MAJOR ARTICLE

Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study

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Background. The pilot phase IIb VIKING study suggested that dolutegravir (DTG), a human immunodeficiency virus (HIV) integrase inhibitor (INI), would be efficacious in INI-resistant patients at the 50 mg twice daily (BID) dose.

Methods. VIKING-3 is a single-arm, open-label phase III study in which therapy-experienced adults with INI-resistant virus received DTG 50 mg BID while continuing their failing regimen (without raltegravir or elvitegravir) through day 7, after which the regimen was optimized with ≥1 fully active drug and DTG continued. The primary efficacy endpoints were the mean change from baseline in plasma HIV-1 RNA at day 8 and the proportion of subjects with HIV-1 RNA <50 c/mL at week 24.

Results. Mean change in HIV-1 RNA at day 8 was −1.43 $\log_{10}$ c/mL, and 69% of subjects achieved <50 c/mL at week 24. Multivariate analyses demonstrated a strong association between baseline DTG susceptibility and response. Response was most reduced in subjects with Q148 + ≥2 resistance-associated mutations. DTG 50 mg BID had a low (3%) discontinuation rate due to adverse events, similar to INI-naive subjects receiving DTG 50 mg once daily.

Conclusions. DTG 50 mg BID–based therapy was effective in this highly treatment-experienced population with INI-resistant virus.

Clinical Trials Registration. www.clinicaltrials.gov (NCT01328041) and http://www.gsk-clinicalstudywww.gsk-clinicalstudyregister.com (112574).

Keywords. dolutegravir; DTG; elvitegravir resistance; integrase inhibitor; raltegravir resistance.

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Dolutegravir (DTG) is a new integrase inhibitor (INI) with demonstrated efficacy in INI-naive patients [1–3] and is approved in the United States for the treatment of human immunodeficiency virus type 1 (HIV-1) infection [4]. In vitro, DTG retained activity against virus with mutations associated with raltegravir (RAL) and elvitegravir (EVG) resistance [5, 6]. In the phase IIb VIKING study, 2 sequential cohorts of subjects with RAL-resistant virus received DTG 50 mg either once (QD) or twice daily (BID) with an optimized background drug regimen (OBR) after an 11-day functional monotherapy period [7]. Data from a healthy subject study demonstrated a variable and less-than-dose-proportional increase in DTG drug exposure

when increasing the dose from 50 to 100 mg; therefore, to optimize exposure, the 50 mg BID dose was investigated in the phase IIb VIKING study.

Based on the greater efficacy of DTG 50 mg BID in VIKING, this dose was selected for phase III evaluation in INI-resistant patients. Here, we report the results from a phase III study in patients with documented RAL- and/or EVG-resistant virus. An initial 7-day functional monotherapy phase was designed to assess the independent activity of DTG, followed by DTG coadministered with OBR to assess durability of response. Factors associated with antiviral response at day 8 and week 24 were explored.

METHODS

Study Design

VIKING-3 (ING112574) is a single-arm, open-label, multicenter study conducted at 65 sites in the United States, Canada, and Europe. A 7-day functional monotherapy period (only DTG activity expected) where DTG 50 mg BID replaced RAL or EVG in the previously failing antiretroviral therapy (ART) regimen was followed by a second phase from day 8, when the background ART was optimized according to baseline resistance data.

Study visits were at screening (day −42 to day −35), days 1 and 8, weeks 4, 8, 12, 16, 24, 32, 40, and 48 and every 12 weeks thereafter.

Ethics committee approval was obtained at all participating sites in accordance with the principles of the 2008 Declaration of Helsinki, with written informed consent obtained from each subject prior to screening procedures. Protocol summaries were posted to www.clinicaltrials.gov (NCT01328041) and www.gsk-clinicalstudyregister.com (112574).

Subjects

Eligible subjects were ART experienced, ≥18 years old, with plasma HIV-1 RNA ≥500 copies/mL (c/mL). Screening and/or documented historic evidence of resistance (genotypic and/or phenotypic) to RAL and/or EVG and to ≥2 other ART classes was mandated, along with at least 1 fully active drug option for their OBR. Subjects were excluded if they had active US Centers for Disease Control and Prevention (CDC) category C disease except for Kaposi's sarcoma; moderate to severe hepatic impairment (Child Pugh criteria); anticipated need for hepatitis C therapy during the first 24 weeks; or defined exclusionary laboratory values and medical conditions, including pregnancy. Based on the observed reductions in DTG exposure with certain antiretrovirals [4] (and considering washout period between treatments), the following criteria also applied: treatments including efavirenz or nevirapine within 14 days of DTG first dose and during the study were exclusionary; etravirine (ETR) was permitted only if coadministered with lopinavir/ritonavir or darunavir/ritonavir (DRV/r); and tipranavir/ritonavir or fosamprenavir/ritonavir were only allowed from day 8 for subjects harboring virus without Q148 + ≥2 associated mutations.

Efficacy Assessments

The primary endpoints were the mean change from baseline in plasma HIV-1 RNA at day 8 and the proportion of subjects with <50 c/mL at week 24 using the Abbott RealTime HIV-1 Polymerase Chain Reaction (PCR) Assay (Abbott Molecular, Des Plaines, IL). Key secondary efficacy outcomes included the impact of covariates on day 8 and week 24 treatment response, change from baseline in $CD4^+$ cell count, and incidence of disease progression.

Safety Assessments

Safety parameters assessed at all visits included adverse events (AEs), serious AEs, and hematology and chemistry laboratory values. Vital signs, electrocardiograms, fasting lipids, dipstick urinalysis, and urine albumin/creatinine ratio were also assessed. Division of AIDS toxicity scales [8] was applied. An independent data monitoring committee (IDMC) assessed ongoing safety. The IDMC also adjudicated events of suspected immune reconstitution inflammatory syndrome (IRIS) [9]. All available data as of the data cutoff, based on the last enrolled subject reaching week 24, are presented.

Viral Genotyping and Phenotyping Assessments

Viral genotyping and phenotyping were carried out on screening and day 1 plasma by Monogram Biosciences (San Francisco, CA), with the exception of the screening integrase (IN) genotype analyzed by Quest Diagnostics (Valencia, CA). PhenoSense and GeneSeq testing were used for nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and INIs, with PhenoSense Entry for enfuvirtide (T-20) and Trofile for maraviroc (MVC). The Monogram 'net assessment' results based on genotypic and/or phenotypic data were used to produce an overall susceptibility score (OSS) for each drug. Genotypic susceptibility scores (GSS) and phenotypic susceptibility scores (PSS) were calculated according to the Stanford HIVdb interpretation of genotypes [10] and the Monogram phenotypic cutoffs, respectively.

Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analyses

Predose (C0) DTG concentrations were obtained at day 8 and weeks 4 and 24 and analyzed as described elsewhere [11]; the average across these time points (C0-avg) was calculated. The phenotypic inhibitory quotient (PIQ-C0) was calculated as DTG C0 divided by the baseline fold change in 50% inhibitory concentration (FC) and protein-binding–adjusted 90% inhibitory concentration relative to wild-type virus. The association

between DTG C0, PIQ-C0 (log transformed), and primary efficacy endpoints and safety measures was evaluated using univariate and multivariate regression analyses.

Statistical Analysis

Assuming at least a 0.7 $\log_{10}$ c/mL response at day 8 (standard deviation of 0.5) vs the no change null hypothesis and a 2-sided 5% significance level testing would require <20 subjects for 90% power. For the primary endpoint at week 24, 100 subjects would provide 4% precision, yielding a 95% confidence interval (CI) of 72% to 88% (assuming response of 80% based on the VIKING study [7]). More subjects were enrolled to allow a more comprehensive assessment of predictors of response and safety [12]. The primary efficacy and safety analyses were based on the intent-to-treat exposed (ITT-E)/safety population comprising all subjects who received ≥1 dose of investigational product (IP). For the day 8 primary analysis, the previous on-treatment observation was carried forward if day 8 data were missing, and the baseline data were carried forward if the subject had no on-treatment data due to premature withdrawal. Response at Week 24, including primary endpoint and multivariate analyses, was assessed with the Snapshot algorithm [13].

Univariate subgroup analyses explored the impact of baseline demographic characteristics (age, gender, race, country, duration of prior INI therapy, viral load, $CD4^+$ cell count, IN phenotype and genotype, PSS, GSS or OSS to background regimen, and OSS to new [never used previously] drugs in the OBR) and pharmacokinetic exposure (C0 or C0-avg) on response.

Multivariate regression analyses of factors affecting response were conducted using a linear regression model for day 8 and a logistic regression model for week 24. For these analyses, virological outcome population was defined to minimize potential confounders; this excluded subjects who received incorrect IP, had IP interruption, received prohibited medication, or who discontinued IP for any reason other than lack of efficacy prior to the time point of interest (ie, day 8 or week 24). Highly correlated factors such as DTG FC and IN mutation subgroups were explored in separate models. All variables in the univariate analyses were explored in multivariate analyses, and the final models were selected using Akaike Information Criterion (AIC) [14].

Prespecified IN mutation categories and a derived IN mutation group categorization (based on analysis of day 8 responses by baseline resistance within this study) were assessed. Three IN mutation subgroups were derived on the basis of their differential impact on response: No Q148 (Y143, N155, T66, or E92 mutations or historical resistance), Q148 +1, and Q148 + ≥2. Based on the prevalence of specific substitutions observed at baseline in the study, the latter 2 groups were defined by the presence of 1 or ≥2 of the following IN secondary mutations: G140A/C/S, L74I or E138A/K/T [15].

RESULTS

Demographic and Baseline Characteristics

Of 323 subjects screened, 183 were enrolled and received at least 1 dose of DTG. Enrollees had advanced HIV disease and extensive prior ART (Table 1). Seventy-three percent of subjects had screening INI resistance (genotypic and/or phenotypic), and 27% (n = 50) had historic evidence only. At baseline (35–42 days post-screening), 33% had no detectable primary INI-resistance mutations, 36% had mutations other than Q148 (ie, primary mutations at codons N155, Y143, T66, and E92), whereas 20% and 11% had virus with Q148 + 1 or + ≥2 associated secondary mutations, respectively. The median (range) FC to RAL was 47.5 (0.49–>maximum assay limit). The median DTG FC was low (1.29); the range (0.45–47) was sufficient to assess efficacy. At baseline, 79%, 70%, and 75% of subjects harbored viruses with ≥2 NRTI, ≥2 PI, and ≥1 NNRTI major resistance mutations, respectively, and 62% had CXCR4 virus detected. Plasma HIV-1 RNA on the failing regimen prior to starting DTG was stable between screening and baseline (Table 1). Day 8 OBRs were diverse; the most commonly used agents were DRV/r (65%), tenofovir/emtricitabine (TDF/FTC; 60%), ETR (37%), T-20 (32%), and MVC (25%). TPV/r was used in 15 (8%) subjects. Fifty-six percent of subjects had an OBR OSS ≥2; however, despite the extensive history of prior NRTI use (90% of subjects had prior use of ≥3 NRTIs), an NRTI was considered the second active agent in 56/77 (73%) subjects with OSS of 2, and the second and third active agents in 12/26 (46%) subjects with OSS of 3. DRV/r was classified as fully active in 25% of participants; TDF, T-20, and ETR were considered fully active in 46%, 28%, and 22% of subjects, respectively. When only drugs never previously used were considered for the OBR activity score, 38% and 42% had an OSS of 0 or 1, respectively, and only 20% of subjects had an OSS ≥2, potentially better reflecting the activity of the OBR.

Efficacy

A strong antiviral response was demonstrated at both day 8 and week 24. Day 8 mean change from baseline in plasma HIV-1 RNA was −1.43 $\log_{10}$ c/mL, and 69% (95% CI, 62%–76%) of subjects achieved <50 c/mL at week 24 (Table 2). The response was rapid, with 54% and 61% of subjects with HIV-1 RNA <50 c/mL by weeks 4 and 8, respectively.

In univariate analyses, DTG FC >10 and the presence of Q148 + ≥2 virus were associated with a day 8 mean reduction of <1 $\log_{10}$ c/mL HIV-1 RNA and a low response at week 24 (Table 3). The No Q148 subgroup had the highest responses. A separate prespecified assessment of Y143 (n = 28) and N155H (n = 33) mutations showed day 8 mean changes in HIV-1 RNA of −1.7 and −1.43 $\log_{10}$ c/mL, respectively, and week 24 HIV-1 RNA <50 c/mL of 75% and 88%, respectively. The antiviral response increased as DTG FC decreased.

Table 1. Demographics and Disease Characteristics

Parameter	DTG 50 mg BID (N = 183)
Age, median (IQR), y	48 (43–52)
Male, n (%)	141 (77)
Race, n (%)	
White	130 (71)
African American/African heritage	49 (27)
Missing	4 (2)
$CD4^+$ cell count, median (IQR), cells/mm^3	140 (40–330)
Screening plasma HIV-1 RNA level, median (IQR), log_{10} c/mL	4.26 (3.64–4.83)
Baseline plasma HIV-1 RNA level, median (IQR), log_{10} c/mL	4.38 (3.67–4.93)
CDC category C, n (%)	102 (56)
Hepatitis coinfection, n (%)	
HBsAg positive	10 (5)
HCV-antibody positive	26 (14)
HBsAg- and HCV-antibody positive	2 (1)
Duration of prior ART, median (IQR), y	14 (8.50–17.33)
Number of prior ARTs, median (IQR)	14 (3–23)
Prior ART treatment, n (%)	
ETR	103 (56)
Enfuvirtide	89 (49)
DRV/r	134 (73)
Genotypic and/or phenotypic INI resistance for study entry, n (%)	
Detected at screening	133 (73)
Prior historic detection only[a]	50 (27)
Baseline genotypic primary INI resistance detected	123 (67)
Derived IN mutation groups at baseline, n (%)	
No Q148 (N155H, Y143C/H/R, T66A, E92Q or historical evidence)	126 (69)
Q148 +1 (secondary mutation from G140A/C/S, E138A/K/T or L74I)	36 (20)
Q148 + ≥2 (secondary mutations from G140A/C/S, E138A/K/T or L74I)	21 (11)
Baseline DTG FC, median (IQR)	1.29 (0.92–3.82)
Baseline RAL FC, median (IQR)	47.5 (1.11–>maximum assay limit)
Other ART resistance at baseline, n (%)	
≥3 NRTI major mutations	133 (73)
≥2 PI major mutations	129 (70)
≥2 NNRTI major mutations	108 (59)
Mixed CCR5/CXCR4 or CXCR4 tropic	113 (62)
T-20 phenotypic resistance	24 (13)
OSS of failing background regimen = 0, n (%)	105 (57)
OSS of day 8 OBR, all / no prior use, n (%)[b]	
0	9 (5) / 69 (38)
1	71 (39) / 77 (42)
2	77 (42) / 35 (19)
>2	26 (14) / 2 (1)
OBR coadministered with DTG (in ≥25%), n (%)	
DRV/r	119 (65)
TDF/FTC	109 (60)
ETR	67 (37)
T-20	59 (32)
MVC	46 (25)
OBR coadministered with DTG (combinations in ≥5%), n (%)	
TDF/FTC + DRV/r	21 (11)
TDF/FTC + DRV/r + T-20	11 (6)
TDF/FTC + DRV/r + T-20 + ETR	11 (6)
TDF/FTC + DRV/r + ETR	10 (5)
DRV/r + MVC	10 (5)
DRV/r + ETR	9 (5)
Most frequently used active antiretroviral in OBR, n (%)[c]	
TDF	84 (46)
T-20	51 (28)
DRV/r	45 (25)
ETR	40 (22)
MVC	33 (18)

Table 1 continued.

Abbreviations: ART, antiretroviral therapy; BID, twice daily; c/mL, copies/mL; DRV/r, darunavir/ritonavir; DTG, dolutegravir; ETR, etravirine; FC, fold change in 50% inhibitory concentration relative to wild-type virus; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INI, integrase inhibitor; IQR, interquartile range; MVC, maraviroc; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OBR, optimized background regimen; OSS, overall susceptibility score; PI, protease inhibitor; RAL, raltegravir; T-20, enfuvirtide; TDF, tenofovir.

[a] Historic resistance for eligibility was as follows: 42/50 subjects had primary mutation at positions 92 (n = 2), 143 (n = 4), 155 (n = 19), 148 (n = 15) or multiple primary mutations (n = 2) and the remaining 8/50 had historic phenotypic resistance to RAL.

[b] OBR includes all drugs in the OBR; OBR, no prior use includes only drugs that had not been previously been administered prior to OBR start.

[c] Activity based on OSS at baseline.

Increasing activity of OBR did not significantly improve day 8 or week 24 responses. There was an improved week 24 response when ≥2 active "nonrecycled" ARTs were coadministered with DTG (Table 3), but this was not a significant predictor of response in multivariate analyses (see below).

Multivariate analyses exploring impact of covariates on day 8 response showed that baseline HIV-1 RNA, DTG phenotype, IN genotype, and DTG day 8 C0 had significant impact on day 8 response with varied magnitude of effect (Table 4). The 2 models with the highest measure of model fitness (lowest AIC value) are presented. Considering the greater model complexity (3 genotype subgroups) of model 2, the model fitness for both models is comparable. The factor with greatest impact was baseline Q148 + ≥2 associated mutations, with day 8 change from baseline in HIV-1 RNA reduced by 0.69 log_{10} c/mL when compared to no Q148 mutation at baseline ($P < .001$). DTG C0 had a very small effect size: increasing DTG C0 by 1 μg/mL only increased response by 0.05 log_{10} c/mL ($P = .021$). The overall geometric mean plasma DTG pre-dose concentration was 2.33 μg/mL,

Table 2. Primary Efficacy Results (ITT-E Population)

Parameter	DTG 50 mg BID (N = 183)
Change from baseline in plasma HIV-1 RNA at day 8 (LOCFDB)	
Plasma HIV-1 RNA level, log_{10} c/mL	
Baseline, mean (SD)	4.26 (0.93)
Change from baseline, mean (SD)[a,b]	−1.43 (0.61)
95% CI	−1.52, −1.34
Subjects with plasma HIV-1 RNA <50 c/mL at Week 24, n (%)[c]	
Virological success (HIV-1 RNA <50 c/mL)	126 (69)
Virological nonresponse	50 (27)
Data in window ≥50 c/mL	28 (15)
Discontinued for insufficient viral load response[d]	9 (5)
Discontinued for other reasons while not <50 c/mL	3 (2)
Change in background ART	10 (5)
No virological data at Week 24	7 (4)
Discontinued due to AE/death[e]	5 (3)
Discontinued for other reasons	2 (1)

Abbreviations: AE, adverse event; ART, antiretroviral therapy; BID, twice daily; CI, confidence interval; c/mL, copies/mL; DTG, dolutegravir; ITT-E, intent-to-treat exposed; HIV-1, human immunodeficiency virus type 1; LOCFDB, last observation carried forward and discontinuation equals baseline; SD, standard deviation.

[a] Based on LOCFDB; 182 subjects are included as 1 subject did not have any on-treatment viral load data at or before day 8 but was still ongoing.

[b] $P < .001$ vs null hypothesis of no change from baseline.

[c] Based on US Food and Drug Administration Snapshot analysis.

[d] Insufficient response as per investigator discretion.

[e] One subject died post withdrawal from progressive multifocal leukoencephalopathy.

with a between-subject coefficient of variation of 68% (Table 5). Increased activity score of the failing background regimen did not improve response; the change from baseline was actually reduced in those with a PSS of 2 or >2 compared with those with a score of 0.

Baseline INI resistance (genotypic or phenotypic) and viral load were highly significant predictors for week 24 response: for every 2-fold increase in DTG FC, the odds of achieving HIV-1 RNA <50 c/mL were 63% lower; the odds of achieving this endpoint were 96% lower in subjects with virus harboring Q148 + ≥2 mutations compared with the response in those with no evidence of Q148 mutations (Table 4). For every 10-fold increase in baseline HIV-1 RNA, the odds of achieving HIV-1 RNA <50 c/mL were about 80% lower. The activity scores of the OBR had insufficient impact for inclusion in the final models.

Similar patterns of association between response and baseline factors (eg, viral load, background regimen activities; data not shown) were observed across the 3 derived IN mutation groups (ie, No Q148, Q148 + 1, and Q148 + ≥2). There was no significant interaction between derived IN mutation groups and other main factors in the multivariate regression analysis.

Table 3. Virological Response at Day 8 and Week 24 by Baseline Factors, Univariate Analyses

	Change From Baseline (Log_{10} c/mL) at Day 8, ITT-E (N = 183)			HIV-1 RNA <50 c/mL at Week 24, ITT-E (N = 183)
Subgroup	N	Mean	SD	n/N (%)
Overall	182	−1.43	(0.61)	126/183 (69)
HIV-1 RNA c/mL				
≤10 000	70	−1.34	(0.52)	60/70 (86)
>10 000 to ≤100 000	72	−1.45	(0.64)	52/72 (72)
>100 000	40	−1.56	(0.68)	16/41 (39)
CD4+ cells/mm^3				
<50	49	−1.23	(0.68)	19/50 (38)
50 to <200	60	−1.53	(0.67)	41/60 (68)
200 to <350	34	−1.55	(0.38)	32/34 (94)
≥350	39	−1.40	(0.53)	34/39 (87)
DTG FC				
0 to ≤4	134	−1.59	(0.52)	102/135 (76)
>4 to ≤10	26	−1.07	(0.58)	14/26 (54)
>10	15	−0.72	(0.73)	3/11 (27)
Missing	7	−1.29	(0.36)	7/7 (100)
Primary IN mutation at baseline				
Detected	122	−1.34	(0.62)	79/123 (64)
Not detected	60	−1.62	(0.55)	47/60 (78)
Derived IN mutation group				
No Q148[a]	126	−1.59	(0.51)	100/126 (79)
Q148 +1[b]	36	−1.15	(0.54)	21/36 (58)
Q148 + ≥2[b]	20	−0.92	(0.81)	5/21 (24)
PSS of background ART[c]				
0	96	−1.45	(0.54)	6/8 (75)
1	67	−1.47	(0.68)	40/58 (69)
2	11	−1.22	(0.50)	58/82 (71)
>2	8	−1.26	(0.73)	22/35 (63)
GSS of background ART[c]				
0	73	−1.44	(0.60)	4/8 (50)
>0 to 1	85	−1.48	(0.61)	43/58 (74)
>1 to 2	15	−1.29	(0.65)	58/87 (67)
>2	9	−1.15	(0.46)	21/30 (70)
OSS of background ART[c]				
0	105	−1.44	(0.58)	7/9 (78)
1	60	−1.50	(0.66)	48/71 (68)
2	11	−1.14	(0.54)	53/77 (69)
>2	6	−1.18	(0.56)	18/26 (69)
OSS of OBR new drugs only[d]				
0	NA	NA	NA	45/69 (65)
1	NA	NA	NA	52/77 (68)
2	NA	NA	NA	27/35 (77)
>2	NA	NA	NA	2/2 (100)

Abbreviations: ART, antiretroviral therapy; c/mL, copies/mL; DTG, dolutegravir; FC, fold change in 50% inhibitory concentration relative to wild-type virus; GSS, genotypic susceptibility score; HIV-1, human immunodeficiency virus type 1; IN, integrase; ITT-E, intent-to-treat exposed; NA, not applicable; OBR, optimized background regimen; OSS, overall susceptibility score; PSS, phenotypic susceptibility score; SD, standard deviation.

[a] Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or only historical evidence of resistance.

[b] Secondary mutations from G140A/C/S, E138A/K/T or L74I.

[c] Failing background regimen for Day 8 response, OBR for Week 24 response.

[d] OSS of OBR when only drugs never previously administered were assessed.

Table 4. Factors Associated With Virological Response at Day 8 (Linear Regression Analysis) and Week 24 (Logistic Regression Analysis); Virologic Outcome Population

	Change From Baseline (Log_{10} c/mL) at Day 8 (N = 179)				HIV-1 RNA <50 c/mL at Week 24 (N = 161)			
	Model 1 With DTG FC (n = 139; AIC = 223.4)		Model 2 With Derived IN Mutation Group (n = 145; AIC = 228.9)		Model 1 With DTG FC (n = 153; AIC = 113.5)		Model 2 With Derived IN Mutation Group (n = 153; AIC = 120.4)	
Factors	Effect (LS Mean[a]) (95% CI)	*P* Value	Effect (LS Mean[a]) (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
10-fold increase in HIV-1 RNA c/mL	−0.12 (−.22, −.02)	.0175	−0.13 (−.23, −.04)	.007	0.20 (.09, .49)	<.001	0.24 (.10, .55)	<.001
50-cell increase in CD4+ cells/mm^3	NR	NR	NR	NR	1.23 (.99, 1.53)	.059	1.26 (1.01, 1.57)	.045
2-fold increase in DTG FC	0.18 (0.12, 0.25)	<.001	. . .[b]		0.37 (.25, .57)	<.001	. . .[b]	
Derived IN mutation group								
No Q148[c]	. . .[b]		Reference group[d]		. . .[b]		Reference group[d]	
Q148 +1[e]	. . .[b]		0.44 (.22, .66)	<.001	. . .[b]		0.31 (.08, 1.19)	.088
Q148 + ≥2[e]	. . .[b]		0.69 (.42, .95)	<.001	. . .[b]		0.04 (.01, .20)	<.001
PSS of background ART[f]								
0	Reference group[d]		Reference group[d]		NR		NR	
1	−0.06 (.25, .12)	.499	−0.04 (−.22, .14)	.685	NR		NR	
2	0.38 (−.01, .78)	.055	0.44 (.07, .80)	.019	NR		NR	
>2	0.52 (.04, 1.00)	.033	0.55 (.07, 1.02)	.024	NR		NR	
GSS, PSS, or OSS of background ART[f]	NR		NR		NR		NR	
1 μg/mL increase in DTG C0[g]	−0.05 (.09, −.01)	.021	−0.05 (−.09, −.01)	.013	NR		NR	

Abbreviations: AIC, Akaike Information Criterion for model fitness; ART, antiretroviral therapy; CI, confidence interval; C0, drug concentration immediately prior to dosing; DTG, dolutegravir; FC, fold change in DTG 50% inhibitory concentration relative to wild-type virus; GSS, genotypic susceptibility score; HIV-1, human immunodeficiency virus type 1; IN, integrase; LS, least squares; NR, not retained (factor not retained in final regression model based on AIC model selection criteria); OBR, optimized background regimen; OSS, overall susceptibility score; PSS, phenotypic susceptibility score.

[a] LS mean: LS mean value of the coefficient derived from multivariate linear regression model after adjusting for other factors.

[b] Factor deliberately excluded from the model as it correlated with another measure of resistance used in the model.

[c] Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or only historical evidence of resistance.

[d] Reference value against which activity of other subfactors was measured.

[e] Secondary mutations from G140A/C/S, E138A/K/T or L74I.

[f] The failing background regimen activity was assessed for the Day 8 response, but the OBR activity (including the OSS for only new drugs) was assessed for the Week 24 response.

[g] For the day 8 analyses, the day 8 C0 was used; for the week 24 analyses, the C0-avg was used (ie, the mean of the C0s at day 8, week 4, and week 24).

The week 24 median (interquartile range) change from baseline in $CD4^+$ cell count was +61 cells/mm^3 (20–130). Only 7% of the 183 subjects developed new (not recurrent) HIV-associated CDC category B or C conditions, with no single condition predominating. Three subjects progressed to CDC category C, and 1 subject, who had CDC category C at baseline, died approximately 3 months after study withdrawal for virologic failure due to progressive multifocal leukoencephalopathy (PML).

Safety

Median exposure to DTG was 336 days (range, 14–509). The most common drug-related AEs were diarrhea, nausea, and headache (Table 6). Five subjects were withdrawn for safety events: hepatitis (3), rash, pruritus, paresthesia (1), and cholelithiasis (1). One subject experienced a drug-related serious AE of syncope, which resolved without recurrence. Another subject developed a "hypersensitivity"-type reaction characterized by full body rash with fever, nausea, and vomiting, followed by increased alanine aminotransferase (ALT) approximately 4.6 times the upper limit of normal (ULN) and direct bilirubin elevation (approximately 6.4 times ULN) after 15 days of DTG treatment and 7 days of treatment with ETR and DRV/r; event resolved after discontinuation of all 3 medications. Five subjects were considered to have IRIS for the following conditions (none of which resulted in withdrawal): PML, fever of unknown origin, herpes zoster, ophthalmic herpes zoster, and

Table 5. Summary of DTG C0 and PIQ-C0 by Visit

	Plasma DTG C0 (μg/mL)			
Parameter	Day 8	Week 4	Week 24	Average
No. of subjects	148	161	134	180
Geometric mean (%CVb)	2.36 (91)	1.90 (113)	2.15 (93)	2.33 (68)
	PIQ-C0			
No. of subjects	142	155	128	173
Geometric mean (%CVb)	19.4 (202)	16.5 (234)	21.6 (181)	19.4 (175)

Abbreviations: C0, drug concentration immediately prior to dosing; %CVb, between-subject coefficient of variation; DTG, dolutegravir; PIQ-C0, C0 divided by fold change in 50% inhibitory concentration at baseline and protein-adjusted 90% inhibitory concentration for wild-type virus.

cryptogenic origin. Grade 3 and 4 clinical chemistry abnormalities were reported for 20% (n = 36) and 3% (n = 6), respectively, with the grade 4 events encompassing increased ALT (1), aspartate aminotransferase (2), bilirubin (1), creatine kinase (2), alkaline phosphatase (2), and creatinine (2). As noted in other DTG studies, serum creatinine increased from baseline by a mean of 12.33 μmol/L (n = 162) at week 24 but was not associated with evidence of albuminuria (small mean decline of urine albumin/creatine ratio of 4.55 μmol/L). Four subjects experienced treatment-emergent liver stopping criteria, but 3 of these subjects continued or restarted DTG without recurrence of hepatitis. One subject with hepatitis B and C coinfection at baseline continued on DTG after rapid resolution of liver chemistry abnormalities. One subject with hepatitis B reactivation after TDF/FTC discontinuation at day 8 was restarted on DTG along with appropriate hepatitis B therapy without recurrence of hepatitis. One subject receiving DRV/r withdrew from the study; rechallenge with DRV/r resulted in hepatitis recurrence, but treatment with DTG in another study was without recurrence of hepatitis. The fourth subject (with hypersensitivity described above) was withdrawn and not rechallenged with DTG. Grade 3 (n = 2, 1%) or grade 4 (n = 2, 1%) hematologic abnormalities were uncommon: neutropenia (n = 3) and thrombocytopenia (n = 1).

Table 6. Summary of Treatment-Emergent Adverse Events (≥Grade 2)

Parameter	All Events[a] (N = 183) n (%)	Drug-related[b] (N = 183) n (%)
Any adverse event (grade ≥2)	106 (55)	27 (15)
Diarrhea	11 (6)	4 (2)
Headache	8 (4)	3 (2)
Injection site reaction	7 (4)	. . .
Pneumonia	7 (4)	. . .
Bronchitis	6 (3)	. . .
Cough	6 (3)	. . .
Nausea	6 (3)	3 (2)
Pyrexia	5 (3)	. . .
Rash	5 (3)	. . .
Arthralgia	5 (3)	. . .
Insomnia	5 (3)	. . .
Any serious adverse event	31 (17)	2 (1)
Syncope		1 (<1)
Drug eruption, hyperbilirubinemia, and alanine aminotransferase increased		1 (<1)

[a] In >2% subjects.

[b] In ≥2% subjects for any adverse event, but all serious adverse events reported as drug related presented.

Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Results

Plasma DTG C0-avg was similar between those who achieved <50 c/mL at week 24 vs those who did not (2.42 μg/mL [n = 125] and 2.12 μg/mL [n = 55], respectively). Multivariate regression identified plasma DTG C0 as a predictive factor for day 8 but not week 24 response; effect size on day 8 response was small (Table 4). There was no association between DTG C0-avg and the 3 most common AEs (diarrhea, headache, or nausea) or change from baseline in ALT, bilirubin, creatinine, creatinine clearance, and urine albumin/serum creatinine ratio.

DISCUSSION

VIKING-3 was designed to confirm the pilot VIKING study results by demonstrating the short- and long-term antiviral activity of DTG in subjects with INI resistance, in addition to assessing the safety of the 50 mg BID dose. The VIKING-3 week 24 efficacy and safety results formed the basis of the FDA approval of DTG for INI-resistant patients, at a dose of 50 mg BID for patients with documented or clinically suspected INI resistance [4].

The open-label, single-arm study design with a short functional monotherapy phase was adopted for this study in view of the challenges of a controlled design for this patient population [12]. Key issues included the risk of further resistance evolution in a placebo control arm and lack of availability of a single comparator drug appropriate for participants with multiclass resistance. Despite the limitations of a single-arm study, the results demonstrate the benefit of DTG for patients with INI resistance and limited treatment options. Long-term assessment of the independent activity of DTG was further challenged by the way the OBR activity could be measured via a snapshot of resistance data at baseline; indeed, when drugs previously used were excluded from the OSS estimations, the activity of the OBR decreased significantly. The lack of impact of the background

ART on the day 8 or week 24 response and the strong relationship between baseline DTG susceptibility and response, revealed in both univariate and multivariate analyses, strongly support the independent antiviral activity of DTG.

At week 24, 69% of subjects achieved HIV-1 RNA <50 c/mL despite their advanced disease and limited options for OBR. Recognizing the limitations of cross-study comparisons, previous studies of new, within-class antiretrovirals in ART-experienced subjects had week 24 response rates in the range of 25%–62%, although the study populations were generally less treatment-experienced than that of VIKING-3 [16–19]. The DUET populations were most similar to that of VIKING-3 ($CD4^+$ approximately 100 cells/mm^3, 58% CDC category C, 66% with 10–15 prior antiretrovirals). Though patients received 2 new within-class antiretrovirals [ETR and DRV/r; 4% had prior DRV/r experience]) [20], the week 24 response of 59% was not higher than in VIKING-3. Even in the combined BENCHMRK studies where a new class was introduced (median years of prior ART use of 10 years and median 12 prior ARTs), only 60% of patients achieved HIV-1 RNA <50 c/mL at week 24 [21].

Based on multivariate analyses, the strongest predictive factor of response was baseline resistance (DTG FC and the genotypic IN mutation group): subjects in the Q148 + ≥2 group had a lower day 8 response than those in the No Q148 virus group, and their odds of achieving HIV-1 RNA <50 c/mL at week 24 were 96% lower. The number of patients with Q148 + ≥2 associated mutations viruses may decrease over time as management of INI failure evolves with earlier interruption and withdrawal of the failing INI.

The safety profile of DTG 50 mg BID in this INI-experienced population was similar to that observed for DTG 50 mg QD in the less treatment-experienced populations [1–3], despite more advanced HIV disease and the coadministration of multiple medications. DTG was well tolerated with few safety-related discontinuations. The types and frequency of AEs were similar to those described for DTG 50 mg QD [1–3]; changes in serum creatinine were consistent despite the higher dose of DTG, and no subjects were withdrawn for renal toxicity. One subject had a suspected hypersensitivity event potentially attributed to DTG, with accompanying rash and hepatitis, but this event was confounded by DRV/r and ETR use. Other subjects with clinically significant hepatitis had alternative diagnoses (eg, hepatitis B reactivation, liver injury due to OBR). IRIS events did not result in discontinuation of DTG.

Subjects receiving DTG 50 mg BID achieved an average C0 2-fold higher than that reported with the 50 mg QD regimen (1.18 μg/mL), with similar between-subject variability [1]. The lack of association between DTG exposure and antiviral response shows that virologic response is primarily driven by baseline resistance rather than DTG exposure, when considering the range of exposures observed in this study. No association was found between DTG exposure and relevant safety parameters.

We continue to follow the VIKING-3 participants through 48 weeks of therapy and until DTG becomes commercially available in the participating countries. Monitoring of the trial after the week 24 primary analysis has shown persistence of the efficacy across the IN mutation groups and no new safety signals.

In summary, DTG 50 mg BID was efficacious in this highly treatment-experienced population with advanced HIV disease. Multivariate analyses demonstrated the independent activity of DTG as the main driver of response.

Notes

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