

Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults

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Objective: To evaluate the antiviral activity, safety, pharmacokinetics, and pharmacokinetics/pharmacodynamics of dolutegravir (DTG), a next-generation HIV integrase inhibitor (INI), as short-term monotherapy.

Design: A phase IIa, randomized, double-blind, dose-ranging study.

Methods: In this study, INI-naive, HIV-1-infected adults currently off antiretroviral therapy were randomized to receive DTG (2, 10, or 50 mg) or placebo once daily for 10 days in an eight active and two placebo randomization scheme per DTG dose. Placebo patients were pooled for the purpose of analysis.

Results: Thirty-five patients ($n = 9$ for DTG 2 and 10 mg, $n = 10$ for DTG 50 mg, and $n = 7$ for placebo) were enrolled. Baseline characteristics were similar across dose groups. Significant reductions in plasma HIV-1 RNA from baseline to day 11 were observed for all DTG dose groups compared with placebo ($P < 0.001$), with a mean decrease of 1.51–2.46 \log_{10} copies/ml. In addition, a well characterized dose-response relationship was observed for viral load decrease. Most patients (seven of 10, 70%) receiving DTG 50 mg achieved plasma HIV-1 RNA less than 50 copies/ml. The pharmacokinetic variability was low (coefficient of variation, range 25–50%). Plasma HIV-1 RNA reduction was best predicted by C_{τ} using an E_{max} model. The most common adverse events were diarrhea, fatigue, and headache; the majority of adverse events were mild or moderate in severity.

Conclusion: Dolutegravir demonstrated potent antiviral activity, good short-term tolerability, low pharmacokinetic variability, and a predictable pharmacokinetics/pharmacodynamics relationship, which support once-daily dosing without a pharmacokinetic booster in integrase-naive patients in future studies.

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Introduction

With the application of highly active antiretroviral therapy (ART) using antiretrovirals with improved potency, tolerability, and resistance profiles, people with HIV are living longer and receiving longer-term care [1,2]. However, there is still a need for additional treatment options that enhance adherence and have better tolerability, higher barriers to resistance, distinct resistance profiles, and fewer drug–drug interactions. These principles have been guiding the development of new agents that are not only focused on traditional targets but also on novel therapeutic targets. The newest class of drugs in HIV treatment is the integrase inhibitor (INI) class.

At the time of this study, the only INI approved by Food and Drug Administration, raltegravir, had been shown to effectively reduce viral load when given twice daily in combination therapy in both ART-naïve and ART-experienced patients with HIV-1 [3,4]. Treatment-emergent resistance, however, has emerged in patients who fail first-generation, INI-containing regimens [5]. Additionally, cross-resistance exists between first-generation INIs; patients experiencing virologic failure with elvitegravir-resistant virus did not adequately respond to raltegravir treatment [6]. To meet the evolving needs of people with HIV, the next generation of INIs should have the following characteristics: improved convenience (once-daily dosing), enhanced potency with a higher genetic barrier to resistance, and a low risk of cross-resistance [1]. Dolutegravir (DTG), discovered by a Shionogi and GlaxoSmithKline research collaboration, is a novel HIV-1 integrase strand transfer inhibitor selected for its activity against INI resistance and its potential for higher genetic barrier to resistance *in vitro*, in addition to its favorable pharmacokinetic properties [7,8]. Early clinical data in healthy individuals demonstrated low pharmacokinetic variability and concentration–time profiles, supporting a once-daily, low-dose regimen without a pharmacokinetic booster [9]. The half-life of DTG was approximately 15 h and the trough concentration for the 50-mg suspension dose was approximately 25-fold above the protein-adjusted 90% inhibitory concentration (IC₉₀) for HIV-1. The objective of this study was to evaluate the antiretroviral activity, safety, pharmacokinetic, and pharmacokinetic/pharmacodynamics of a range of DTG doses (2–50 mg) in short-term monotherapy with DTG in approximately 30 HIV-1-infected patients.

Methods

Patients

ART-naïve and ART-experienced (INI-naïve) HIV-1-infected adults (including nonpregnant women of

nonchildbearing potential), at least 18 and less than or equal to 65 years of age, with a CD4⁺ cell count of 100 cells/ μ l or more, and plasma HIV-1 RNA 5000 copies/ml or more were eligible for enrollment. Patients were excluded if they had received any ART within the 12 weeks before the first study dose, had previously received an INI, or had recently received another investigational product. Patients were not enrolled if they had an active Centers for Disease Control and Prevention Category C disease (except cutaneous Kaposi's sarcoma), a preexisting condition potentially interfering with the absorption, metabolism, or excretion of the study drug, or were anticipated to require a concomitant medication that could potentially interfere with the absorption or metabolism of DTG. Due to the early nature of this study, to better ensure safety, patients with inadequate renal function at screening (serum creatinine >1.5 mg/dl or creatinine clearance \leq 50 ml/min) or with evidence of hepatitis (liver transaminases at least three times the upper limit of normal) were also excluded.

This study was conducted in accordance with good clinical practice procedures, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Copernicus Group Institutional Review Board. All patients provided written informed consent before the entry in the study.

Study design

This was a phase IIa, multicenter, randomized, parallel, double-blind, placebo-controlled, dose-ranging study of DTG monotherapy. Patients were randomized to receive one of three doses of DTG (2, 10, or 50 mg) or placebo every 24 h for 10 days in an eight active and two placebo randomization scheme per dose. Patients were followed for 11 days (to day 21) after the end of treatment. Three cohorts of approximately 10 patients (planned $N \sim 30$) each were planned: eight to receive DTG and two to receive placebo. DTG or placebo was administered in tablet form after a 10-h fast.

Efficacy assessments

The primary efficacy endpoint was the change from baseline in plasma HIV-1 RNA on day 11 based on an analysis of the intent-to-treat-exposed population (patients receiving at least one dose of study medication and with at least one postbaseline HIV-1 RNA measurement). Two HIV-1 RNA samples were collected on days 1, 10, and 11 and one HIV-1 RNA sample was collected on days 2 through 4, 7 through 9, 14, and 21. Plasma HIV-1 RNA was determined with the COBAS Amplicor HIV-1 Monitor Test version 1.5, ultrasensitive preparation (Roche Diagnostics, Branchburg, New Jersey, USA) on days 7 through 11 and on day 14 [lower limit of detection (LLOD) of 50 copies/ml]; retesting with the COBAS Test, standard preparation

was conducted if values were above the upper limit of detection. On days 1 through 4 and at follow-up, plasma HIV-1 RNA loads were measured with the COBAS Test, standard preparation (LLOD of 400 copies/ml); retesting with the ultrasensitive preparation was performed if values fell below the LLOD. Whole venous blood samples were obtained on days 1 and 11 to assess CD4⁺ cell counts and to analyze viral genotype and phenotype.

Whole venous blood samples were obtained from each patient to provide plasma for resistance analyses carried out by Monogram Biosciences using their GeneSeq and PhenoSense assays for INIs (Monogram Biosciences Inc, South San Francisco, California, USA) [10].

Safety assessments

Safety parameters, including adverse events, concomitant medications, laboratory parameters (chemistry, hematology, and urinalysis), electrocardiograms (ECGs), and vital signs, were evaluated intermittently throughout the study. Specifically, safety evaluations were completed as follows: adverse events and concomitant medications on days 1–4, 7–11, 14, and 21; laboratory parameters on days 1, 3, 7, 11, and 21; and ECGs and vital on days 1, 4, 7, 10, and 21. The severity of adverse events and laboratory abnormalities was assessed using grading table from the Division of Acquired Immunodeficiency Syndrome, National Institute of Allergy and Infectious Diseases [11].

Pharmacokinetic assessments

Serial blood pharmacokinetic samples were collected on days 1 and 10; one predose blood pharmacokinetic

sample was obtained on days 3, 4, and 7 through 9. Plasma extracts were analyzed using a validated, liquid chromatography–mass spectrometry method (LC–MS) method to determine plasma concentrations of DTG (LLQ 5 ng/ml), as previously described [6]. Pharmacokinetic parameters [including maximum observed plasma concentration (C_{\max}), time of occurrence of C_{\max} (t_{\max}), area under the plasma concentration–time curve during one dosing interval (AUC_{0– τ}), terminal elimination phase half-life ($t_{1/2}$), and concentration at the end of the dosing interval (C_{τ})] were estimated based on the observed concentration–time data by the noncompartmental pharmacokinetic approach using WinNonlin version 5.2 (Pharsight Corporation, Mountain View, California, USA).

Statistical analyses

The sample size for this study was based primarily on feasibility and prior similar trial experience to provide adequate precision for the estimations. Placebo patients were pooled across doses for final analyses. Baseline characteristics (HIV-1 RNA and CD4⁺ cell count) and antiviral activity by treatment were summarized using descriptive statistics. The mean value of two samples of plasma HIV-1 RNA obtained on days 1, 10, and 11 were calculated and used as the value for each day to determine the change from baseline (day 1). Plasma HIV-1 RNA change from day 1 to 11 or maximum change (nadir) was summarized by treatment and compared between each active treatment and placebo group using analysis of covariance. For computations, HIV-1 RNA values of less than 50 copies/ml were assigned values of 49 copies. No adjustments for multiple comparisons were made. The proportion of

Table 1. Demographics and baseline characteristics.

Characteristic	Dolutegravir once-daily dose			
	2 mg (n = 9)	10 mg (n = 9)	50 mg (n = 10)	Placebo (n = 7)
Male [N (%)]	9 (100)	9 (100)	10 (100)	7 (100)
Race [N (%)]				
African–American/African heritage	2 (22)	0	3 (30)	2 (29)
Caucasian/European heritage	7 (78)	9 (100)	7 (70)	5 (71)
Mean age [years (range)]	41 (20–55)	40 (32–45)	34 (22–53)	40 (21–54)
CDC classification				
Asymptomatic, lymphadenopathy, or acute HIV	8 (89)	8 (89)	9 (90)	6 (86)
Symptomatic, not AIDS	1 (11)	0	1 (10)	1 (14)
AIDS	0	1 (11)	0	0
Plasma HIV-1 RNA [\log_{10} copies/ml, mean \pm SD (min, max)]	4.40 \pm 0.27 (4.03, 4.85)	4.58 \pm 0.39 (4.25, 5.54)	4.47 \pm 0.42 (3.85, 5.17)	4.25 \pm 0.27 (4.03, 4.74)
Mean CD4 ⁺ cell count [cells/ μ l (min, max)]	435 (175, 797)	398 (171, 509)	502 (232, 577)	427 (123, 1222)
Prior antiretroviral therapy [N (%)]				
Any NRTI	4 (44)	2 (22)	3 (30)	1 (14)
Any NNRTI	4 (44)	2 (22)	3 (30)	1 (14)
Any protease inhibitor	2 (22)	0	2 (20)	1 (14)
	1 (11)	1 (11)	3 (30)	0

CDC, Centers for Disease Control and Prevention; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; SD, standard deviation.

Table 2. Change from baseline in plasma HIV-1 RNA levels on day 11 and proportion of patients with less than 400 and less than 50 copies/ml of plasma HIV-1 at nadir.

	Dolutegravir once-daily dose			
	2 mg (n=9)	10 mg (n=9)	50 mg (n=10)	Placebo (n=7)
Change from baseline on day 11				
Mean plasma HIV-1 RNA levels [log ₁₀ copies/ml (SD)]	-1.51 (0.58)	-2.03 (0.49)	-2.46 (0.35)	0.05 (0.26)
Adjusted mean difference ^a [log ₁₀ copies/ml (95% CI)]	-1.54 (-2.00 to -1.07) ^b	-2.04 (-2.52 to -1.55) ^b	-2.48 (-2.94 to -2.02) ^b	NA
Patients with plasma HIV-1 copies at nadir [N (%)]				
<400 copies/ml	5 (56)	5 (56)	9 (90)	0
<50 copies/ml	1 (11)	0	7 (70)	0

CI, confidence interval; NA, not applicable; SD, standard deviation.

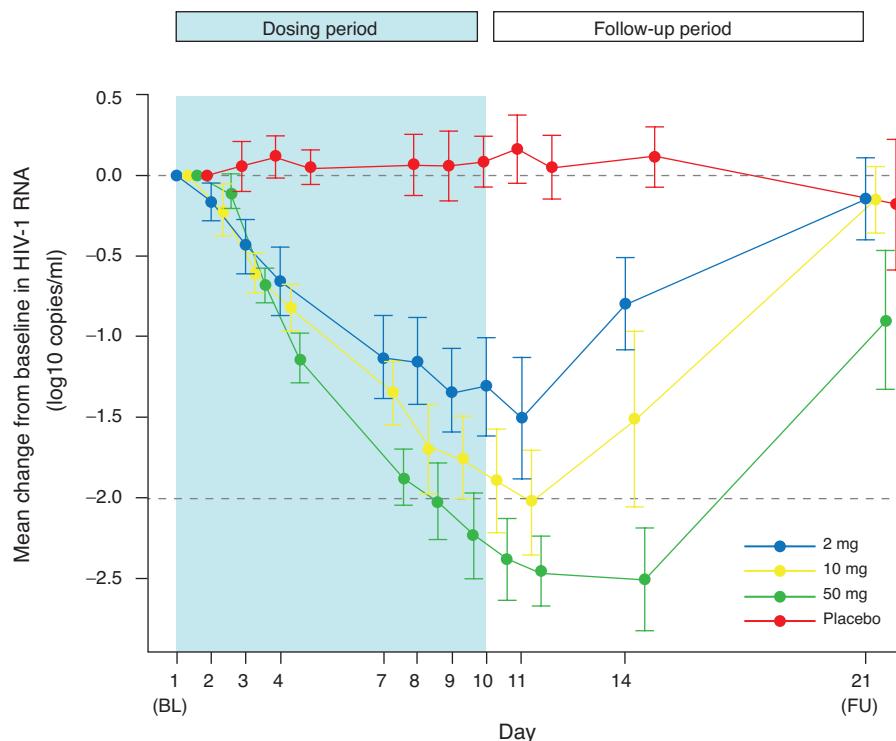
^aActive versus placebo.^bP<0.001.

patients achieving HIV-1 RNA levels less than 400 and less than 50 copies/ml was also summarized. Descriptive statistics, including geometric mean and 95% confidence intervals, were calculated for all pharmacokinetic parameters and summarized by treatment. Dose proportionality of DTG pharmacokinetic parameters was assessed using the power model: $y = \alpha \text{dose}^\beta$. The relationships between various pharmacokinetic parameters ($\text{AUC}_{0-\tau}$, C_{\max} , and C_τ) and reduction in viral load were explored using linear and E_{\max} models with SAS PROC NLMIXED (SAS version 9.1; SAS Institute Inc., Cary, North Carolina, USA). Model selection was based on Akaike Information Criterion [12].

Results

Patients

The planned sample size was 30 patients. Due to rapid screening and enrollment, a total of 35 patients (28 in the DTG treatment arms and seven in the placebo group) were randomized to dose groups and completed all study visits between 25 June 2008 and 26 August 2008. Demographics and baseline characteristics were similar among the four dose groups (Table 1). Approximately one-third (10/35, 29%) of all patients had received ART before study entry: a nucleoside or nucleotide reverse transcriptase inhibitor for 10 of

**Fig. 1.** Mean change from baseline in HIV-1 RNA. BL, baseline; FU, follow-up.

35 (29%) and a nonnucleoside reverse transcriptase or protease inhibitor for five (14%). For patients who had received antiretroviral treatment in the past, adequate treatment options to construct HIV therapy with at least three active antiretrovirals for future treatment were verified prior to enrollment, based on review and agreement by the investigator and the GlaxoSmithKline medical monitor.

Efficacy

Patients in all DTG dose groups demonstrated a statistically significant reduction in plasma HIV-1 RNA from baseline to day 11 compared with placebo ($P < 0.001$; Table 2). In addition, a well characterized dose-response relationship was observed (Fig. 1). In patients receiving DTG 50 mg once daily, antiviral response was sustained between day 11 and 14 despite dosing discontinuation on day 10 (Fig. 1). Furthermore, a higher proportion of patients who received DTG 50 mg had less than 400 or less than 50 copies/ml of plasma HIV-1 RNA at nadir compared with those who received DTG 2 or 10 mg (Table 2). Patients receiving DTG 50 mg had the most rapid HIV-1 RNA decline (Fig. 1). Numeric increases in CD4⁺ cell counts were observed for patients in all DTG dose groups on day 11 (median change, +15 to +106 cells/ μ l), but CD4⁺ cell counts tended to decrease in patients receiving placebo (median change -28.5). No patients experienced a new or recurrent HIV-associated condition or disease progression during the study.

Pharmacokinetics

Although all 28 patients in the DTG dose groups provided blood samples for pharmacokinetic analysis, two patients in the 10-mg dose group were not included in the pharmacokinetic summary population because of protocol deviations in dosing (one patient received 20 mg of DTG on day 1 and one patient missed a 10-mg dose on day 7). All patients receiving DTG had detectable concentrations on day 1 (after dosing commenced) and day 10. DTG was readily absorbed, with the maximum concentration achieved at a median of approximately 1.5–2.5 h after dosing and a mean $t_{1/2}$ of 11.1–12.0 h (Table 3). Plasma concentrations of DTG reached steady state by day 7 of dosing. After 10 days of dosing, the accumulation ratios for $AUC_{0-\tau}$, C_{max} , and C_τ were

estimated to be 1.25–1.43, 1.23–1.40, and 1.27–1.42, respectively, across all dose levels. In addition, the increase in DTG exposure ($AUC_{0-\tau}$ and C_{max}) with increasing dose was slightly less than dose proportional after both single-dose (day 1) and repeat-dose administration (day 10). On average, plasma steady-state C_τ was three and 13 times higher than the in-vitro protein-adjusted IC90 of viral suppression (0.064 μ g/ml) at doses of 10 and 50 mg, respectively.

Significant negative correlations between DTG exposure and change in plasma HIV-1 RNA from baseline to day 11 (i.e., greater antiviral activity with higher DTG plasma exposure) were observed. When relationships between various pharmacokinetic parameters and pharmacodynamic measure (HIV-1 RNA) were explored using linear and E_{max} models, the exposure-response relationship was best described by an E_{max} model with E_{max} fixed to 2.6, Hill factor fixed to 1, and pharmacokinetic parameter on the linear scale. Using this model, C_τ was the pharmacokinetic parameter that best predicted day 11 plasma viral load reduction from baseline or maximum plasma viral load reduction from baseline (Fig. 2).

Viral genotyping and phenotyping

Genotypic and phenotypic data were available at baseline and day 11 for six of seven patient viruses within the placebo group. Of the patients receiving DTG, genotypic and phenotypic data were available at baseline and on day 11 for 19 and 18 patient viruses, respectively. No raltegravir-associated or elvitegravir-associated resistance mutations at codons 92, 138, 140, 143, 148, or 155 [13,14], or other resistance-associated substitutions as listed in the Stanford HIV Drug Resistance Database [15,16], were observed during therapy, with the exception of one patient. In this patient receiving DTG 2 mg, a change at the nonsignature position 74 of L to mixture I/L/M was observed without a corresponding phenotypic change. This patient had a day 11 HIV-1 RNA less than 50 copies/ml. None of the currently identified mutations selected by DTG during in-vitro passage with wild-type HIV-1 (at codons 92, 153, and 193) [7,17] were observed.

The number and position of amino acid changes from day 1 to 11 were evaluated in placebo and DTG patients.

Table 3. Steady-state pharmacokinetics on day 10.

DTG dose	n	C_{max} (μ g/ml) ^a	t_{max} (h) ^b	$AUC_{0-\tau}$ ($\text{h} \times \mu\text{g}/\text{ml}$) ^a	$t_{1/2}$ (h) ^a	C_τ (μ g/ml) ^a
2 mg	9	0.22 (25)	1.00 (0.42–3.00)	2.56 (29)	11.1 (24)	0.04 (50)
10 mg	7	0.80 (23)	1.48 (0.50–3.00)	10.1 (20)	11.6 (21)	0.19 (25)
50 mg	10	3.34 (16)	2.00 (0.97–4.00)	43.4 (20)	12.0 (22)	0.83 (26)

$AUC_{0-\tau}$, area under the plasma concentration-time curve during one dosing interval; C_τ , concentration at the end of dosing interval; C_{max} , maximum observed plasma concentration; CV, coefficient of variation; DTG, dolutegravir; $t_{1/2}$, terminal elimination phase half-life; t_{max} , time of occurrence of C_{max} .

^aGeometric mean (CV %).

^bMedian (range).

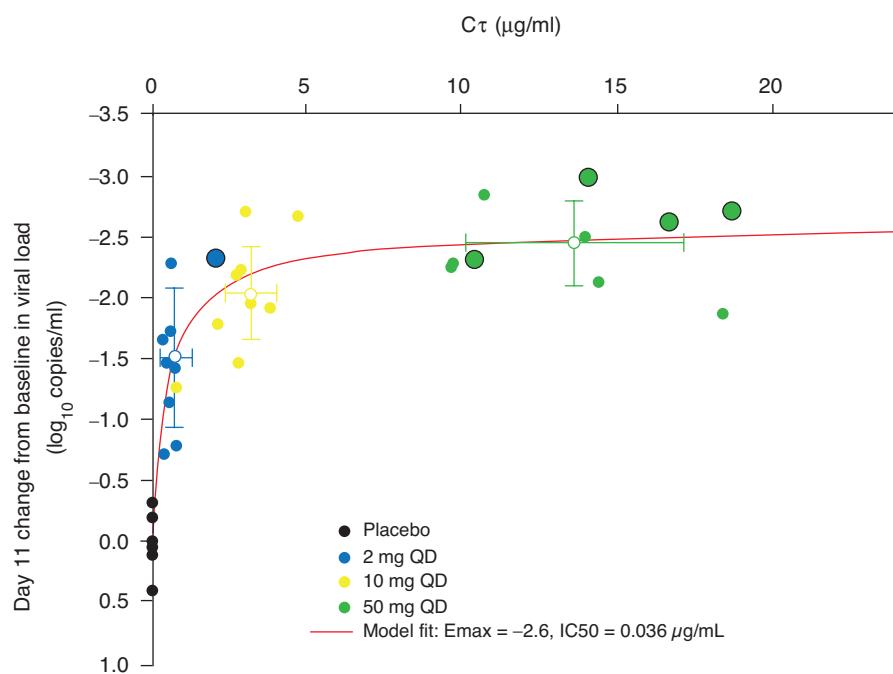


Fig. 2. Relationship of dolutegravir C_T and reduction of plasma HIV-1 RNA on day 11 from baseline with E_{max} model. Patients with viral load less than 50 copies/ml are represented by black-bordered circles; open circles with lines denote mean \pm standard deviation. C_T , concentration at the end of the dosing interval; IC50, 50% inhibitory concentration; QD, once daily.

Genotypic changes were common in evaluable patient viruses from the placebo (83%, five of six) and the DTG (85%, 17 of 20) groups between day 1 and 11. In placebo patients, the greatest number of genotypic changes was observed at position 196 ($n=2$). For patients receiving DTG, genotypic changes for more than two patient viruses from day 1 to 11 were observed only at position 112 ($n=4$), three in the 2-mg and one in the 50-mg dose groups.

Finally, there was no significant decrease in DTG susceptibility from day 1 to 11 for any patient. The largest decrease in susceptibility from day 1 to 11 was a 1.36-fold change in one patient in the placebo group.

Safety

DTG was generally well tolerated. There were no deaths, serious adverse events, or withdrawals during the study. Drug-related adverse events were reported by 16 of 35 patients (46%), and the proportion of patients who reported drug-related adverse events was similar across DTG dose groups (2 and 10 mg: three of nine, 33%; 50 mg: five of 10, 50%), although there was a higher percentage in the placebo group (five of seven, 71%). The most frequent drug-related adverse event was diarrhea (2 and 10 mg: one of nine, 11%; 50 mg: two of 10, 20%; placebo: three of seven, 43%). No drug-related adverse events occurred with greater frequency in a DTG dose group than in the placebo group, and no dose-related trends were observed for adverse events. Most

adverse events were mild to moderate in severity, with the exception of four severe adverse events reported by one patient each: hypertriglyceridemia (10 mg), lipase increase (10 mg), migraine (50 mg), and night sweats (placebo).

There were no consistent or clinically significant changes in hematology, clinical chemistry, vital signs, or urinalysis values. Two patients had treatment-emergent, grade 3 laboratory abnormalities after receiving 10 mg of DTG. On the last day of dosing, one patient had an asymptomatic grade 3 lipase increase, which resolved by the end of follow-up (day 21). Another patient had an asymptomatic grade 3 triglyceride elevation, which resolved with continued dosing and was not considered drug related. No clinically significant electrocardiogram abnormalities or trends (i.e., no QTc >480 ms or QTc change >60 ms) were observed.

Discussion

Monotherapy with DTG once daily was associated with potent antiretroviral activity in a phase IIa trial, with a 2.5 log₁₀ mean decline in HIV-1 RNA after 10 days of treatment with a 50-mg dose [18–26]. At the 10-mg dose, observed antiviral responses (2.0 log₁₀ mean decline in HIV-1 RNA) were similar to or higher than

those seen in short-term studies of other antiretrovirals, including INIs [8,9]. The majority of patients who received the two highest doses (10 or 50 mg) achieved plasma HIV-1 RNA levels less than 400 copies/ml on day 11 (10 mg, five of nine or 56%; 50 mg, nine of 10 or 90%) despite not receiving any other antiretroviral. In addition, seven of 10 patients (70%) in the 50-mg dose group achieved an HIV-1 RNA level less than 50 copies/ml during the study. Importantly, a sustained virologic response was also observed from day 11 to 14 among patients receiving the 50-mg dose, without continued dosing of DTG. On the basis of the observed half-life of DTG and modeled pharmacokinetic exposures between day 11 and 14 (data on file, GlaxoSmithKline, Research Triangle Park, North Carolina, USA), the likely explanation is that DTG exposures remained above the protein-adjusted IC50 (0.016 µg/ml) through day 14. In addition to the antiviral activity observed, patients who received DTG had median increases in CD4⁺ cell counts on day 11 compared with decreases in those receiving placebo.

No clinically significant genotypic or phenotypic changes to DTG or other INIs were observed in patients receiving DTG or placebo. Observed missing resistance data were typically associated with low plasma viral RNA levels on day 11. In cases wherein assays failed and plasma RNA levels met assay recommendations (e.g., as occurred in one of seven placebo virus examples), assay failure causes may have included reduced viral fitness or compromised sample processing. No patients had raltegravir-associated or elvitegravir-associated resistance mutations, with the exception of one patient virus. For that patient virus, the HIV-1 RNA result on day 11 was below the limit of detection, which limits the reliability of the genotype result; the change was at a nonsignature position for raltegravir (position 74) and not associated with a change in susceptibility to DTG. No resistance mutations identified in DTG in-vitro passage studies were observed in any patient virus. Similar numbers of genotypic changes were observed in patients receiving DTG and placebo. Additionally, no clinically significant changes in DTG susceptibility were observed. One placebo patient had a minor change in susceptibility (1.36-fold) to DTG, which is consistent with the approximately two-fold variability in DTG susceptibility of the integrase phenotype assay (data on file, GlaxoSmithKline, Research Triangle Park, North Carolina, USA). Therefore, there was no evidence of genotypic or phenotypic resistance to DTG in patients receiving DTG or placebo.

DTG tablets are dosed once daily without the need for a pharmacokinetic booster, supported by a half-life of approximately 12 h and exposures with the 10 and 50 mg doses that remain well above the protein-adjusted IC90 (0.064 µg/ml) throughout the dosing interval. The inhibitory quotient (C_{τ} divided by protein-adjusted

IC90) for the 10 and 50 mg doses was 3 and 13, respectively, which suggests that DTG will have good activity in longer term combination treatment studies. A well characterized exposure-response relationship was demonstrated; levels of antiviral activity increased with increasing doses of DTG. The finding that C_{τ} was the pharmacokinetic parameter that best predicted a reduction in plasma viral load from baseline to day 11 is consistent with the observation that antiviral activity is associated with the maintenance of therapeutic plasma concentrations throughout the dosing interval, as was also observed in a trial with the boosted INI elvitegravir [19]. However, the current study with DTG did not differentiate among pharmacokinetic parameters (AUC_{0- τ} , C_{\max} , and C_{τ}), given that all treatments were administered once daily. This well described exposure-response relationship distinguishes DTG from raltegravir in which plasma exposure has not been shown to correlate with clinical outcome [14]. The low interpatient pharmacokinetic variability and predictable pharmacokinetic/pharmacodynamic relationship of DTG provide greater confidence that the doses selected for dose-ranging phase IIb trials will demonstrate potent antiviral activity.

In this short-term monotherapy study, DTG was generally well tolerated in HIV-infected adult patients and no major safety issues or dose-related trends were identified. Overall, the safety profile observed in HIV-1-infected patients was similar to that previously observed in both single-dose and short-term repeat-dose studies of DTG suspension in healthy adult individuals [9].

These results support expanded evaluation of DTG in larger and longer term phase IIb dose-ranging studies of HIV-1-infected patients; these ongoing clinical studies will assess the long-term efficacy of DTG in combination with other antiretroviral agents. Given its potent antiviral activity, distinct resistance profile, predictable exposure-response relationship, and unboosted, low-dose, once-daily dosing profile, DTG has considerable promise as a next-generation INI, with the potential to deliver benefits for HIV-infected patients across the treatment spectrum.

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S.M. was the clinical leader and GlaxoSmithKline medical monitor for the study, contributed to study

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L.S. was the investigator with primary management responsibilities in the study and provided critical review of the data and contributed to the editing/writing of the manuscript.

E.D.J. was the investigator with primary management responsibilities in the study and provided critical review of the data and contributed to the editing/writing of the manuscript.

T.H. was the investigator with primary management responsibilities in the study and provided critical review of the data and contributed to the editing/writing of the manuscript.

L.M.C. was the investigator with primary management responsibilities in the study and provided critical review of the data and contributed to the editing/writing of the manuscript.

I.S. was the pharmacokineticist for the study, contributed to study design, protocol development, and data analysis, and was the author for the pharmacokinetic sections of the manuscript.

R.S. was the study manager and contributed to study design, protocol development, data analysis, and writing/editing of the manuscript.

S.C. was the statistician and contributed to study design, protocol development, data analysis (developed statistical analysis plan), and writing/editing of the manuscript.

T.F. was the project leader and contributed to study design, protocol development, data analysis, and writing/editing of the manuscript.

M.U. was the virologist and contributed to study design, protocol development, data analysis (analyzed resistance data), and writing/editing of the manuscript.

S.P. was the clinical pharmacologist and contributed to study design, protocol development, data analysis, and writing/editing of the manuscript.

J.L. was the investigator with primary management responsibilities in the study and provided critical review of the data and contributed to the editing/writing of the manuscript.

Conflicts of interest

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Achillion, Avexa, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Hoffman LaRoche Laboratories, Merck, Pfizer, Schering Plough, Taimed, Tobira, Tibotec, and Vertex Pharmaceuticals. He is currently serving as a consultant or has received honoraria from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Tibotec, and Vertex. He is on the Speakers Bureau at Gilead Sciences, Merck, Tibotec, and Virco. T.H. is currently serving as a consultant to Gilead Sciences, Merck, and Tibotec. He has previously served as a consultant to Bristol-Myers Squibb. He is on the Speakers Bureau at Bristol-Myers Squibb, Gilead Sciences, Merck, and Tibotec. He is currently receiving research support from Gilead Sciences, GlaxoSmithKline, Pfizer, Salix Pharmaceuticals, Tibotec, and ViiV Healthcare. He has previously received research support from Bristol-Myers Squibb, Merck, and Napo. S.M., I.S., J.B., R.S., S.C., Y.L., M.U., and S.P. are employees of GlaxoSmithKline and receive company stock as part of their incentive packages. T.F. is an employee of Shionogi & Co. Ltd. L.S. is currently serving on the Speakers Bureau at Pfizer and ViiV Healthcare.

J.L. and L.M.C. have no conflicts of interest.

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References

1. Serrao E, Odde S, Ramkumar K, Neamati N. **Raltegravir, elvitegravir, and metoegravir: the birth of 'me-too' HIV-1 integrase inhibitors.** *Retrovirology* 2009; **6**. <http://www.retrovirology.com/content/6/1/25>. [Accessed 11 June 2010]
2. Hawkins T. **Understanding and managing the adverse effects of antiretroviral therapy.** *Antiviral Res* 2010; **85**:201–209.
3. Markowitz M, Nguyen B-Y, Gotuzzo E, Mendo F, Ratanasuwann W, Kovacs C, et al., and the Protocol 004 Part II Study Team. **Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: results of a 48-week controlled study.** *J Acquir Immune Defic Syndr* 2007; **46**:125–133.
4. Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al., for the BENCHMRK Study Teams. **Raltegravir with optimized background therapy for resistant HIV-1 infection.** *N Engl J Med* 2008; **359**:339–354.
5. Cooper DA, Steigbigel RT, Gatell JM, Rockstroh JK, Katlama C, Yeni P, et al., for the BENCHMRK Study Teams. **Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection.** *N Engl J Med* 2008; **359**:355–365.
6. DeJesus E, Cohen C, Elion R, Ortiz R, Maroldo L, Franson S, et al., for the 183–0101 Study Team. **First report of raltegravir (RAL, MK-0518) use after virologic rebound on elvitegravir (EVT, GS 9137) [abstract TUPEB032].** Presented at the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 22–25 July 2007; Sydney, Australia.
7. Sato A, Kobayashi M, Yoshinaga T, Fujiwara T, Underwood M, Johns B, et al. **S/GSK1349572 is a potent next generation HIV integrase inhibitor.** Poster presented at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 19–22 July 2009; Cape Town, South Africa.

8. Underwood M, Johns B, Sato A, Fujiwara T, Spreen W. **S/GSK1349572: a next generation integrase inhibitor with activity against integrase inhibitor-resistant clinical isolates from patients experiencing virologic failure while on raltegravir therapy.** Poster presented at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 19–22 July 2009; Cape Town, South Africa.
9. Min S, Song I, Borland J, Chen S, Lou Y, Fujiwara T, et al. **Pharmacokinetics (PK) and safety in healthy subjects of S/GSK1349572, a next generation, once-daily HIV integrase inhibitor (INI).** Poster presented at the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 19–22 July 2009; Cape Town, South Africa.
10. Fransen S, Gupta S, Paxinos EE, Huang W, Parkin N, Miller M, et al. **Integrase inhibitor (IN) susceptibility can be measured using recombinant viruses that express patient virus IN alone, or in combination with protease (PR) and reverse transcriptase (RT).** Poster presented at the 12th Conference on Retroviruses and Opportunistic Infections; 22–25 February 2005; Boston, MA.
11. Division of AIDS table for grading severity of adult and pediatric adverse events. **National Institutes of Allergy and Infectious Diseases, Division of Acquired Immunodeficiency Syndrome.** http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GradingTable_Clarification_August2009_Final.pdf. [Accessed 10 June 2010]
12. Akaike H. **A new look at the statistical model identification.** *IEEE Trans Automat Contr* 1974; **19**:716–723.
13. Hazuda DJ, Miller MD, Nguyen BY, Zhao J, for the P005 Study Team. **Resistance to the HIV-integrase inhibitor raltegravir: analysis of protocol 005, a Phase II study in patients with triple-class resistant HIV-1 infection.** *Antivir Ther* 2007; **12**:S10.
14. McColl DJ, Fransen S, Gupta S, Parkin N, Margot N, Chuck S, et al. **Resistance and cross-resistance to first generation integrase inhibitors: insights from a Phase II study of elvitegravir (GS-9137).** *Antivir Ther* 2007; **12**:S11.
15. INI resistance notes. **Stanford University HIV Drug Resistance Database.** http://hivdb6.stanford.edu/asi/deployed/xmlTools/rules_scores_hivdb.cgi?class=INI. [Accessed 17 April 2010]
16. Shafer RW. **Rationale and uses of a public HIV drug-resistance database.** *J Infect Dis* 2006; **194** (Suppl 1):S51–S58.
17. Sato A, Seki T, Kobayashi M, Yoshinaga T, Fujiwara T, Underwood M, et al. **In vitro passage of drug resistant HIV-1 against a next generation integrase inhibitor (INI), S/GSK1349572.** Poster presented at the 49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting; 12–15 September 2009; San Francisco, CA.
18. Markowitz M, Morales-Ramirez JO, Nguyen B-Y, Kovacs CM, Steigbigel RT, Cooper DA, et al., and the Protocol 004 Study Team. **Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naïve HIV-1-infected individuals.** *J Acquir Immune Defic Syndr* 2006; **43**:509–515.
19. DeJesus E, Berger D, Markowitz M, Cohen C, Hawkins T, Ruane P, et al., for the 183-0101 Study Team. **Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naïve and treatment-experienced patients.** *J Acquir Immune Defic Syndr* 2006; **43**:1–5.
20. Goebel F, Yakovlev A, Pozniak AL, Vinogradova E, Boogaerts G, Hoetelmans R, et al. **Short-term antiviral activity of TMC278 – a novel NNRTI – in treatment-naïve HIV-1-infected subjects.** *AIDS* 2006; **20**:1721–1726.
21. Gruzdev B, Rakhamanova A, Doubrovskaya E, Yakovlev A, Peeters M, Rinehart A, et al. **A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naïve, HIV-1 infected subjects.** *AIDS* 2003; **17**:2487–2494.
22. Fätkenheuer G, Staszewski S, Plettenburg A, Hackman F, Layton G, McFadyen L, et al. **Short-term monotherapy with UK-453 061, a novel NNRTI, reduces viral load in HIV infected patients [abstract WESS202].** Presented at the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 22–25 July 2007; Sydney, Australia.
23. Adkins JC, Noble S. **Efavirenz.** *Drugs* 1998; **56**:1055–1064; discussion 1065–1056.
24. Kilby JM, Hopkins S, Venetta TM, DiMassimo B, Cloud GA, Lee JY, et al. **Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry.** *Nat Med* 1998; **4**:1302–1307.
25. Murphy RL, Brun S, Hicks C, Eron JJ, Gulick R, King M, et al. **ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results.** *AIDS* 2001; **15**:F1–F9.
26. Pozniak AL, Fatkenheuer G, Johnson M, Hopelman IM, Rockstroh J, Goebel F, et al. **Effect of short-term monotherapy with UK-427 857 on viral load in HIV-infected patients.** Slides presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 14–17 September 2003; Chicago, IL.