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Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study

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Objective: To evaluate the efficacy and safety/tolerability of dolutegravir (DTG, S/GSK1349572), a potent inhibitor of HIV integrase, through the full 96 weeks of the SPRING-1 study.

Design: ING112276 (SPRING-1) was a 96-week, randomized, partially blinded, phase IIb dose-ranging study.

Methods: Treatment-naive adults with HIV received DTG 10, 25, or 50 mg once daily or efavirenz (EFV) 600 mg once daily (control arm) combined with investigator-selected dual nucleos(t)ide reverse transcriptase inhibitor backbone regimen (tenofovir/emtricitabine or abacavir/lamivudine). The primary endpoint of the study was the proportion of participants with plasma HIV-1 RNA less than 50 copies/ml, based on time to loss of virologic response at 16 weeks (conducted for the purpose of phase III dose selection), with a planned analysis at 96 weeks. Safety and tolerability were also assessed.

Results: Of 208 participants randomized to treatment, 205 received study drug. At week 96, the proportion of participants achieving plasma HIV-1 RNA less than 50 copies/ml was 79, 78, and 88% for DTG 10, 25, and 50 mg, respectively, compared with 72% for EFV. The median increase from baseline in $CD4^+$ cells was 338 cells/μl with DTG (all treatment groups combined) compared with 301 cells/μl with EFV ($P = 0.155$). No clinically significant dose-related trends in adverse events were observed, and fewer participants who received DTG withdrew because of adverse events (3%) compared with EFV (10%).

Conclusion: Throughout the 96 weeks of the SPRING-1 study, DTG demonstrated sustained efficacy and favorable safety/tolerability in treatment-naive individuals with HIV-1.

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Introduction

Integrase inhibitors (INIs) are one of the newer classes of therapies to become part of the anti-HIV armamentarium. INIs block integration of the HIV genome into that of the host, an essential process in the viral replication cycle [1]. The first-generation INI raltegravir (RAL; the first INI approved for use; Isentress;

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Merck & Co Inc., Whitehouse Station, New Jersey, USA) and elvitegravir (EVG; approved as a component of Stribild; Gilead Sciences Inc., Forest City, California, USA) have both shown efficacy against HIV in treatment-naive and treatment-experienced individuals [2–8]. However, RAL must be taken twice daily, and EVG requires a pharmacokinetic booster such as ritonavir [1,7] or cobicistat [8]. Furthermore, there is extensive cross-resistance between RAL and EVG [9].

Dolutegravir (DTG) is a newer, potent INI with low nanomolar activity that is suitable for once-daily, unboosted dosing [10,11]. Furthermore, *in vitro*, DTG retains activity against most isolates carrying major integrase resistance mutations to RAL and/or EVG [11]. In clinical trials conducted to date, DTG was generally well tolerated and effective in a broad range of patients, including those with genotypic resistance to RAL [10,12–15].

The ING112276 (SPRING-1) study is a phase IIb, multicenter, partially blinded, dose-ranging study of DTG (10, 25, and 50 mg) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naive individuals. The primary goal of SPRING-1 was to select a DTG dose for phase III development. The study included a 96-week randomized period and an open-label phase for continued provision of DTG, which is ongoing. Initial analysis of the randomized SPRING-1 study showed a rapid antiviral response to DTG (93% of participants who received DTG achieved HIV-1 RNA less than 50 copies/ml by 16 weeks) that was generally sustained for up to 48 weeks (90, 88, and 91% in the DTG 50, 25, and 10 mg groups, respectively) [13]. All three doses of DTG were generally well tolerated through 48 weeks, and the 50 mg dose was selected for phase III evaluation. In this study, we report the efficacy and tolerability of DTG through the full 96 weeks of the SPRING-1 randomized phase. The week 96 data are being analyzed and presented as a preplanned analysis included in the initial study design, prior to withdrawal of participants on the efavirenz (EFV) arm.

Methods

Study design

The SPRING-1 phase IIb study design (ClinicalTrials.gov identifier: NCT00951015) has previously been described [13]. Briefly, this was a 96-week, randomized, multicenter, parallel-group, dose-ranging study in treatment-naive, HIV-1-infected individuals that included a partially blinded randomized phase from 9 July 2009 to 12 September 2011, with an ongoing open-label phase. Participants were randomized (1 : 1 : 1 : 1) to treatment with DTG 10, 25, or 50 mg once daily (q.d.) or EFV 600 mg q.d. that was blinded to dose of DTG but not study drug. Prior to or at the time of randomization, investigators selected an open-label dual NRTI backbone regimen of a fixed-dose combination tablet of either abacavir/lamivudine (ABC/3TC; Epzicom; Kivexa; ViiV Healthcare, Research Triangle Park, North Carolina, USA) or tenofovir/emtricitabine (TDF/FTC; Truvada; Gilead Sciences Inc.), which was administered to participants q.d. Participants receiving ABC as part of the backbone regimen were screened and negative for the *HLA-B*5701* allele. At 96 weeks, participants randomized to the DTG arms were switched to the selected 50 mg q.d. dose, and participants randomized to EFV were discontinued from further study follow-up.

Participants

Inclusion and exclusion criteria have been described elsewhere [13]. Briefly, eligible participants were HIV-1-infected, treatment-naive adults (≥18 years of age) with a plasma HIV-1 viral load of at least 1000 copies/ml and a $CD4^+$ cell count of at least 200 cells/μl at screening. Eligible participants also had no evidence of viral resistance to any antiretroviral drug (not just study drugs) indicative of primary transmitted resistance in screening genotype or phenotype or historic resistance test result.

All participants provided written informed consent before screening procedures. This study was conducted in accordance with good clinical practice procedures, all applicable participant privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008. The study was approved by national regulatory authorities and ethics review committees for each site.

Assessments and statistical analysis

Clinical assessments and blood and/or urine were collected at baseline and at regular intervals thereafter. Plasma HIV-1 RNA was quantified using the Abbott RealTime HIV-1 Assay (lower limit of detection, 40 copies/ml; Abbott Laboratories, Abbott Park, Illinois, USA). Procedures for laboratory and statistical analyses have been described [13].

The primary endpoint of the study was the proportion of participants with plasma HIV-1 RNA less than 50 copies/ml at 16 weeks as determined using the US Food and Drug Administration (FDA) time to loss of virologic response (TLOVR) algorithm and has previously been reported [13]. This analysis was repeated at 96 weeks. Efficacy was analyzed in the intent-to-treat exposed population (i.e. all participants who received ≥1 dose of study drug). Secondary endpoints included the change from baseline in $CD4^+$ cell counts and the incidence of treatment-emergent genotypic and phenotypic resistance to DTG and other antiretroviral therapies used in the study [13]. Protocol-defined virologic failure (PDVF) was defined as a decrease less than

1.0 $\log_{10}$ copies/ml by week 4 or confirmed HIV-1 load of at least 400 copies/ml (on or after week 24). Once a participant was confirmed as having PDVF, samples were sent for genotypic and phenotypic resistance testing.

Safety assessments included monitoring and recording of all adverse events, serious adverse events (SAEs), and laboratory parameters and were analyzed in the safety population (i.e. all participants who received ≥1 dose of study drug) [13].

Results

Participant disposition and baseline characteristics

Of the 208 participants randomized to treatment, 205 received at least one dose of study drug and were included in the intent-to-treat exposed and safety populations. The three participants who were randomized but not treated all withdrew their consent after randomization, but prior to receiving any doses of study drug. Fifty-three participants received DTG 10 mg, 51 received DTG 25 mg, 51 received DTG 50 mg, and 50 received EFV. A summary of demographic characteristics has been previously presented [13]. Most participants were white (80%) and men (86%), and the mean age was 37 years. As previously described, baseline characteristics were relatively well distributed across the study groups, with the exception of HIV-1 RNA, which was higher in the DTG 50 mg group [13]. Through the full 96 weeks of the randomized phase of the study, a total of 26 participants (13%) withdrew from the study (see Table, Supplemental Digital Content 1, http://links.lww.com/QAD/A338, which shows the participant accountability at 96 weeks).

Efficacy

A sustained antiviral response was observed across all DTG doses, with 82% of all participants who received DTG achieving plasma HIV-1 RNA less than 50 copies/ml through week 96 (Fig. 1). Individually, at week 96, response rates for each DTG dose remained higher at 88, 78, and 79% for 50, 25, and 10 mg, respectively, compared with EFV (72%; Table 1). There were no dose trends or differences across the DTG doses through week 84. However, after week 84, there were more nonresponders among participants receiving DTG 10 or 25 mg. In a sensitivity analysis using missing or discontinuation = failure (MD = F), the response rates were typically higher than using TLOVR (87, 80, and 86% for DTG 50, 25, and 10 mg, respectively), which mainly reflects the participants who were resuppressed after prior rebound. Samples from participants meeting PDVF criteria were sent for resistance testing. No participants on DTG have had emergence of a virus with an INI resistance mutation. One participant receiving DTG 10 mg developed virus with the mutation M184M/V in reverse transcriptase. Participants who received EFV were primarily nonresponders because of adverse events, stopping criteria, or

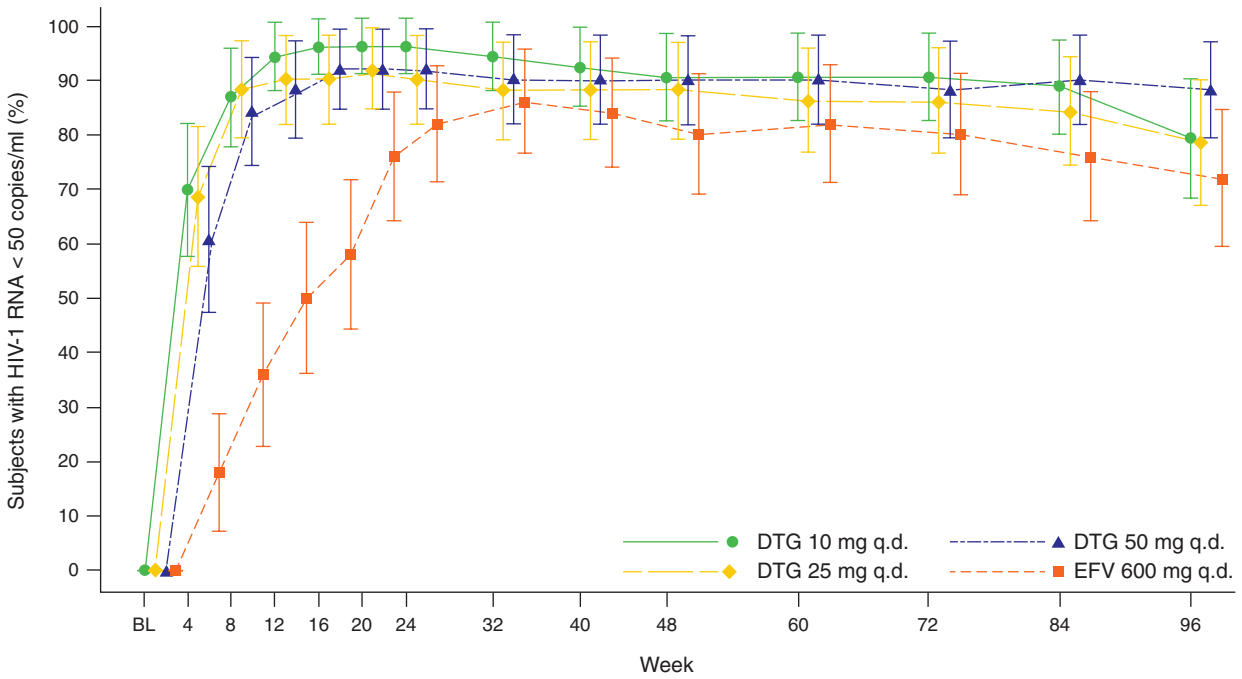

Fig. 1. Proportion of participants with plasma HIV-1 RNA less than 50 copies/ml as determined using the time to loss of virologic response algorithm. Error bars indicate 95% confidence intervals, which were derived using the normal approximation. BL, baseline; DTG, dolutegravir; EFV, efavirenz; q.d., once daily.

Table 1. Outcomes for HIV-1 RNA less than 50 copies/ml at 96 weeks (time to loss of virologic response analysis).

Outcome, *n* (%)	DTG 10 mg (*n* = 53)	DTG 25 mg (*n* = 51)	DTG 50 mg (*n* = 51)	EFV 600 mg (*n* = 50)
Responder	42 (79)	40 (78)	45 (88)	36 (72)
Virologic nonresponders[a]				
Discontinued for insufficient viral load response	1 (2)	0	0	0
Rebound	6 (11)	4 (8)	2 (4)	4 (8)
Other nonresponders				
Adverse event	0	1 (2)	1 (2)	5 (10)
Protocol deviation or nonpermitted change in ART	1 (2)	2 (4)	1 (2)	0
Lost to follow-up or participant discontinuation	2 (4)	3 (6)	2 (4)	2 (4)
Reached protocol-defined stopping criteria	0	0	0	1 (2)[b]
Death	1 (2)	0	0	0
Not discontinued, but no data at week 96 and beyond	0	1 (2)	0	2 (4)

ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz.
[a]Virologic nonresponse defined as any of discontinuation due to insufficient viral load response, never suppressed less than 50 copies/ml (no cases by week 96), or rebound.
[b]Met stopping criteria for liver toxicity.

virologic rebounds (50 to <400 copies/ml), with no treatment-emergent mutations. Importantly, there were no new PDVFs (confirmed viral load ≥400 copies/ml) between weeks 48 and 96 on any treatment arm.

Median $CD4^+$ cell counts increased from baseline to week 96 in all treatment groups and were numerically greater with DTG than EFV (Fig. 2). The median increase from baseline in $CD4^+$ cells was 338 cells/μl with DTG (all treatment groups combined) compared with 301 cells/μl with EFV ($P = 0.155$).

Through week 96 of the study, six participants reported new HIV-associated conditions: four participants had Herpes zoster [DTG 10 mg ($n = 2$), DTG 50 mg ($n = 1$), and EFV ($n = 1$)], one participant (DTG 50 mg) developed Burkitt's lymphoma, and one participant (DTG 10 mg) died (in a traffic accident). Two cases of Herpes zoster and the development of Burkitt's lymphoma were previously reported in the 48-week analysis [13].

Safety

The adverse event profile overall was similar to what was seen at week 48. At week 96, adverse events were reported by 92% of participants each who received DTG (all groups combined) and who received EFV (Table 2). There were no clinically significant dose-related trends in

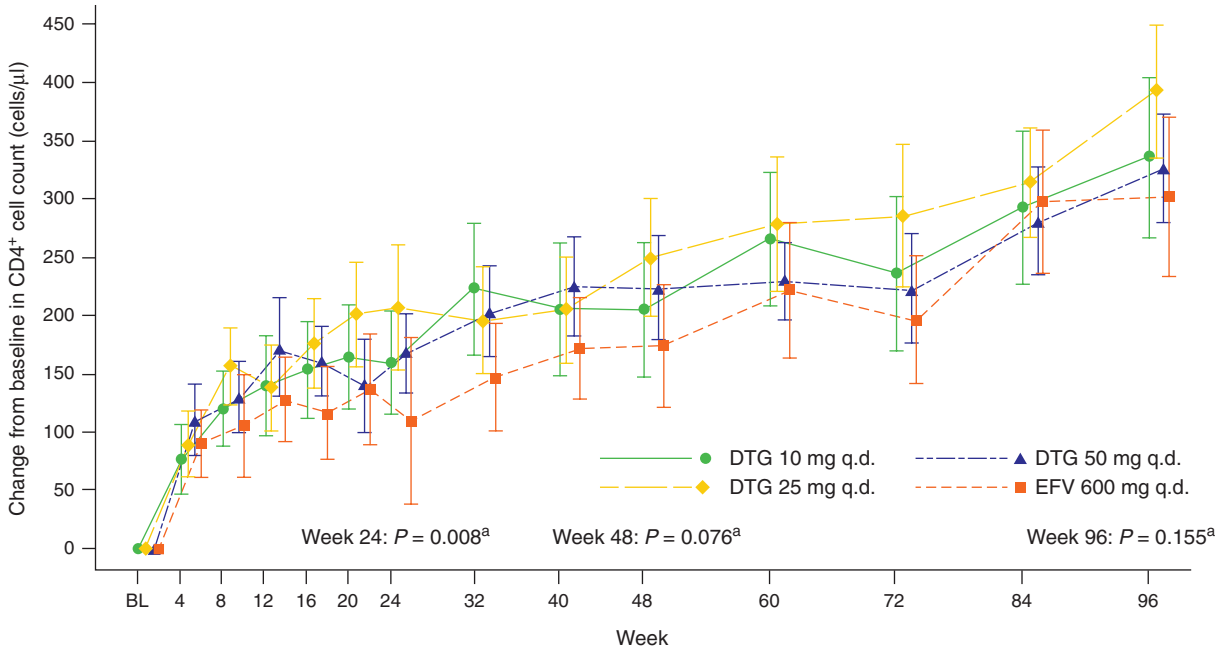

Fig. 2. Median (95% confidence interval) change from baseline in $CD4^+$ cell counts. BL, baseline; DTG, dolutegravir; EFV, efavirenz; q.d., once daily. [a]*P* value determined for all DTG doses vs. EFV using the Wilcoxon two-sample test.

Table 2. Adverse events at 96 weeks.

Adverse event, *n* (%)	DTG				EFV
	10 mg (*n* = 53)	25 mg (*n* = 51)	50 mg (*n* = 51)	Subtotal (*n* = 155)	600 mg (*n* = 50)
Any AE	50 (94)	46 (90)	46 (90)	142 (92)	46 (92)
Any serious AE	5 (9)	5 (10)	7 (14)	17 (11)	7 (14)
Any drug-related AE (all grades)[a]	26 (49)	19 (37)	28 (55)	73 (47)	31 (62)
Nausea	7 (13)	6 (12)	6 (12)	19 (12)	3 (6)
Diarrhea	4 (8)	4 (8)	5 (10)	13 (8)	3 (6)
Dizziness	2 (4)	0	3 (6)	5 (3)	9 (18)
Headache	2 (4)	4 (8)	5 (10)	11 (7)	2 (4)
Fatigue	1 (2)	3 (6)	1 (2)	5 (2)	4 (8)
Insomnia	0	0	3 (6)	3 (2)	5 (10)
Rash	2 (4)	0	0	2 (1)	5 (10)
Any AE leading to withdrawal and permanent discontinuation of study drug	1 (2)	1 (2)[b]	2 (4)[c]	4 (3)	5 (10)[b]

AE, adverse event; DTG, dolutegravir; EFV, efavirenz.
[a]Any term with at least 3% incidence overall.
[b]Drug-related.
[c]One event considered drug-related (i.e. lipoatrophy).

adverse events in participants who received DTG. Drug-related adverse events were reported for a smaller proportion of participants who received DTG compared with EFV (47 and 62%, respectively; Table 2). Nausea and headache occurred more frequently with DTG, whereas dizziness, rash, insomnia, and fatigue occurred more frequently with EFV. Between weeks 48 and 96, two participants receiving DTG (motor vehicle accident and lipoatrophy) and one participant receiving EFV (fatigue) withdrew due to adverse events. A total of 24 participants (12%) reported SAEs through week 96 (11 and 14% with DTG and EFV, respectively; Table 2). SAEs leading to permanent discontinuation of study drug included Burkitt's lymphoma (DTG 50 mg), suicide attempt (EFV), and multiple injuries/road traffic accident (DTG 10 mg). Two SAEs were considered possibly related to study drug: myocardial infarction in a individual with a smoking history and hyperlipidemia who received DTG 50 mg along with TDF/FTC, and a suicide attempt in a participant who received EFV along with ABC/3TC, which was previously described [13].

A summary of treatment-emergent clinical chemistry toxicities for selected laboratory parameters is presented in Table, Supplemental Digital Content 2, http://links.lww.com/QAD/A338. Two participants had grade 3 or 4 elevations in alanine aminotransferase (ALT; without concomitant bilirubin elevations) and were subsequently diagnosed with acute hepatitis C infection: one participant who received DTG 25 mg had a grade 3 elevation in ALT and continued the study, and one participant who received EFV had a grade 4 elevation in ALT and was discontinued from the study at week 84 for meeting the liver toxicity stopping criteria. A similar proportion of participants who received DTG and EFV had grade 3 or 4 lipase elevations (5 vs. 4%, respectively), all of which were asymptomatic and spontaneously resolved. Grade 1 to 2 increases in bilirubin were noted with DTG but did not correlate with changes in other liver chemistries (e.g. ALT). Grade 3 and 4 elevations in creatine kinase were only reported in participants who received DTG and were without a dose-related trend. Most elevations in creatine kinase were asymptomatic and related to preceding exercise, resolved spontaneously, and did not lead to discontinuation of study drug.

As noted in the 48-week analysis, a small mean increase in serum creatinine was observed at week 1 with DTG that remained stable through week 24 and then declined by week 48 (see Table, Supplemental Digital Content 3, http://links.lww.com/QAD/A338, which shows a summary of serum creatinine and urine protein) [13]. At week 96, there was a relative increase in mean serum creatinine from week 48 in both the DTG and EFV groups. However, the mean change from baseline in creatinine at week 96 was similar to that observed at week 24 for all DTG doses and for EFV. As previously reported at week 48 [13], the mean change from baseline in creatinine did not appear to be driven by NRTI backbone therapy. Quantitative assessments of urine albumin:creatinine ratio indicated that there was no evidence of higher levels of urinary albumin in patients who received DTG compared with EFV at week 96 (see Table, Supplemental Digital Content 3, http://links.lww.com/QAD/A338).

At 96 weeks, mean changes in cholesterol parameters were lower with DTG than EFV, but mean changes in triglycerides were variable across the DTG treatment groups and the EFV group. There were no clinically significant differences in maximum toxicity changes in lipid parameters noted between treatment with DTG and EFV.

No clinically significant changes in corrected QT or vital signs were noted for either DTG or EFV.

Discussion

SPRING-1 is the first long-term (96-week) study of DTG in treatment-naive individuals with HIV-1. The high early response rate for DTG (≥90% had HIV-1 RNA <50 copies/ml [13]) was sustained for the selected 50 mg q.d. dose through 96 weeks. The proportion of participants with HIV-1 RNA less than 50 copies/ml at 96 weeks was 88% with DTG 50 mg, the dose selected for phase III evaluation, and 79 and 78% for DTG 10 and 25 mg, respectively (using TLOVR). The DTG response rates compared favorably with that observed for EFV (72%), which was consistent with previously reported EFV response rates [5]. When using MD = F, the response rates for the lower doses are typically higher than the TLOVR response rates (87, 80, and 86% for DTG 50, 25, and 10 mg, respectively) and still better than the corresponding virologic response seen in the EFV arm (78%). The MD = F analysis is a close approximation to the FDA Snapshot analysis, which was used in the DTG phase III studies [14,15]. The response rates for DTG in this participant population are similar to those reported for RAL and EVG at the marketed dose in studies of similar design [8,16]. Thus, the response rates for all doses of DTG assessed in this study were similar to those observed with other potent antiviral therapies in a treatment-naive population.

Data from recent DTG phase III studies SPRING-2 and SINGLE, both conducted in treatment-naive individuals and utilizing the selected DTG 50 mg q.d. dose, also compare favorably with data reported for other INIs and support the selected DTG dose from SPRING-1. The response rate for DTG in the SPRING-2 study was noninferior to RAL at 48 weeks (88% for DTG vs. 85% for RAL) using the FDA Snapshot analysis [14]. The response rate for a regimen of DTG along with ABC/3TC in the SINGLE study was superior to TDF/FTC/EFV (Atripla; Bristol-Myers Squibb, Princeton, New Jersey, USA, and Gilead Sciences Inc.) at 48 weeks (88 vs. 81%, respectively; $P = 0.003$) [15].

There were no confirmed PDVFs (HIV-1 RNA ≥400 copies/ml) in participants who received the phase III-selected dose (DTG 50 mg). Furthermore, the rates of confirmed PDVF in participants who received DTG 10 mg, DTG 25 mg, or EFV were low [13], and there were no new cases after week 48. No INI resistance was observed in participants receiving any of the DTG doses through week 96, and in the 25 and 50 mg DTG dose arms, no participants developed NRTI resistance. In contrast, half of participants with PDVF in a similar study of RAL developed INI resistance by week 96 [16], and over half of the participants meeting criteria for resistance testing in a similar and recent study of EVG developed INI resistance by week 96 [8].

The safety profile of DTG at 96 weeks was favorable, with no dose-response relationship with adverse events and fewer discontinuations due to adverse events and fewer drug-related adverse events than EFV. Tolerability was also generally better with DTG in comparison with EFV, as higher rates of drug-related dizziness, rash, insomnia, and fatigue were noted with EFV, events known to be associated with the drug [17].

Our dose-selection strategy for DTG was to select the maximum tolerated dose to compensate for potential reductions in exposure caused by drug interactions without the need for dose adjustment, specifically in the treatment-experienced, INI-naive patient population. Additionally, higher doses could provide a pharmacological barrier to the development of antiviral resistance. Therefore, the DTG 50 mg q.d. dose was selected for phase III studies with INI-naive patient populations. At week 96, the safety profile was comparable across DTG doses, and the efficacy at the 50 mg q.d. selected dose continued to be robust. Additionally, no participants at this dose developed PDVF or evidence of resistance to either INIs or the NRTI backbone. The data at week 96 and the data from the DTG phase III studies, thus, continue to support the phase III dose selection of DTG 50 mg q.d. for the INI-naive population. As all participants randomized to DTG were given the opportunity to switch to the 50 mg q.d. dose at week 96, longer-term safety evaluation is ongoing in this study.

Small, nonprogressive increases in serum creatinine observed with DTG through 96 weeks were similar to those described previously at 48 weeks [13] and have been observed in other studies [12,18]. Based on the week 96 data from SPRING-1, the small, nonprogressive increases (~12% or 10.1 μmol/l for 50 mg) in creatinine observed with DTG represent a resetting of the baseline creatinine level due to nonpathologic blockade of the organic cation transporter 2 responsible for tubular creatinine secretion [18] rather than nephrotoxicity, as evidenced by the lack of withdrawals due to renal adverse events and lack of significant increases (e.g. grade 3 or 4) in creatinine. This has been confirmed in two large phase III studies of DTG in treatment-naive individuals [14,15].

Although changes in urine protein (dipstick) results were observed, without time-dependency or dose-dependency to these results at week 48 [13], quantitative assessments (spot urine albumin:creatinine ratio) were similar across DTG doses and between DTG and EFV at week 48 and week 96. Further evaluation is being conducted in the adult phase III and pediatric phase II studies.

The study did have some limitations. First, the study population was not fully representative of the global HIV population. Participants with advanced immunosuppression (screen $CD4^+$ cell count <200 cells/μl) and chronic active hepatitis B (as evidenced by hepatitis B surface antigen) were excluded. The study was conducted predominately in high-income countries (i.e. United

States and western Europe) and had requirements for frequent visits, which resulted in a relatively low representation of women and nonwhite participants. Second, as this was a phase IIb study, the sample size was not large, and the study was not powered for direct statistical testing vs. EFV nor within subgroups. Third, EFV served as a control arm, and as such, participants and investigators were not blinded to treatment assignment of DTG or EFV. As the purpose of the study was dose-finding for DTG, only the dose of DTG was blinded to allow for comparisons. The ongoing phase III studies involve a greater number of participants in general, and in particular, a greater diversity in terms of race and sex. The sample sizes in the phase III studies also make subgroup explorations more reasonable.

Conclusion

In conclusion, once-daily DTG with two NRTIs was efficacious through 96 weeks at all doses studied, with 88% of participants who received the phase III-selected dose of 50 mg achieving plasma HIV-1 RNA less than 50 copies/ml. No INI mutations had emerged by 96 weeks with any dose of DTG, and no participants receiving DTG 50 mg q.d. developed PDVF or resistance mutations to INIs or NRTIs. DTG had a favorable safety profile to 96 weeks. Overall, the durable efficacy and tolerability of DTG 50 mg q.d. in combination with two NRTIs at 96 weeks support the selection of this dose for continued phase III development in INI-naive individuals.

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Conflicts of interest

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