13% (n=24) of the subjects resistant to ENF and 12% (n=21) not susceptible to MVC with CXCR4 virus at baseline. Most of the subjects (90%) had an OSS of 0 or 1 (Table 29).

INSTI Resistance Inclusion Criteria for this study included substitutions T66I or A or K, E92Q or V, Y143C or R or H, Q148H or K or R and N155H.

Sixty-four percent of the subjects had phenotypic resistance to RAL at baseline with a >1.5-fold change in RAL susceptibility (Table 29). Most of the subjects had prior exposure to RAL (179/183; 98%) with only 5 subjects (Subjects 242, 403, 463, 1841 and 1962) having prior exposure to EVG (note one subject had prior exposure to both RAL and EVG).

Table 29. Treatment Experience of Subjects in VIKING-3 at Baseline

	Number of Subjects (%) N=182
OSS	
0	**106 (58%)**
1	**59 (32%)**
2	**11 (6%)**
>2	**6 (3%)**
Resistance to at least one NNRTI	**133/182 (73%)**
Resistance to at least one NRTI	**149/182 (82%)**
Resistance to at least one PI	**131/182 (72%)**
RAL-R >1.5X	**116/182 (64%)**
ENF-R >6.48	**24/182 (13%)**
MVC (X4 at BL)	**21/182 (12%)**

<u>Prevalence of INSTI Substitutions at Baseline in Study ING112574</u>

The patterns and prevalence of INSTI resistance substitutions were assessed in the VIKING-3 patient population. Primary INSTI substitutions, which have been shown to confer resistance to raltegravir (RAL), include L74M, E92Q, T97A, E138A or K, G140A or S, Y143C or H or R, Q148H or K or R and N155H [IAS USA drug resistant

substitutions 2013]. Primary INSTI substitutions, which have been shown to confer resistance to elvitegravir (EVG) include T66A or I or K, E92Q or C, T97A, S147G, Q148H or K or R and N155H [IAS USA drug resistant substitutions 2013].

In the study, 15% (n=28) of subjects had Y143 substitutions and 18% (n=33) of subjects had the N155H substitution in Baseline viral isolates (Table 30). The L74M and T97A substitutions were detected in 11% (n=20) and 16% (n=29), respectively, of the baseline viral isolates from subjects in this study. E92Q was detected with other INSTI primary substitutions in two Baseline viruses. The T66A or K substitutions were detected in two subjects at baseline also with other INSTI primary substitutions. The subjects with the detection of either E92Q or T66A/K had prior exposure to RAL, but not EVG.

Viruses with substitutions at position Q148 have shown moderate to high changes in DTG susceptibility. Of the 182 subjects with baseline data, 30% (54/182) harbored virus with a substitution at Q148 at Baseline (Table 30). Of these subjects' isolates, 18% (n=32) had Q148 substitutions with 1 INSTI resistance substitutions and 12% (n=21) had Q148 substitutions with 2 or more INSTI resistance substitutions. Almost all (97%; 31/32) of the Q148+1 group had the Q148+G140 substitution combination and most (67%; 14/21) of the Q148+≥2 group had the combination of Q148+G140+E138 substitutions. Four percent of the subject baseline isolates had 2 or more primary INSTI substitutions. Importantly, 33% of this patient population had no primary INSTI substitutions at baseline.

Table 30. Number of Subjects with Baseline INSTI Resistance Substitutions

	Number of Subjects (%) N=182
T66A/K	**2 (1%)**
L74M	**20 (11%)**
E92Q	**2 (1%)**
T97A	**29 (16%)**
Y143R/C	**28 (15%)**
Q148	**54 (30%)**
Q148+1	**32 (18%)**
Q148+G140	**31**
Q148+≥2	**21 (12%)**
Q148+G140+E138	**14 (67%)**
Q148+G140+V151	**1**
Q148+E138+V151	**1**
Q148+G140+L74I+G163S/R	**2**
Q148+G140+G193E	**1**
Q148+G140+E157Q	**1**
Q148R+G140A+E138+V151+T97 (@screening)	**1**
N155H	**33 (18%)**
≥2 Primary INSTI	**8 (4%)**
No Primary INSTI Group	**60 (33%)**

Subject 1087 had no baseline visit timepoint

Reference ID: 3310743

Since 33% of this study population had no primary INSTI substitutions at baseline, it was critical to analyze the historical resistance evidence. Of the 33% subjects (n=60) in Study ING112574 with no primary INSTI substitutions, 83% (n=50) had historical resistance data of which 78% was genotypic evidence and 22% was phenotypic evidence (Table 31). Most of the subjects with historical genotypic evidence had the Q148H or N155H substitutions. The ten subjects (Subjects 107, 381, 463, 633, 1015, 1048, 1243, 1265, 1273 and 1611) who were designated in the No Primary INSTI group and had no evidence of historical resistance did have genotypic and phenotypic evidence of INSTI substitutions (i.e., L74L/Q, T97A, E138A, G140S, Q148Q/H and G163E) at screening. Most of the subjects with historical genotypic evidence had the Q148H or N155H substitutions. The 75% response rate at Week 24 for the subset of subjects with historical of resistance was higher than the overall response rate of 63%.

Table 31. Historical Resistance of Subjects in Study ING112574

	Number of Subjects (%) N=183	Response Rate at Week 24
Subjects with Historical Genotypic or Phenotypic Evidence (Overall)	**59 (32%)**	**75% (30/40)**
Subjects without Historical Genotypic or Phenotypic Evidence (Overall)*	**124 (68%)**	**68% (49/72)**
No Primary INSTI Group	**60 (33%)**	**77% (33/43)**
No Historical Evidence**	**10 (17%)**	**83% (5/6)**
With Historical Data	**50 (83%)**	**76% (28/37)**
Historical Phenotypic Evidence (1.6, 33, 28, 65, 66, 84 and 5 >Max)	**11 (22%)**	**83% (5/6)**
Historical Genotypic Evidence	**39 (78%)**	**74% (23/31)**
E92Q	**2 (5%)**	
N155H	**16 (41%)**	**92% (11/12)**
E92Q+N155H	**1 (2.6%)**	
Q148H	**12 (31%)**	**44% (4/9)**
Q148R	**3 (8%)**	**67% (2/3)**
T66A+Q148R	**1 (2.6%)**	
Y143R	**3 (8%)**	**33% (1/3)**
Y143C/R/H	**1 (2.6%)**	
Number of Subjects with Historical Evidence also with Baseline Genotypic Evidence of INSTI (Y143, Q148, N155)	**9**	
N155H	**4**	
Q148H	**3**	
Y143C/G/R	**2**	
Number of Subjects with Historical Evidence also with Baseline RAL Phenotypic Resistance (>1.5 RAL)	**9**	

***These subjects had baseline evidence of INSTI substitutions**
****Subject 107 (G163E at screening and baseline; RAL FC=1X), Subject 381** (G140G/S and Q148Q/H; RAL FC =110X at screening), **Subject 463 (**L74M, Q95K, T97A, S147G at screening and baseline; RAL FC= 48X)**, Subject 663 (**E138A at screening and baseline; RAL FC = 2X**), Subject 1015** (T97A at screening

and baseline; RAL FC = 4.6X)**, Subject 1048, 1243 (**G140S, Q148H at screening; RAL FC = 110X)**, Subject 1265, Subject 1273** (T97A and G163G/R at baseline ; RAL FC = 3X)**, Subject 1611** (L74L/Q, T97A at baseline; RAL FC =4X)

Minor Variants in HIV-1 Integrase at Baseline in Subjects having only Historic Evidence of Primary INSTI Resistance

Ultra deep pyrosequencing (UDS) (454 sequencing) was used to identify minor variants of INSTI primary resistance associated substitutions in HIV integrase in subjects with only historic evidence of INSTI resistance at the time of enrolment to ING112574.
Of the 52 Baseline samples tested by UDS for minor variants in integrase, 5/52 (9.6%) samples (Subjects 381, 1001, 1243, 1273, 1402) tested had minor variants of INSTI primary resistance associated substitutions (i.e., T66A, Q148H, N155H) (at a 0.5% detection threshold). All 5 viral samples had HIV-1 RNA >10,000 copies/mL at the time of testing and all 5 subjects had been on prior RAL treatment for more than one year. The minor variants of INSTI primary resistance substitutions detected in these samples were identified at <11%. For these 5 subjects, the average number of days off RAL treatment to Baseline testing was 163 days compared to 504 days for all subjects tested and the number of days on prior RAL treatment was 806 days compared to 676 for the 52 samples tested.

Of the 52 Baseline samples tested by UDS for minor variants in integrase, 48% (25/52) of samples had evidence of INSTI secondary resistance associated substitutions (i.e., L68V, L74M, Q95K, T97A, E138A, S147G, V151I, E157Q, G163R) (at a 0.5% detection threshold). For 10/25 of these samples, only historic RAL or EVG fold-change >1.5 or 2.5, respectively, was provided to qualify for study enrollment.

Eleven subjects (Subjects 228, 1001, 1041, 1056, 1201, 1206, 1209, 1241, 1243, 1274, and 1401) with no INSTI primary resistance substitutions at Day 1 were in the FDA Week 24 resistance analysis set; 6 of whom had post-Day 8 resistance data. Results from population INSTI genotyping performed at the timepoint of virologic failure showed 3 of these 6 subjects had treatment-emergent INSTI resistance (subjects 1206, 1241 and 1243). In each case, the virus at virologic failure had treatment emergent Q148H. For these 3 subjects the historic IN resistance that was provided was Q148H, but only subject 1243 had minor variants of Q148H detected at Day 1 (at 4%) in the UDS analysis.

RESPONSE BY BASELINE FACTORS

Response at Day 8 and Week 24 by Baseline Genotype

The response at Day 8 by Baseline INSTI substitution category (specific INSTI primary substitution or Q148+number of additional INSTI substitutions was analyzed (Table 32). At Day 8, the overall response rate based on ≥1 $\log_{10}$ decline from baseline (or <50 copies/mL) was 82% (n=150). At Day 8, subjects in the INSTI substitution category Q148+≥2 secondary substitutions had 50% achieving a >1.0 $\log_{10}$ copies/mL decrease or <50 copies/mL (Table 32) and the Q148+1 category had response rates of 69% (n=22). Other INSTI baseline substitutions that contributed to a decreased response to DTG at Day 8 were E138A/K/T, G140S, S147G, Q148H or R and G193E/R. The

highest response of 96% (n=27) was observed for those subjects harboring virus with the Y143 substitution.

Response was examined at Week 24 using two different subsets, one with only those subjects who had reached Week 24 (**Subset N=112)** and the other includes those subjects who had discontinued or rebounded before Week 24 (**Subset N=125)**. In both subsets, responses at Week 24 based on INSTI category were lower overall than responses at Day 8. We used the "N=125 subset" because it provided a more conservative look at responses based on baseline INSTI substitutions. The overall response rate at Week 24 in this subset was 63% (Table 32). Subjects had lower response rates of 35% (13/37) at Week 24 when their baseline viral isolates had a Q148H or R substitution. Almost all (36/37) of the subjects' isolates with Q148 substitutions also had a G140 substitutions; subjects with the two G140S+Q148H substitutions in their isolates had response rates at Week 24 of 34% (11/32). At Week 24, subjects in the INSTI substitution category Q148+1 category had response rates of 57% achieving <50 copies/mL and in the Q148+≥2 secondary substitutions category had very low response rates of 7% (1/14) achieving <50 copies/mL. In particular Q148+E138 had low response rates of 14%; all these subjects' isolates had at least 3 INSTI substitutions with 13 of 14 having substitutions at Q148+G140+E138. The other subject's isolate had substitutions at T66A, L74I, S147G and G163R in addition to Q148R and E138K.

Response rates at Week 24 were 47% (n=9) for subjects with G163 substitutions in their baseline viral isolates and 17% (n=1) for subjects with the G163+Q148 substitutions. Response rates were also lower (18-40%) than the overall response when substitutions L74M/I/Q, E138A/K/T, G140S, Y143R or E157Q were present at baseline (Table 32). Subjects with isolates harboring G193E or R substitutions had low response rates of 29% with even lower response rates (0%) when G193 was in combination with Q148. Subjects with isolates containing substitution S147G had a 20% response rate (n=5) at Day 8 and 0% (n=1) at Week 24. It should be noted that the number of subjects whose isolates had substitutions at S147 and G193 was small (<10).

Table 32. Response at Day 8 and Week 24 by Baseline Genotype

Baseline Genotype (excluded subjects with only screening data and no BL data)	Response at Day 8 (≥1 Log_{10} Change from Baseline or <50 copies/mL) (N=182*)	Response at Week 24 (<50 copies/mL) Subset N=112	Response at Week 24 (<50 copies/mL) Subset N=125
Overall Response	82% (150/182)	71% (79/112)	63% (79/125)
Primary INSTI Not Detected	95% (57/60)	77% (33/43)	75% (33/44)
No Q148 Substitutions	89% (115/128)	79% (66/84)	75% (66/88)
Q148	60% (32/53)	46% (13/28)	35% (13/37)
Q148H	60% (27/45)	46% (11/24)	34% (11/32)
Q148R	63% (5/8)	50% (2/4)	40% (2/5)
Q148+1	69% (22/32)	67% (12/18)	57% (12/21)

Q148+H51Y	0		
Q148+T66A	0/1	0	
Q148+L68	0		
Q148+L74I	1/4	0/2	0/3
Q148+E92	0		
Q148+Q95	0/1		1/1
Q148+T97	0		
Q148+G118	0		
Q148+E138A/K/T	47% (8/17)	20% (2/10)	14% (2/14)
Q148H+G140S	60% (27/45)	46% (11/24)	34% (11/32)
Q148R +G140S	1/1		
Q148R+G140A	75% (3/4)	67% (2/3)	67% (2/3)
Q148H+Y143H/R	1/2		1/2
Q148+P145	--		
Q148R+S147G	1/2		0/1
Q148H+ V151I	2/2		0
Q148+ S153	0		0
Q148+N155H	0		0
Q148H+E157Q	1/2		0/2
Q148+G163S/E/R	63% (5/8)	25% (1/4)	17% (1/6)
Q148R/H+G193E	1/4	0/3	0/4
Q148+R263K	0	0	0
Q148+≥2	50% (10/20)	11% (1/9)	7% (1/14)
Q148+G140+E138	47% (7/15)	22% (2/9)	15% (2/13)
≥2 primary substitutions	75% (6/8)	60% (3/5)	50% (3/6)
G140	63% (32/51)	43% (13/30)	35% (13/37)
G140S	57% (29/47)	42% (11/26)	33% (11/33)
G140A (+Q148R)	75% (3/4)	67% (2/3)	67% (2/3)
Y143	96% (27/28)	63% (12/19)	57% (12/21)
Y143C	7/7	80% (4/5)	4/4
Y143G	1/1	1/1	1/1
Y143H	1/1	1/1	1/1
Y143R	91% (21/23)	46% (6/13)	40% (6/15)
T66A/K	1/2	1/1	1/1
V72I	84% (122/146)	70% (63/90)	62% (62/100)
L74M/I/Q	87% (27/31)	59% (10/17)	50% (10/20)
E92Q	2/2	0	0
Q95K/R	100% (9/9)		67% (4/6)
T97A	88% (28/32)	65% (11/17)	58% (11/19)
E138A/K/D/T	62% (18/29)	47% (8/17)	35% (8/23)
E138D	88% (7/8)	83% (5/6)	83% (5/6)
E138A	56% (5/9)	50% (3/6)	30% (3/10)
E138K	57% (4/7)	0% (0/3)	0/5
E138T	67% (2/3)	0/2	0/2
S147G	20% (1/5)	1/1	0/1
N155H	84% (26/31)	85% (17/20)	80% (16/20)

E157Q	79% (11/14)		36% (5/14)
G163E/K/R/Q/S/T/N	87% (26/30)		47% (9/19)
G193E/R	57% (4/7)		29% (2/7)
R263R/G	1/1		1/1
Polymorphic Sites			
T112	83% (45/54)	70% (21/30)	64% (21/33)
V113I/L	81% (120/148)	66% (61/92)	58% (61/105)
V234L	84% (137/163)	68% (69/101)	62% (69/112)

*Subject 2063 had no Day 8 visit and was not included in the Day 8 analysis

In summary, INSTI baseline substitutions that contributed to a decreased response to DTG at Week 24 were L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, Q148H or R, E157Q, G163E/K/R/Q/S/T/N and G193E/R (Table 33). These substitutions were often in combination with Q148H or R substitutions and the response rates at Week 24 were decreased. Response rates for subjects with no primary INSTI detected in baseline isolates had greater than the overall response at both Day 8 and Week 24. Notably, due to the small number of subjects in this study that had reached Week 24 at the time of NDA submission, the numbers in some of the subgroups are small making it difficult to make definitive conclusions from the limited data.

Table 33. Summary of INSTI Substitutions that Decrease Response

Baseline Genotype (excluded Subjects with only Screening data and no BL data)	Response at Day 8 (≥1 Log_{10} Change from Baseline or <50 copies/mL) (N=182*)	Response at Week 24 (<50 copies/mL) Subset N=125
Overall Response	82% (150/182)	63% (79/125)
Primary INSTI Not Detected	95% (57/60)	75% (33/44)
No Q148 Substitutions	89% (115/128)	75% (66/88)
Q148H	60% (27/45)	34% (11/32)
Q148R	63% (5/8)	40% (2/5)
Q148+1	69% (22/32)	57% (12/21)
Q148+≥2	50% (10/20)	7% (1/14)
≥2 primary substitutions	75% (6/8)	50% (3/6)
L74M/I/Q	87% (27/31)	50% (10/20)
E138A/K/T	58% (11/19)	18% (3/17)
G140S	62% (29/47)	33% (11/33)
Y143R	91% (21/23)	40% (6/15)
S147G	20% (1/5)	0/1
E157Q	79% (11/14)	36% (5/14)
G163E/K/R/Q/S/T/N	87% (26/30)	47% (9/19)
G193E/R	57% (4/7)	29% (2/7)

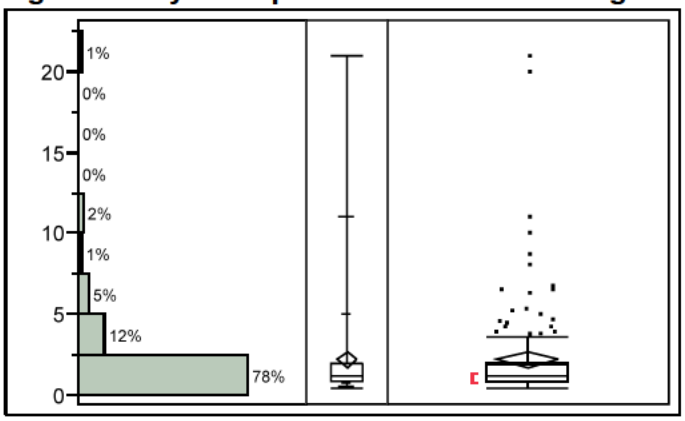
*Subject 2063 had no Day 8 visit and was not included in the Day 8 analysis

Response at Day 8 and Week 24 by Baseline DTG Phenotype

The median fold-change in the Day 8 responders was 1.2 and the mean was 2.3 (Figure 1). The 25% and 75% quartile were 0.9 and 2, respectively. The median fold-change in

the Day 8 failures was 6.4 and the mean was 9.8 with 25% and 75% quartiles of 2 and 14, respectively (Figure 2).

Figure 1. Day 8 Responders DTG Fold Change from Reference



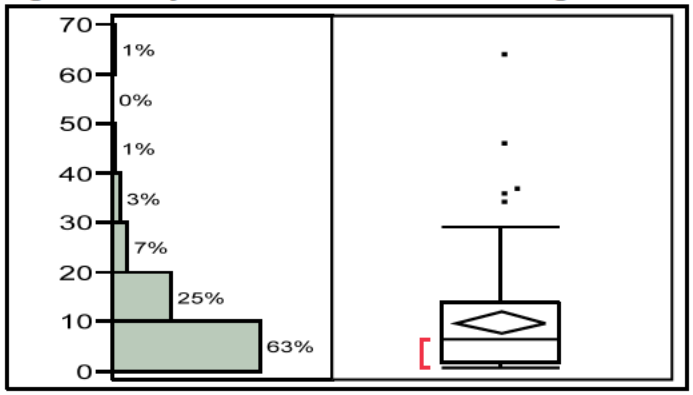
Quantiles

100.0%	maximum	21
99.5%		21
97.5%		11
90.0%		4.973
75.0%	quartile	2.01
50.0%	median	1.175
25.0%	quartile	0.89
10.0%		0.781
2.5%		0.5325
0.5%		0.45
0.0%	minimum	0.45

Moments

Mean	2.2745
Std Dev	3.014707
Std Err Mean	0.2547892
Upper 95% Mean	2.7782636
Lower 95% Mean	1.7707364
N	140

Figure 2. Day 8 Failures DTG Fold Change from Reference



Quantiles

100.0%	maximum	64
99.5%		64
97.5%		43.975
90.0%		23.1
75.0%	quartile	14
50.0%	median	6.35
25.0%	quartile	1.8425
10.0%		1.144
2.5%		0.84025
0.5%		0.72
0.0%	minimum	0.72

Moments

Mean	9.9753409
Std Dev	10.916797
Std Err Mean	1.1637345
Upper 95% Mean	12.288389
Lower 95% Mean	7.6622927
N	88

Using the quartile information above, we examined response based on incremental subgroups of baseline DTG phenotype (fold-change) (i.e., 0-2, 2-4, etc.). Based on this analysis, response rates at Day 8 by baseline DTG phenotype began to decline when baseline DTG phenotypes >4-fold, whereas at Week 24, response rates decreased starting at DTG phenotypes >2-fold (Table 34). Increments of <2, 2-4, >4-<10 and ≥10-fold in baseline DTG phenotype (highlighted in Table 34) elucidate differential response rates both at Day 8 and Week 24 and should provide physicians with valuable clinical response information based on baseline DTG phenotype. At Day 8, subjects with baseline DTG phenotype of <4 had response rates of 92-94%, greater than the overall response. At Week 24 using the N=125 subset, subjects with baseline DTG phenotype <2-fold had response rates greater than the overall response. Subjects with baseline DTG phenotype of ≥2 but <10-fold had decreased response rates of 48% compared to the overall response rate of 63%. The most dramatic reduction in response rates was seen for subjects with baseline DTG phenotypes of ≥10-fold with response rates of 18%. Again, the numbers in some of these subgroups were small and may affect the interpretability of these results.

Table 34. Response Based on Incremental Subgroups of Baseline DTG Phenotype (Fold-Change)

Baseline DTG Phenotype	Response ≥1 Log_{10} Change from Baseline or <50 copies/mL at Day 8 N=182*	Response at Week 24 (<50 copies/mL) Subset N=112	Response at Week 24 (<50 copies/mL) Subset N=125
Overall Response	82% (150/182)	71% (79/112)	63% (79/125)
<2	92% (104/113)	75% (55/73)	71% (55/77)
2 - 4	94% (16/17)	64% (7/11)	58% (7/12)
>4 - 6	64% (9/14)	43% (3/7)	33% (3/9)

2 - 6	81% (25/31)	56% (10/18)	48% (10/21)
>4 - 10	64% (16/25)	50% (7/14)	39% (7/18)
2 - <10	76% (31/41)	58% (14/24)	48% (14/29)
>4 - <10	63% (15/24)	54% (7/13)	42% (7/17)
>6 - 14	47% (9/19)	50% (5/10)	36% (5/14)
>6 - 10	64% (7/11)	57% (4/7)	44% (4/9)
10 - 14	33% (3/9)	25% (1/4)	17% (1/6)
≥10	33% (5/15)	29% (2/7)	18% (2/11)
>10	29% (4/14)	33% (2/6)	20% (2/10)
>14	33% (2/6)	33% (1/3)	20% (1/5)

Increments of baseline DTG phenotype highlighted in yellow show differential response rates at Day 8 and Week 24

There were 11 subjects with baseline susceptibility to DTG of ≥10-fold (Table 35). Nine of these subjects were failures in the Week 24 analysis; 6 with an OSS=1, 3 with an OSS=2, and 5 adding ENF to their background regimen. All nine failures had baseline Q148 subitutions plus at least 2 other INSTI resistance substitutions. The two subjects who responded at Week 24 had an OSS of 1 and >2 and had susceptible anchor drugs in their background regimen. One of the responder subjects was in INSTI subgroup Q148+1 while the other had Q148+G140S+E138A+Y143H.

Table 35. Week 24 Subjects with Baseline >10-Fold DTG Fold change from Reference (n=11)

PID	WK24 Response (OSS*)	Baseline INSTI Group	Baseline INSTI Substitutions	Emergent INSTI Substitutions at Failure	Baseline DTG FC	Failure DTG FC
15	No (OSS=2; FTC **TDF ENF**)	Q148+>=2	E138E/A/K/T G140S Q148H	E157E/Q	13	16
504	No (OSS=1; FTC TDF **ENF** d4T)	Q148+>=2	L74I G140S Q148H G163S	T97A	14	103
545	Yes (OSS>2; **DRV ETR**; FTC TDF)	Q148+1	G140A G148R		11	17 (Day 8)
566	No (OSS=1; **d4T TDF**)	Q148+>=2	E138T G140S Q148H	V72I N155H	10	209
1012	No (OSS=1; DRV FTC TDF **ENF** ETR AZT	Q148+>=2	E138T G140S G148H G163E/G	T97A T125T/A V282V/M	11	99
1049	Yes (OSS=1; **EFV**, DRV FTC TDF)	>=2 Primary substitutions	E138E/A G140S Y143H Q148H	NO POST BL	20	NO POST BL

1067	No (OSS=1; ABC DRV LPV **TDF**)	Q148+>=2	E138A G140S G148H		37	46
1806	No (OSS=2; **DRV TDF**)	Q148+>=2	E138A G140S Q148H		11	15
1842	No (OSS=1) **ENF** LAM ABC TDF	Q148+>=2	E138A G140S Q148H	NO POST BL	16	NO POST BL
1901	No (OSS=1 **DLV** TDF)	>=2 Primary substitutions	E138K G140S G143R Q148H E157Q G163E G193E	T97T/A S119S/T	17	66
1964	No (OSS=2; FTC TDF **ENF TPV**)	>=2 Primary substitutions	T66A L74I E138K S147G Q148R	K188R	27	36

*Susceptible background drugs are bolded.

Response by Background Drug

Response was analyzed by the anchor drug in the background regimen with both the failing Baseline regimen and new optimized Week 4 regimen (Table 36). Response rates were the highest (80%) when DRV/r was used in the background regimen either at Baseline or Week 4 and lowest (50%) when ENF was used in the Baseline or Week 4 background regimen. If RAL was a background drug in the failing regimen at Screening or Baseline, response rates were 62 and 63%, respectively.

Table 36. Response by the Anchor Drug in the Background Regimen (Both the failing Baseline Regimen and New Optimized Week 4 Regimen)

	Week 24 Outcome by Background Drug (Regimen Week 4)	Week 24 Outcome by Background Drug at Baseline
Overall	**71% (79/112)**	**71% (79/112)**
MVC	**72% (23/32)**	**78% (18/23)**
DRV/r	**80% (55/69)**	**81% (25/31)**
ENF	**53% (20/38)**	**50% (17/34)**
ETR	**76% (32/42)**	**78% (28/36)**
RAL		**62% (34/55) screening; 63% (12/19) baseline**

Response by OSS

Analysis of response at Day 8 and Week 24 by overall susceptibility score (OSS) did not show an obvious effect of OSS on response (Table 37). In fact, response rates were numerically higher for lower OSS scores, which is the opposite of what would be expected.

Table 37. Response at Day 8 and Week 24 by OSS

	Day 8 Outcome by Background Drug (OSS at Day 1)	Week 24 Outcome by Background Drug (OSS at Day 8)
0	**84% (88/105)**	**5/5**
1	**85% (51/60)**	**65% (34/52)**
2	**73% (8/11)**	**74% (29/39)**
>2	**50% (3/6)**	**69% (11/16)**

A closer examination of the 6 subjects who had OSS of ≥2 at Baseline and were failures at Day 8 (≥1 $\log_{10}$ decline from baseline) showed that 3 subjects had low viral loads at Baseline and did not reach >1 $\log_{10}$ decline by Day 8, but were subsequently successes at Week 24 or discontinued while suppressed (Table 38). This provides an explanation for why these subjects with >2 OSS had lower response rates of 50% at Day 8. Our conclusion is that the OSS did not affect response rates at Day 8 or Week 24.

Table 38. Subjects who failed at Day 8 with ≥2 Baseline OSS

PID	OSS	Drugs and Susceptibility (Res= resistant)	INSTI Genotype Group	Changes in Regimen	Outcome
221	2	ABC, **DRV/R (Res)**, FTC, TDF, **ETR (Res), RAL (Res)**	Q148+G140	switched to DRV/R, FTC, TDF, ENF,	Never suppressed
324	2	AZT, LAM, **RAL (Res)**	N155H	switched to DRV/r, AZT, LAM	Low viral load at BL=1331; DC Week 8 while suppressed
1203	2	**FTC (Res),** TDF, **ENF (Res),** MVC, **RAL (Res**)	Q148H +G140S	stayed on FTC, TDF, ENF and MVC	Never suppressed
1048	>2	DRV/R FTC, TDF	Primary not detected	stayed on regimen	Low viral load at BL=2212; Week 24 success
1274	>2	DRV/r, FTC, TDF and **ETR (Res)**	Primary not detected	added ENF to FTC, TDF	Never suppressed
2067	>2	DRV/R, FTC, TDF	N155N/H	stayed on regimen but added DTG	Low viral load at BL= 6882; Week 24 success

ATV/r+DTG

ATV/r boosts DTG drug levels 2-fold. In an effort to see if increasing DTG concentration would help to overcome the resistance barrier for the Q148+≥2 subgroup, we examined the subjects who were taking ATV/r concomitantly with DTG (Table 39). Unfortunately, there were not any subjects on both ATV/r and DTG within the Q148+2 subgroup. Subject 569 had Q148Q/H+G140G/S+G163S and responded at Day 8. All subjects, except one, were on ATV/r just the first 8 days (only one took ATV/r following Day 8).

Table 39. Subjects who were Taking ATV/r Concomitantly with DTG

PID	INSTI GROUP	BASELINE INSTI SUBTITUTIONS	Day 8 OUTCOME	WK 24 OUTCOME
026	≥2 Primary	E92E/Q V151V/I N155H G163E/K	YES	N/A
228	PRIMARY NOT DETECTED		YES	N/A
569	Q148+1	Q148Q/H+G140G/S G163S	YES	N/A
1008	N155	E138E/D V151I N155H E157Q G163K	NO (0.97 log_{10} decrease)	N/A
1403	PRIMARY NOT DETECTED	HIST: T66A Q148R	YES	N/A
1965	PRIMARY NOT DETECTED	HIST: Q148H	YES	N/A
1036	PRIMARY NOT DETECTED	HIST: N155H	YES (DRV/R)	YES

ON TREATMENT RESISTANCE ANALYSIS

There were 183 subjects in Study 112574. Subject 2063 had no Day 8 visit and therefore was not included in the Day 8 analysis so there were 182 subjects for the Day 8 analysis. The mean HIV-1 log_{10} decline from baseline was 1.43 at Day 8 (Table 40). At Day 8, 89% of the subjects had >0.5 log_{10} decline from baseline and 82% had >1 log_{10} decline from baseline. There were 32 subjects with <1 log_{10} decline from baseline and ≥50 copies/mL at Day 8 who were included in the Day 8 Resistance Analysis Set; 28 of them had post-baseline data. Five subjects had <400 copies/mL at Day 8. The genotypic and phenotypic data from Day 8 was used to determine treatment-emergent INSTI-resistance detected during the functional monotherapy phase of the study.

Table 40. Day 8 Resistance Analysis Set in Study ING112574

	DTG 50 mg BID
Subjects[a]	182
Mean HIV RNA Log_{10} Change from Baseline at Day 8	1.43
Median HIV RNA Log_{10} Change from Baseline at Day 8	1.5
>0.5 log_{10} at Day 8	92% (168/182)

>1 log_{10} or <50 copies/mL at Day 8	82% (150/182)
Subjects in Day 8 Resistance Analysis Set (<1 log_{10} and ≥50 copies/mL at Day 8)	32
Subjects with <400 copies/mL at Day 8[b]	5
Subjects with >0.5 log_{10} change from BL in Resistance Analysis Day 8 Set	19
Subjects in Day 8 Resistance Analysis Set with post baseline IN data	28
Subjects in Day 8 Resistance Analysis Set with Emergent INSTI Substitutions[c]	5

[a]Subject 2063 had no Day 8 visit and was not included in the Day 8 analysis
[b]Subjects 21, 324, 1063, 1271, 1844
[c]Subjects 10, 15, 221, 231 and 585

Genotypic Changes at Day 8

As shown in Table 41, 18 subjects had treatment-emergent substitutions in integrase (IN) at Day 8. Six subjects had treatment-emergent INSTI substitutions at Day 8: Subject 0010 with emergent G140A and G148R from mixtures at baseline, Subject 0015 with emergent E157E/Q, Subject 0221 and Subject 0231 with emergent T97T/A, Subject 0585 with emergent L74M and G140A from mixtures at baseline, and Subjects 227 and 1281 had emergent M154I [1281 had no post-Day 8 data]. All of these subjects' isolates (except 1281 which was not a failure at Day 8 by the FDA analysis) had Q148R or H substitutions or mixtures plus at least one other INSTI substitution (e.g., G140S or A) at baseline.

Table 41. Day 8 IN Substitution Emergence Analysis in Subjects with <1 log_{10} Decrease from Baseline at Day 8 and ≥50 copies/mL (n=32)

PID	Day 8 Viral Load	Log_{10} HIV RNA Decline from BL	<50 copies /mL at Week 24	Baseline or Historical INSTI Substitutions	Emerging INSTI Substitutions	DTG Fold Change at Day 8 (fold change from BL/screen)	INSTI Group
8	14608	0.93	N	V31I, V72I, T122M V113I, **G140S**, **Q148H**, K173R, I203M, T218S, V234L, V259I	T122T/I	7 (1.2)	Q148+1
10	1532	0.78	N	V31I, K34R, S39S/R, V54V/I, L63L/I, **L74I**, V79I, L101I, V113I, S119S/T, T122T/S, T125T/P, **G140G/A**, **Q148Q/R**, I203M, I208M, V234L, V259I, M275M/V,	**G140A, Q148R**	23 (32)	Q148+1

				R284R/G			
15	9917	0.41	N	D6D/N K14K/R S17N A21A/S V31I D41D/N M50I L63I V72I L101I T112I/M/V V113I T124T/A K136K/E **E138E/A/K/T** F139F/Y **G140S Q148H** V201V/I V234L N254Q	T112M **E157E/Q**	16 (1.2)	Q148+≥2
21	150	0.78	Y	M50T V72I L101I V113I T124N V151I **N155H** T218I V234L	NO POST BL	NO POST BL	N155H
181	74106	0.44	N	S17N V72I V79I E96E/D K111K/E V113I T124A T125A **E138K G140S Q148H** V201I T206T/S V234L D288QNMA	K7K/R Y99Y/F	7.5 (1.2)	Q148+≥2
221	18475	0.49	N	M50I V72I L101I V113L **G140S Q148H** I203I/M I208L T218S V234I	**T97T/A** I203M	9.9 (1.1)	Q148+1
231	2471	0.69	N	S39C L63I V72I L101I T112T/S V113I T124A **G140S Q148H** Y227F	P90P/S **T97T/A** T112T/A	8.6 (1.6)	Q148+1
324	219	0.78	N	E11D A21T D41D/N K111R T112K V113I S119P T122I T125A M154L **N155H** E198Q V201I K219Q I220L V234L	D41N	1.8 (1.1)	N155H
408	50	0.93	N	S39C V72I L101I V113I S119P T122I T125A **V151V/I N155H** A179S T206S Q216H S255N	NO POST BL	NO POST BL	N155H
461	14916	0.91	N	S17N V72I V113I T124A T125A **E138T**	NONE	17 (1.3)	Q148+≥2

Reference ID: 3310743

				G140S Q148H F181L T206S I208M V234L			
504	9893	0.46	N	S17N V31V/I S39N I60I/M L63I V72I I73V **L74I** L101I T112S V113I T125A **G140S Q148H G163S** H171Q F181L F185F/Y K188R V201I Q216H V234I D256E D270H R284R/G		24 (1.7)	Q148+≥2
545	34343	0.19	Y	K14R R20K V31I V72V/I V79I G106A K111R T112V V113I S119P T122T/I T124N T125V/A **G140A Q148R** V201I T218S V234L D253D/E		17 (1.5)	Q148+1
585	14513	-0.14	N	E11D S24N V31I **L74I/M** V79I **T97T/A** S119P T122I **G140G/A Q148R V151V/I/M** I208M K219Q R284G	**L74M** V113I **G140A**	64 (1.9)	Q148+≥2
1008	314041	0.97	N	D6E E11D S17C A23V M50M/I V72I L101I T112T/S V113I S119P T122I G123S A124T R127K **E138E/D V151I N155H E157Q** K160I **G163K** V201I K211K/R T218S N232D V234V/L R284G D288N	V31V/I	2.2 (1.5)	N155
1048	655	0.53	Y	V72V/I L101I/V V113I T124N T125A V126L I208L V234L	L101I N117N/S R284R/G	1.2 (1.3)	NONE

1063	64	0.78	Y	D10E K14R S17N H51H/Q V54V/I V72I Q95Q/R T112V I113V G123S T125A R127K G134N K136T N155H K173R V201I I208L D232D L234I D256E S283G	NO POST BL	NO PHENO	N155
1067	5673	0.36	N	E11D V31I V72I L101I V113L T124N **E138A G140S G148H** G189R V201I K215N N222K V234L A265V R284G D288QSMA		46 (1.2)	Q148+≥2
1090	30124	0.99	N	E11D A23A/V D25D/E S39C A49A/P I60M V72I **L74I T97A** L101I K111T V113I S119P I135V **E138E/A/K/T Y143R E157E/Q** K160K/Q V234I D253E R284G		1.3 (0.9)	Y143
1203	1799501	0.11	N	***HIST: Q148H*** K14R A23V S24G D25E L28I S39C G59G/E V72I L101I T112V V113I S119P **G140S Q148H** V165I V201I T218S V234L		4.3 (0.97)	Q148+1
1216	2624	0.72	Y	V72I L101I V113I T122I T124N T125T/A **G140S Q148H** M154M/I/ L F181F/L V201I V234L		4.5 (0.7)	Q148+1
1264	20195	0.56	N	K14R A23V L28I S39C L63L/I L101I V113I S119P T122T/I T124T/N	Q216Q/H	6.4 (1.5)	Q148+≥2

				E138E/A/K/T G140G/S Q148Q/H G193E I200L V201I D279D/N R284R/G D286N			
1271	388	0.53	Y	***HIST: N155H*** D10E E11D S24V V31I M50I/L V72I L101I K111K/N/T S119A/G G123S A124T R127K Q216H S230N N232E	NO POST BL	NO POST SCREEN	HIST: N155H
1274	121823	0.72	N	*HIST: N155H* S24N D25D/E I84V V113I T122V T125A V126L I135V M154I V165I K219N I220I/L N222K V234I D256E		NO POST SCREEN	HIST: N155H
1806	7509	0.24	N	S17N L28I V72I L101I K111K/E V113I S119P I135I/V **E138A G140S Q148H** M154I V234L	S39S/R	15 (1.4)	Q148+≥2
1842	307807	0.11	N	S17N S39C L63L/I V72I G94G/A L101I V113I T124A K136K/E/Q **E138A G140S Q148H** K211K/R Q216H V234L		20 (1.3)	Q148+≥2
1844	133	0.73	N	S24N M50I Q53K V72I L101I V113I T124N T125M G140S Q148H K211R Q216H V234L		7.6X (2.2X)	Q148+1
1865	24113	0.59	N	E11D S24A V31I S39C L45Q V72I L101I V113L S119T G140S Q148H V165I	V250V/A	15 (1.3)	Q148+1

				V234I V259I			
1901	99185	0.49	N	K14K/R R20K V72I L101I V113I T124T/A K136E E138K G140S Y143R Q148H E157Q K160Q G163E G193E V201I I203I/M I208L K211K/T Q221R V234I V281V/M D286N	K14R T125V V234M	14 (0.8)	Q148+≥2
1964	4295	0.24	N	K14K/R V31I S57S/N I60I/V L63L/M **T66A** V72I **L74I** V79V/I V113I T124T/A **E138K S147G Q148R** K156G G163R K188K/R V201I T218S D288QNME	K188R	36 (1.3)	Q148+≥2
2001	1644	0.32	N	E11D S39C V72I V113I S119P T124N T125A V126L **G140S Q148H** G193E V201I V234L D278N	R20R/K T112T/I T206T/S I220I/L	2 (0.5)	Q148+1
2042	2554	0.99	N	E11D V37I I60V V72I L101I T112L V113I T124T/N **G140S Q148H** V201I Q221T V234L D256E	I252I/L	8.44 (1.5)	Q148+1
2067	1067	0.81	N	S17N T124A **N155H** V234I A265V	P90P/S I204I/M	1.0 (1.2)	N155H

Subjects with emergent INSTI substitutions are in bold; INSTI substitutions are also bolded

Phenotypic Changes at Day 8

In the Day 8 failure subset (n=32), the median and mean fold-changes from reference in baseline DTG susceptibility were 5.6 and 8.2, respectively (range 0.72 to 37). In comparison, the Day 8 responders (n=150) had median and mean fold-changes from reference in baseline DTG susceptibility of 1.2 and 2.3, respectively (range 0.45 to 21). The median and mean fold-changes from baseline of DTG susceptibility at Day 8 in the Day 8 failures were 1.3 and 2.4, respectively (range 0.48 to 32). The median and mean fold-changes from baseline of DTG susceptibility in responders at Day 8 were 1.0 for both (range 0.59 to 1.8).

The baseline DTG phenotype of the 5 subjects' isolates with emergent INSTI substitutions at Day 8 ranged from 0.7- to 34-fold and the fold change in DTG susceptibility from baseline at Day 8 ranged from 1.1- to 32-fold. Subject isolate 0010 had a 32-fold change in DTG susceptibility from baseline at Day 8 with emergent G140A and G148R from baseline mixtures at these positions. In addition to Subject 0010, only one other subject's isolate had a >2-fold change in DTG susceptibility from baseline at Day 8. Subject 1844 had a 2.2-fold change in DTG susceptibility from baseline at Day 8 but no emergent substitutions in IN (Table 41).

Genotypic Changes at Week 24

There were 40 subjects with >400 copies/mL at Week 24, failure timepoint or the last timepoint (interim analysis) who were included in the FDA resistance analysis set. Of these subjects, 22 of these subjects had post-Day 8 data (Table 42). This subset of subjects was used to analyze treatment-emergent substitutions that contribute to resistance and virological failure. In the FDA resistance analysis, 18 subjects had treatment-emergent INSTI substitutions post Day 8 (Table 43). The most common treatment-emergent INSTI substitution was T97A, which emerged in 45% of subjects' isolates on DTG treatment (Table 44). Other frequently emergent substitutions, which emerged in 10-20% of subjects' isolates, included E138K or A, G140S or A, Y143H or C, Q148H or R or K and M154I. Substitution M154I emerged in 2 subjects (227 and 1281[1281 had no post-Day 8 data]) at Day 8 and another subject (569) at Week 8. Substitutions L74M, V75M, E92Q, S147G, V151A, and N155H each emerged in 1 or 2 subjects' isolates (<10% of subjects' isolates) (Table 44).

Table 42. FDA Week 24 Resistance Analysis Set in Study ING112574

	DTG 50 mg BID
Subjects	183
Subjects in Week 24 Resistance Analysis Set (>400 copies/mL at Failure or Week 24)	40
Subject with <400 copies/mL at Week 24[a]	8
With Post-Day 8 Resistance Data[b]	22
Subjects with Treatment-Emergent INSTI Substitutions post-Day 8[c]	18
Subjects with Treatment-Emergent INSTI Substitutions at Day 8[d]	6

[a]Subjects 103, 483, 544, 1021, 1041, 1209, 1616, 2063
[b]Subjects 8, 41, 226, 227, 228, 461, 504, 566, 569, 1008, 1012, 1056, 1203, 1206, 1241, 1242, 1243, 1274, 1821, 1843, 1901, 2021
[c]Subjects 8, 41, 227, 461, 504, 566, 569, 1008, 1012, 1203, 1206, 1241, 1242, 1243, 1821, 1843, 1901, 20
[d]Subjects 10, 15, 221, 231, 585 and 1281

Table 43. Week 24 INSTI Substitution Emergence in the FDA Resistance Analysis Set (n=22) (>400 copies/mL at Week 24 or Last Time Point [interim analysis])

PID	Failure Timepoint (VL copies/mL)	Baseline or Historical IN Substitutions	Emerging IN Substitutions	DTG Fold Change at Week 24/Failure (fold change from BL/screen)	Baseline INSTI Group
0008	WK16 (17083)	V31I V72I T112M V113I **G140S Q148H** K173R I203M T218S V234L V259I	I60I/T **T97A** T122T/I	89 (14.5)	Q148+1
0041	Follow Up (49864)	V75V/I/M T97T/A Y143R G163N	**V75M T97A** G163H/K/N/Q S255S/N	0.92 (1.1)	NO Q148
0226	Follow up (34483)	G140S Q148H	G140G/S Q148Q/H	1.8 (0.7)	Q148+1
0227	WK12 (557)	M50T V72I L101I V113I T124A **E138A G140A Q148R G193E** I208M S230N V234L D288N	V54VI/I V79V/I **Q148Q/K/R M154M/I: emerged Day 8**	46 (5.7)	Q148+≥2
0228	WK8 (2048)	V31I V72I L101I K111Q A124N I135V K173R I182V V201V/I V234L		1 (1)	NO Q148
0461	Follow Up (80427)	E138T G140S Q148H	**T97A**	100 (8)	Q148+≥2
0504	WK16 (35549)	S17N V31V/I S39N I60I/M L63I V72I I73V **L74I** L101I T112S V113I T125A I135V **G140S Q148H G163G/S** H171Q F181L F185F/Y K188R V201I Q216H V234I D256E I268L D270H R284R/G	V31I I60M **T97A** G149G/A	103 (7.4)	Q148+≥2
0566	WK32 (196890	S17N S39N V113I **E138T G140S Q148H** K219N I220L N222K V234L S283N D288QNMA	V72I **N155H**	209 (21)	Q148+≥2
0569	WK8 (12316)	K34R V113I T124A G140G/S Q148Q/H G163S	V72I **E138K G140S Q148H M154I**	12 (7.6)	Q148+1

1008	WK24 (2374)	D6E E11D S17C A23V M50I/M V72I L101I T112T/S V113I S119P T122I **E138E/D V151I N155H** E157Q K160I G193K V211K/R T218S V234V/L R284G D288N	T112T/C/S **Y143Y/H**	1.8 (1.2)	N155
1012	WK16 (18178)	V31I V72I T112V V113I T124N **E138T G140S Q148H** G193G/E S230N L234H/L	**T97A** T125T/A V281V/M	99 (9)	Q148+≥2
1056	WK16 (94609)	HIST: Q148R S17N I84L G106G/A V113I T124A T125A V126L K136K/N **G163Q** V201I T206T/S V234L R284R/G	G70G/E	0.87 (0.98)	NO Q148
1203	WK12 (NEVER SUPP)	G140S Q148H	**T97A/T**	17 (3.9)	Q148+1
1206	WK24 (511569)	HIST: Q148H V31I D41D/N V54I V72I V113L T124A T125A V201I K215N V234L S283G	D41N I60I/M **L74L/M E92E/Q T97T/A E138E/K G140S Q148H** G149G/A	104 (118)	NO Q148
1241	WK12 (94263)	HIST: Q148H K14R V32I S39C V72I L101I V113I V201I T206S S230N V234H V259I R284G	**T97A** V113L **E138A G140S Q148H**	88 (64)	NO Q148
1242	WK 16 (58145)	A23V S24G L28I V72I L101I V113I **G140G/S Q148H** V165I F181L Q216H V234L	**E92E/Q G140S** G149G/A **V151V/A**	98 (29)	Q148+1
1243	WK24 (2805)	S17N S39S/N D41D/N V72I T112S V113I T125T/A G140G/S Q148H(screening) I220L V234L	**E138E/K** Q148Q/H	4.3 (4.1)	NO Q148
1274	WK24 (10481)	S24N D25D/E I84V V113I S119P	A21A/T D25E T122I	1 (1.1)	N155H

		T122I/V T125A V126L N135V M154I V165I K219N I220I/L N222K V234I D256E			
1281	WK4 (914)	L74M T97A Y143R	**M154M/I D167D/E (both emerged Day 8)**	0.9 (0.8)	NO Q148
1821	WK12 (10637)	L74I V151I N155H E157Q G163K	A128A/T **S147G**	15 (4)	N155H
1843	WK8 (37906)	S17N L45M V72I L101I T112I V113I G140S Q148H E157Q K160Q V201I T218I V234L D256E	**N155H**	49 (11)	Q148+≥2
1901	WK16 (31960)	K14K/R R20K V72I L101I V113I T124T/A K136E **E138K G140S Y143R Q148H** E157Q K160Q G163E G193E V201I I203I/M I208L K211K/T Q221R V234I V281V/M D286D/N	**T97T/A** S119S/T **Y143R/C**	66 (4)	Q148+≥2
2021	WK12 (7471)	V31I L63L/I V72I L101I V113I T122I T124N T125T/A/S I135V **G140S Q148H** F181L I208I/M V234L	L63I **T97A** T125A	94 (19)	Q148+1

Subjects with no Post Day 8 Data: 804, 1201, 1264, 1401, 1842, 1844

Table 44. Emergent INSTI Substitutions at Day 8 and Week 24 Summary

	Number Subjects with Emergent Substitutions by Day 8 (n=28 with Post-BL Data)	**Number Subjects with Emergent Substitutions at Week 24 or Last Timepoint (n=22 with Post-Day 8 Data)**
I60T/M (emerged with T97A)	**0**	**3 (14%)**
T66	**0**	**0**
L74M	**1 (4%)**	**1 (5%)**
V75M	**0**	**1 (5%)**
E92E/Q	**0**	**2 (9%)**
T97A	**2 (7%)**	**10 (45%)**
T112M/I	**2 (7%)**	**1 (5%)**
T122I	**1 (4%)**	**2 (9%)**
E138K/A	**0**	**4 (18%)**

Y143H/C	**0**	**2 (9%)**
G140S/A	**2 (7%) (A)**	**4 (18%) (S)**
S147G	**0**	**1 (5%)**
Q148H/R/K	**1 (4%)**	**4 (18%)**
V151A	**0**	**1 (5%)**
M154I/L	**1**	**3 (14%)**
N155H	**0**	**2 (9%)**
E157E/Q	**1 (4%)**	**0**
G163	**0**	**0**
G193	**0**	**0**

Phenotypic Changes at Week 24

In the Week 24 FDA resistance subset (n=40) (>400 copies/mL at Week 24, failure or last timepoint (interim), the median fold-change from reference in DTG susceptibility at Baseline was 4 (range 0.45 to 37). In comparison, the Week 24 responders (n=79) had median fold-change from reference in baseline DTG susceptibility of 1.2 -fold (range 0.47 to 20). In the Week 24 failures with post Day 8 resistance date (n=22), the mean and median fold- change from reference of DTG susceptibility at the failure timepoint was 52- and 34-fold, respectively, (range 0.87 to 209) and the mean and median fold-change from baseline of DTG susceptibility at the failure timepoint was 15- and 7-fold, respectively, (range 0.72 to 119).

Of the isolates in the FDA resistance failure subset with emergent INSTI substitutions (n=18), the baseline mean and median DTG fold-change from reference was 6 and 4.4, respectively. At failure, the mean and median DTG fold-change from reference was 49 and 23, respectively, with a range of 0.92 to 209. The mean and median fold-change from baseline was 9-fold and 7-fold, respectively.

There were 4 subjects' isolates with emergent Q148 substitutions which had a mean of 49-fold and median of 36-fold change from baseline and mean of 63-fold and median of 100-fold change from reference in DTG susceptibility. Ten subjects had emergent T97A. One subject had T97A emerge in the background of V75M Y143R and G163N, but had no change in DTG susceptibility with a fold change <1.0. Of the other 9 subjects' isolates with emergent T97A in the presence of G140S and Q148H (either present at baseline or emergent), the mean DTG fold change from baseline was 28-fold with a mean 85-fold-change from reference. The 5 subjects with emergent T97A plus G140S+Q148H and E138 substitutions had a mean 41-fold change from baseline (mean 92-fold change from reference) in DTG susceptibility.

The 3 subjects' isolates with emergent E138 substitutions with emergent G140S and/or Q148H had a 52-fold change from baseline (mean 72-fold change from reference) in DTG susceptibility. One subject (1243) had emergent E138E/K when G140S and Q148H were present at baseline; the fold change for this subjects' isolate was 4-fold from baseline. The 2 subjects' isolates (1008, 1901) with emergent Y143R or H in the context of several other INSTI substitutions had a mean DTG fold-change of 2.6 from baseline (34-fold change from reference).

Background Drug Resistance Emergence

Resistance to background drugs in the regimen was also analyzed (Table 45). NNRTI resistance substitutions emerged in 3 subjects' isolates (14%) with 2 of the isolates having emergent ETR phenotypic resistance. NRTI substitutions emerged in 5 subjects' isolates (23%); 3 isolates had emergent phenotypic resistance to TDF and one had emergent ABC phenotypic resistance. Genotypic and/or phenotypic resistance emerged in 4 subjects' isolates (18%) on a PI in the background regimen. Seven subjects' isolates (32%) had emergent phenotypic resistance to ENF.

Many of these subjects were resistant to most of the background drugs in their regimen at baseline. With the new regimens starting at Day 8, 11 (50%) of the 22 subjects with post-Day 8 resistance data had an OSS=1, 9 (41%) subjects had an OSS=2 and 2 subjects (9%) had an OSS >2.

Table 45. Week 24 NRTI/NNRTI/PI/ENF Resistance Emergence in the FDA Resistance Analysis Set (n=22) (>400 copies/mL at Week 24 or Last Time Point [interim analysis])

PID	Background Drugs after Day 8 (NEW)*	OSS	Emergent RT Subst	Emergent PI Subst	RT Phenotype	PI Phenotype	ENF RES
0008	DRV FTC TDF (**ETR)**	1	K66K/N **V106V/I K219K/E M230I**	K55R	FTC-R (BL) TDF-R (BL) **ETR-R** (65X)	DRV-R (BL)	
0041	DRV/r FTC TDF ENF	1	NO POST BL	NO POST BL	NO POST BL	NO POST BL	
0226	DRV/r FTC TDF	2	NO POST BL	NO POST BL	NO POST BL	NO POST BL	
0227	**(ENF)** LAM TDF	1	NO POST BL	NO POST BL	NO POST BL	NO POST BL	NO POST BL
0228	**DRV/R** FTC TDF	2			FTC-R (BL)		
0461	**(ENF)** LAM ABC TDF	>2	NO POST BL	NO POST BL	NO POST BL	NO POST BL	
0504	**(ENF)** FTC TDF d4T	1	NO POST BL	NO POST BL	NO POST BL	NO POST BL	**25 (5.3)**
0566	**(d4T)** TDF	1	**A62A/V** V90I **T215F**		**TDF-R** (2.3x)		
0569	**DRV/R ENF**	2		**I47V I50V** K55R G73D/E **L76V L89V**		**DRV-R**	**22 (15)**

				T91T/S Q92Q/R			
1008	**(DDI ENF TDF TPV)**	2	**A98G/A**		**TDF-R (1.6)**		**8.3 (1.5)**
1012	DRV FTC TDF (**ENF ETR**) AZT	1	V10V/A	T91T/S	FTC-R (BL) TDF-R (BL) AZT-R (BL) ETR (7XBL)	DRV-R (BL)	**171 (51)**
1056	DRV FTC TDF (**ENF**) MVC	1	**L74I** R172R/K P176P/S H208H/Y L228H/R	P39P/L **M46I/L**	FTC-R (BL)	DRV-R (BL)	0.7 (1.6)
1203	FTC TDF ENF MVC	2	NO POST BL	NO POST BL	FTC-R (BL) ENF-R (BL)		ENF-R (BL) 68
1206	**(ENF MVC)** TDF	2	V60V/I F214L	**V82T**			**56 (42)**
1241	DRV (**ETR**) LAM	1	**V179I** **Y181C** **G196E** **H221Y**		LAM-R (BL) **ETR-R (97X)**	DRV-R (BL)	
1242	FTC TDF (**MVC SQV)**	2	E194E/K L228D	L10V K20I/V **M46I** I47I/T **A71A/V** **L90L/M**	FTC-R (BL) **TDF (1.39)**	**SQV-R** (36)	
1243	**(DRV LAM ABC)**	1	**D67N** from mixture at BL		ABC-R LAM-R		
1274	FTC TDF (**ENF)**	≥2	P176P/L				2.3 (0.7)
1821	FTC TDF (**ENF)**	2			FTC-R (BL) TDF (0.9)		**24 (11)**
1843	**FTC TDF ENF**	2	**T69G** V118I from mixtures	I93L from mixture	FTC-R (BL) TDF-R (BL)		**41 (15.6)**
1901	**(DLV)** TDF	1	P236P/L	G27G/E	TDF-R	DLV-R	

				H69Y	(BL)	(17)	
2021	FTC TDF	1			FTC-R (BL)		

Subjects with no Post Day 8 Data: 804, 1201, 1264, 1401, 1842, 1844
***Bolded** drugs in parentheses are new drugs added to the regimen after Day 8

Failures after Week 24

Two subjects failed after Week 24 (Table 46). Subject 2 rebounded to 988 copies/mL HIV-1 RNA at Week 40, but had no evidence of emergent genotypic or phenotypic DTG resistance. Subject 566 rebounded to 19689 copies/mL HIV-1 RNA at Week 32 and had an emergent N155H substitution associated with 209-fold DTG resistance.

Table 46. Subjects who Failed after Week 24

PID	Backgrd Drugs	Failure Timepoint	Baseline INSTI Substitutions	Emergent INSTI Substitutions	Emergent RT PR Subst	Failure Phenotype
Subject 2	DRV/r FTC TDF MVC	Week 40	T97A Y143R	V234L K236R		DTG 1.1 FTC 1.1 TDF 0.89 DRV 449
Subject 566	D4T TDF	Week 32	E138T G140S Q148H	V72I **N155H**	A62A/V V90I T215F	DTG 209 d4t 1.4 TDF 2.3

Effect of Duration of INSTI Use and Time from End of INSTI Use on Response

We next examined whether the duration of prior INSTI use (EVG or RAL) or Time for INSTI use affected response rates to DTG at Day 8 or Week 24 (Table 47). In this protocol, the screening period ranged from -49 days to -4 days with a median of -35 days and mean of -34 days. The duration of prior INSTI use ranged from 2 months to 132 months. Subjects who had ≤6 months duration of prior INSTI use had lower response rates that subjects who had >6 months or >24 months duration of prior INSTI use (Table 47). If subjects had ≤6 months duration of prior INSTI use, response rates at Day 8 and Week 24 were 64% and 33%, respectively, compared to response rates of 83-85% at Day 8 and 74% at Week 24 in subjects with >6 months or >24 months prior INSTI duration. These results might indicate that subjects who failed on an INSTI regimen in <6 months (perhaps because of an inadequate regimen, compliance issues or PK issues) had more INSTI resistance emergence than subjects who were on an INSTI regimen longer than 6 months. In support of this suggestion, the three subjects with ≤6 months prior INSTI duration use who responded at Week 24 had no primary INSTI substitutions but historical N155H, whereas the six subjects who failed at Week 24 had historical or screening Q148+1 or +≥2 INSTI substitutions.

The time from the end of INSTI use to DTG start date ranged from 1 day to 54 months. Subjects with a shorter time (<50 days) from end of prior EVG or RAL use to start of DTG had lower response rates than subjects who had discontinued from a EVG or RAL regimen for 2 months - >12 months prior to starting DTG (Table 47). This result may reflect the presence of more INSTI resistance substitutions if subjects were failing on an EVG or RAL regimen just prior to the start of DTG. An analysis combining the time from end of INSTI use with duration of prior INSTI use was performed. Subjects who had a

Reference ID: 3310743

longer duration (>24 months) of INSTI use and a short time from INSTI End Date (<50 days) to DTG start had response rates of 80% at Day 8 and 63% at Week 24. The short time from switching from EVG or RAL to DTG appeared to contribute to lower response rates even if it subjects had been on the INSTI for >24 months. Subjects who had durations of INSTI use of ≤6 months and short time from INSTI End Date (<50 days) to DTG start had low response rates of 56% at Day 8 and 0% at Week 24. At Day 8 in this group, 3 of 4 failure subjects had INSTI substitutions of Q148+G140S plus E138 (Subject 15, Subject 585 and Subject 1842) and the fourth subject (Subject 8) had INSTI substitutions Q148H+G140S. All four subjects were all on RAL prior to switching to DTG. In the Week 24 group of failures, all had INSTI substitutions at baseline: Subjects 8 and 1242 had substitutions Q148H+G140S, Subject 1842 had substitutions Q148, G140 and E138 and Subject 483 had N155H at baseline. It appears likely that the low response rates can be explained by the presence of baseline INSTI substitutions, particularly Q148H +G140S.

Table 47. Effect of Duration of INSTI Use and Time from End of INSTI Use on Outcome

	Day 8 Outcome	Week 24 Outcome
Duration of Prior INSTI (range 2 months to 132 months)		
≤6 months	**64% (9/14)**	**33% (3/9)[a]**
>6 months - ≤24 months	**83% (53/64)**	**74% (31/42)**
>24 months	**85% (87/102)**	**74% (45/61)**
Time from INSTI End Date to DTG Start Date (range 1 day to 54 months)		
1-3 days	**75% (73/97)**	**ND**
<50 Days	**75% (77/102)**	**63% (36/57)**
2 months – 12 months	**86% (30/35)**	**83% (19/23)**
>12 months	**96% (43/45)**	**75% (24/32)**
Long Duration (>24 months) + Short time from INSTI End Date (<50 days)	**80% (52/65)**	**63% (24/38)**
≤6 months durations of INSTI and short time from INSTI End Date (<50 days)	**56% (5/9)[b]**	**0/4[c]**

[a]3 responders at Week 24 had no primary INSTI substitutions but historical N155H, whereas the 6 subjects who failed at Week 24 had historical or screening evidence of Q148+1 or +≥2 INSTI substitutions
[b]4 Day 8-Failures: Subject 8 (Q148H + G140S), Subject 15 (Q148, G140 and E138), Subject 585 (Q148, G140 and E138) and Subject 1842 (Q148, G140 and E138); all on RAL; 5 Day 8-Responders had INSTI substitutions Y143, N155, V151, G163 (one G140/Q148)
[c]4 Week 24-Failures: Subject 8 (Q148H + G140S), Subject 483 (N155H), Subject 1242 (Q148H + G140S), Subject 1842 (Q148, G140 and E138)

CROSS-RESISTANCE

In the treatment-naïve studies (IND113086 and 114467), none of the DTG FDA resistant analysis subjects with post-baseline resistance data were resistant to RAL

In the treatment-experienced INSTI-naïve study (ING111762), none (n=18) of the DTG FDA resistant analysis subjects with post-baseline resistance data were resistant to RAL. Additionally, none of the subjects' isolates in the DTG arm with emergent INSTI substitutions (n=5) had phenotypic changes in susceptibility to either DTG or RAL. The 11 subjects' isolates in the RAL arm with emergent INSTI substitutions all had RAL phenotypic resistance and of these 4 (36%) isolates had DTG phenotypic resistance (≥4-fold change from reference in DTG susceptibility).

In the VIKING-3 study (112574), all the subjects' isolates of Week 24 FDA resistance subset with INSTI substitution emergence were cross-resistant to RAL. The study was designed to enroll only INSTI-experienced subjects, so it is not surprising that DTG failures in this study were resistant to RAL.

RESPONSE BY CLADE

Of the 125 subjects in the Week 24 outcome subset, 115 were clade B, 2 were clade D, and there were 1 each in Clade, A, AG and Complex. The response rates in the clade B subjects were 63% (72/115) at Week 24 same as the overall response. The numbers of subjects in other clades are too small to determine response rates by clade.

5. CONCLUSION

Dolutegravir is approvable with respect to virology for the treatment of HIV-1 in combination with other antiretrovirals. DTG should be administered as 50 mg once daily for treatment-naïve and treatment-experience integrase strand transfer inhibitor-naïve adults and children age 12 and older weighing at least 40 kg. DTG should be administered 50 mg twice daily for integrase strand transfer-experienced adults and patients taking the anti-HIV drugs fosamprenavir/ritonavir, efavirenz (EFV) or tipranavir/ritonavir.

The following point should be considered when initiating therapy with dolutegravir:

- The presence of integrase substitutions at amino acid position Q148 in HIV-1 reduced response rates to dolutegravir-containing regimens. Moreover, subjects with an integrase Q148 substitution plus 2 or more integrase strand transfer inihibitor-resistance substitutions including L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, E157Q, G163E/K/R/Q/S/T/N, or G193E/R in their HIV-1 had poor response rates.

Complete efficacy and resistance data from VIKING-3 and VIKING-4 should be submitted to confirm the initial findings in the Week 24 data.

Reference ID: 3310743

6. PACKAGE INSERT

APPLICANT PROPOSED PACKAGE INSERT

(b) (4)

Reference ID: 3310743

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

FDA NEGOTIATED PACKAGE INSERT

INDICATIONS AND USAGE

(b) (4)

12.1 Mechanism of Action

(b) (4)

12.4 Microbiology

Mechanism of Action:

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture:

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM to 2.1 nM in MT-4 cells and peripheral blood mononuclear cells (PBMCs). Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G and 3 group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents:

The antiviral activity of dolutegravir was not antagonistic when combined with the integrase strand transfer inhibitor (INSTI) raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs) abacavir or stavudine; the protease inhibitors (PIs) amprenavir or lopinavir; the CCR5 co-receptor antagonist maraviroc or the fusion

Reference ID: 3310743

inhibitor enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor adefovir or with the antiviral ribavirin.

Resistance

Cell Culture:

Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decrease susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir. The additional integrase substitutions included L74M, E92Q, T97A, E138K, G140S, M154I, and N155H.

Treatment-Naïve Subjects:

(b) (4)

Treatment-Experienced, Integrase Strand Transfer Inhibitor (INSTI)-Naive Subjects:

(b) (4)

Integrase Strand Transfer Inhibitor (INSTI)-Experienced Subjects:

(b) (4)

Response by Baseline Genotype

(b) (4)

(b) (4)

Response by Baseline Phenotype

(b) (4)

Resistance to background drugs in the dolutegravir BID regimen also emerged in 30% (12/40) of the subjects in the Week 24 resistance analysis set.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains:
The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. Single INSTI substitutions T66K, I151L and S153Y conferred a >2-fold decrease in dolutegravir susceptibility (range 2.3 to 3.6-fold). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148H and substitutions at E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range 2.5- to 21-fold). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains:
Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

7. APPENDICES

APPENDIX A: SPRING-2 STUDY ING113086

FDA DTG RESISTANCE SET (N=2)
ING113086.0003999
ING113086.0004335

FDA RAL RESISTANCE SET (N=8)
ING113086.0003073
ING113086.0003617
ING113086.0003864
ING113086.0004130
ING113086.0004314
ING113086.0004316
ING113086.0004424
ING113086.0004640

EMERGENT SUBSTITUTIONS IN RAL ARM OF STUDY ING113086
INSTI Emergent Substitutions (n=3)
Subjects 3617, 4316, and 4424

NRTI Emergent Substitutions (n=4)
Subjects 3173, 3294, 3617 and 4424

APPENDIX B. SINGLE STUDY ING114467

FDA DTG RESISTANCE ANALYSIS SET (>400 copies/ml or resistance data at failure) **(N=5)**
ING114467.0005233
ING114467.0005252
ING114467.0006860
ING114467.0006934
ING114467.0007912: Emergent INSTI-Resistance Substitution (E157Q/P)

FDA ATRIPLA RESISTANCE ANALYSIS SET (N=12)
ING114467.0005441
ING114467.0005506
ING114467.0005576
ING114467.0005692
ING114467.0005772
ING114467.0006033
ING114467.0006186
ING114467.0006639
ING114467.0006707
ING114467.0006772
ING114467.0006856
ING114467.0006886

EMERGENT SUBSTITUTIONS IN ATRIPLA ARM OF STUDY ING114467
Emergent NNRTI Substitutions (n=6)
Subjects 5506, 5576, 6033, 6707, 6856, 6886

Emergent NRTI Substitutions (n=1)
Subject 6707

APPENDIX C. SAILING STUDY ING111762

FDA DTG RESISTANCE ANALYSIS SET in ING111762 (n=33)

ING111762.0000262
ING111762.0000283
ING111762.0000351
ING111762.0000420
ING111762.0000556
ING111762.0000573
ING111762.0000672
ING111762.0000941
ING111762.0000942
ING111762.0001067
ING111762.0001070
ING111762.0001113
ING111762.0002141
ING111762.0002418
ING111762.0002467
ING111762.0002500
ING111762.0002516
ING111762.0002568
ING111762.0002591
ING111762.0002618
ING111762.0002662
ING111762.0002785
ING111762.0002812
ING111762.0002920
ING111762.0009026
ING111762.0009046
ING111762.0009068
ING111762.0009080
ING111762.0009098
ING111762.0009103
ING111762.0009402
ING111762.0009412
ING111762.0009990

FDA DTG RESISTANCE ANALYSIS SET WITH POST BASELINE DATA IN ING111762 (n=18)

ING111762.0000262
ING111762.0000351
ING111762.0000672
ING111762.0000941
ING111762.0001067
ING111762.0001113
ING111762.0002141
ING111762.0002467
ING111762.0002516
ING111762.0002568

Reference ID: 3310743

ING111762.0002618
ING111762.0002785
ING111762.0002812
ING111762.0002920
ING111762.0009046
ING111762.0009068
ING111762.0009080
ING111762.0009103

SUBJECTS IN DTG ARM WITH TREATMENT EMERGENT INSTI RESISTANCE SUBSTITUTIONS AND/OR PHENOTYPIC RESISTANCE (n=5)
Subjects 351, 672, 1067, 2568, and 2785 (substitutions at L74, Q95, T97, E138, V151, G163, R263)

SUBJECT IN DTG ARM WITH TREATMENT EMERGENT NRTI RESISTANCE SUBSTITUTIONS (n=1)
Subject 2516

SUBJECTS IN DTG ARM WITH TREATMENT EMERGENT NNRTI RESISTANCE SUBSTITUTIONS (n=4)
Subjects 941, 1113, 2568 and 2785

FDA RAL RESISTANCE ANALYSIS SET IN ING111762 (n=49)
ING111762.0000004
ING111762.0000254
ING111762.0000260
ING111762.0000294
ING111762.0000419
ING111762.0000492
ING111762.0000587
ING111762.0000588
ING111762.0000655
ING111762.0000742
ING111762.0000785
ING111762.0000793
ING111762.0000947
ING111762.0000963
ING111762.0000976
ING111762.0000977
ING111762.0001128
ING111762.0001146
ING111762.0001909
ING111762.0002201
ING111762.0002214
ING111762.0002360
ING111762.0002371
ING111762.0002425
ING111762.0002427

ING111762.0002430
ING111762.0002457
ING111762.0002472
ING111762.0002489
ING111762.0002495
ING111762.0002513
ING111762.0002571
ING111762.0002632
ING111762.0002688
ING111762.0002727
ING111762.0002734
ING111762.0002765
ING111762.0002766
ING111762.0002769
ING111762.0002807
ING111762.0002835
ING111762.0002851
ING111762.0009048
ING111762.0009071
ING111762.0009088
ING111762.0009095
ING111762.0009125
ING111762.0009415
ING111762.0009461

FDA RAL RESISTANCE ANALYSIS SET WITH POST-BASELINE DATA IN ING111762 (n= 38)

ING111762.0000004
ING111762.0000260
ING111762.0000294
ING111762.0000419
ING111762.0000492
ING111762.0000587
ING111762.0000588
ING111762.0000655
ING111762.0000785
ING111762.0000793
ING111762.0000947
ING111762.0000963
ING111762.0000976
ING111762.0000977
ING111762.0001128
ING111762.0001146
ING111762.0001909
ING111762.0002201
ING111762.0002360
ING111762.0002425
ING111762.0002427
ING111762.0002430

ING111762.0002472
ING111762.0002495
ING111762.0002513
ING111762.0002571
ING111762.0002632
ING111762.0002688
ING111762.0002727
ING111762.0002734
ING111762.0002765
ING111762.0002766
ING111762.0002769
ING111762.0002851
ING111762.0009048
ING111762.0009071
ING111762.0009088
ING111762.0009125

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT INSTI RESISTANCE SUBSTITUTIONS AND/OR PHENOTYPIC RESISTANCE (n=10)
Subjects 260, 419, 785, 963, 977, 1146, 2427, 2688, 2769 and 9088 (substitutions at L74, E92, T97, G140, Y143, Q148, V151, N155, G163)

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT NRTI RESISTANCE SUBSTITUTIONS (n=6)
Subjects 260, 492, 2201, 2427, 2495, and 2571

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT NNRTI RESISTANCE SUBSTITUTIONS (n=4)
Subjects 260, 2201, 2360, and 2571

SUBJECTS IN RAL ARM WITH TREATMENT EMERGENT PI RESISTANCE SUBSTITUTIONS (n=5)
Subjects 419, 963, 2765, 2769, and 9048

Reference ID: 3310743

APPENDIX D. VIKING-3 STUDY ING112574

DTG SUBJECTS IN DAY 8 FDA RESISTANCE ANALYSIS SET (<1 $\log_{10}$ change from baseline at Day 8 and ≥50 copies/mL) (N=32)

ING112574.0000008
ING112574.0000010
ING112574.0000015
ING112574.0000021
ING112574.0000181
ING112574.0000221
ING112574.0000231
ING112574.0000324
ING112574.0000408
ING112574.0000461
ING112574.0000504
ING112574.0000545
ING112574.0000585
ING112574.0001008
ING112574.0001048
ING112574.0001063
ING112574.0001067
ING112574.0001090
ING112574.0001203
ING112574.0001216
ING112574.0001264
ING112574.0001271
ING112574.0001274
ING112574.0001806
ING112574.0001842
ING112574.0001844
ING112574.0001865
ING112574.0001901
ING112574.0001964
ING112574.0002001
ING112574.0002042
ING112574.0002067

DTG SUBJECTS IN WEEK 24 FDA RESISTANCE ANALYSIS SET (>400 copies/mL at Failure or Week 24) (N=40)

ING112574.0000008
ING112574.0000010
ING112574.0000015
ING112574.0000041
ING112574.0000181
ING112574.0000221
ING112574.0000226
ING112574.0000227
ING112574.0000228

ING112574.0000461
ING112574.0000504
ING112574.0000566
ING112574.0000569
ING112574.0000585
ING112574.0000804
ING112574.0001008
ING112574.0001012
ING112574.0001056
ING112574.0001067
ING112574.0001089
ING112574.0001090
ING112574.0001201
ING112574.0001203
ING112574.0001206
ING112574.0001219
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001264
ING112574.0001274
ING112574.0001281
ING112574.0001401
ING112574.0001821
ING112574.0001842
ING112574.0001843
ING112574.0001844
ING112574.0001865
ING112574.0001901
ING112574.0002001
ING112574.0002021

DTG SUBJECTS IN WEEK 24 FDA RESISTANCE ANALYSIS SET (>400 copies/mL at Failure or Week 24) WITH POST-DAY 8 RESISTANCE DATA (N=22)

ING112574.0000008
ING112574.0000227
ING112574.0000504
ING112574.0000566
ING112574.0001008
ING112574.0001012
ING112574.0001056
ING112574.0001206
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001274
ING112574.0001821
ING112574.0001843
ING112574.0001901

ING112574.0002021

DTG SUBJECTS WITH TREATMENT EMERGENT INSTI SUBSTITUTIONS AT DAY 8 (n=6)

ING112574.0000010
ING112574.0000015
ING112574.0000221
ING112574.0000231
ING112574.0000585
ING112574.0001281

DTG SUBJECTS WITH TREATMENT EMERGENT INSTI SUBSTITUTIONS IN WEEK 24 FDA RESISTANCE ANALYSIS SET (n=18)

ING112574.0000008
ING112574.0000041
ING112574.0000227
ING112574.0000461
ING112574.0000504
ING112574.0000566
ING112574.0000569
ING112574.0001008
ING112574.0001012
ING112574.0001203
ING112574.0001206
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001821
ING112574.0001843
ING112574.0001901
ING112574.0002021

APPENDIX E. WEEK 24 BASELINE OUTCOME SET (N=125)

ING112574.0000001
ING112574.0000002
ING112574.0000003
ING112574.0000004
ING112574.0000007
ING112574.0000008
ING112574.0000021
ING112574.0000022
ING112574.0000024
ING112574.0000102
ING112574.0000103
ING112574.0000182
ING112574.0000222
ING112574.0000227
ING112574.0000261
ING112574.0000301
ING112574.0000302
ING112574.0000343
ING112574.0000345
ING112574.0000381
ING112574.0000403
ING112574.0000462
ING112574.0000481
ING112574.0000483
ING112574.0000504
ING112574.0000507
ING112574.0000544
ING112574.0000545
ING112574.0000561
ING112574.0000562
ING112574.0000565
ING112574.0000566
ING112574.0000567
ING112574.0000570
ING112574.0000582
ING112574.0000651
ING112574.0000663
ING112574.0000804
ING112574.0001001
ING112574.0001002
ING112574.0001004
ING112574.0001006
ING112574.0001007
ING112574.0001008
ING112574.0001009
ING112574.0001011
ING112574.0001012
ING112574.0001013

ING112574.0001021
ING112574.0001026
ING112574.0001031
ING112574.0001036
ING112574.0001038
ING112574.0001041
ING112574.0001046
ING112574.0001048
ING112574.0001049
ING112574.0001051
ING112574.0001055
ING112574.0001056
ING112574.0001057
ING112574.0001061
ING112574.0001063
ING112574.0001066
ING112574.0001201
ING112574.0001202
ING112574.0001205
ING112574.0001206
ING112574.0001208
ING112574.0001209
ING112574.0001210
ING112574.0001212
ING112574.0001213
ING112574.0001214
ING112574.0001215
ING112574.0001216
ING112574.0001217
ING112574.0001221
ING112574.0001233
ING112574.0001234
ING112574.0001241
ING112574.0001242
ING112574.0001243
ING112574.0001263
ING112574.0001264
ING112574.0001271
ING112574.0001272
ING112574.0001273
ING112574.0001274
ING112574.0001401
ING112574.0001402
ING112574.0001403
ING112574.0001481
ING112574.0001601
ING112574.0001611
ING112574.0001612
ING112574.0001616

ING112574.0001802
ING112574.0001841
ING112574.0001842
ING112574.0001843
ING112574.0001844
ING112574.0001861
ING112574.0001862
ING112574.0001901
ING112574.0001902
ING112574.0001961
ING112574.0001962
ING112574.0001982
ING112574.0001983
ING112574.0002021
ING112574.0002063
ING112574.0000015
ING112574.0000181
ING112574.0000221
ING112574.0000228
ING112574.0000569
ING112574.0001067
ING112574.0001090
ING112574.0001203
ING112574.0001219
ING112574.0001806
ING112574.0001821
ING112574.0001964
ING112574.0002001

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

/s/

LISA K NAEGER
05/17/2013

JULIAN J O REAR
05/17/2013

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 204790 **Applicant: ViiV Healthcare** **Stamp Date: 12/17/2012**

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 submitted 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 submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			n/a
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant submitted 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?			standardized
9	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant submitted 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		

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.

Lisa K. Naeger 01/23/2013
Reviewing Microbiologist Date

Microbiology Team Leader Date

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

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

/s/

LISA K NAEGER
01/23/2013

JULIAN J O REAR
01/23/2013