Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial

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Summary

Background **Dolutegravir (S/GSK1349572) is a new HIV-1 integrase inhibitor that has antiviral activity with once daily, unboosted dosing. SPRING-1 is an ongoing study designed to select a dose for phase 3 assessment. We present data from preplanned primary and interim analyses.**

Methods **In a phase 2b, multicentre, dose-ranging study, treatment-naive adults were randomly assigned (1:1:1:1) to receive 10 mg, 25 mg, or 50 mg dolutegravir or 600 mg efavirenz. Dose but not drug allocation was masked. Randomisation was by a central integrated voice-response system according to a computer-generated code. Study drugs were given with either tenofovir plus emtricitabine or abacavir plus lamivudine. Our study was done at 34 sites in France, Germany, Italy, Russia, Spain, and the USA beginning on July 9, 2009. Eligible participants were seropositive for HIV-1, aged 18 years or older, and had plasma HIV RNA viral loads of at least 1000 copies per mL and CD4 counts of at least 200 cells per µL. Our primary endpoint was the proportion of participants with viral load of less than 50 copies per mL at week 16 and we present data to week 48. Analyses were done on the basis of allocation group and included all participants who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00951015.**

Findings **205 patients were randomly allocated and received at least one dose of study drug: 53, 51, and 51 to receive 10 mg, 25 mg, and 50 mg dolutegravir, respectively, and 50 to receive efavirenz. Week 16 response rates to viral loads of at most 50 copies per mL were 93% (144 of 155 participants) for all doses of dolutegravir (with little difference between dose groups) and 60% (30 of 50) for efavirenz; week 48 response rates were 90% (139 of 155) for all doses of dolutegravir and 82% (41 of 50) for efavirenz. Response rates between nucleoside reverse transcriptase inhibitor subgroups were similar. We identified three virological failures in the dolutegravir groups and one in the efavirenz group—we did not identify any integrase inhibitor mutations. We did not identify any dose-related clinical or laboratory toxic effects, with more drug-related adverse events of moderate-or-higher intensity in the efavirenz group (20%) than the dolutegravir group (8%). We did not judge that any serious adverse events were related to dolutegravir.**

Interpretation **Dolutegravir was effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses. Our findings support the assessment of once daily 50 mg dolutegravir in phase 3 trials.**

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See Comment page 90

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Introduction

Integrase inhibitors are a new class of antiretroviral drugs that block the action of HIV integrase, which catalyses several key steps in the life cycle of the virus and is essential for insertion of the viral genome into the DNA of the host cell. Because integration is a vital step in retroviral replication, integrase is a natural target for the treatment.[1] The first integrase inhibitor to receive market approval, raltegravir, is effective with good tolerability in combination therapy for HIV in both treatment-naive patients and those who have previously received antiretroviral treatment.[2,3] However, raltegravir must be given twice daily.[4,5] Elvitegravir, another integrase inhibitor in development, is given once daily but needs to be given with a pharmacokinetic booster such as ritonavir or cobicistat.[6] Dolutegravir (S/GSK1349572) is a new drug in this class; in cell-culture assays at low nanomolar concentrations it is an effective inhibitor of HIV integrase and HIV replication.[7] Pharmacokinetic studies in people have shown a long plasma half-life (about 14 h) without the need for a booster; in short-term monotherapy studies in adults with HIV, change from baseline in HIV RNA viral load ranged from $1 \cdot 5$ $\log_{10}$ copies per mL to $2 \cdot 5$ $\log_{10}$ copies per mL with 2 mg, 10 mg, and 50 mg of dolutegravir once daily.[8,9] Data from in-vitro passage experiments showed the potential for a higher barrier to resistance compared with raltegravir and elvitegravir.[7] Finally, in-vitro experiments and data from the ongoing VIKING study (registered with ClinicalTrials.gov, number NCT00950859) suggest that dolutegravir retains activity

against viral strains harbouring major integrase-inhibitor resistance mutations selected for by both raltegravir and elvitegravir, including Glu92Gln, Gln148His/Lys/Arg, Asn155His, and Gly140Ser/Gln148His.[7,10–13] Therefore, dolutegravir has low cross-resistance with the potential for a higher barrier to resistance than other integrase inhibitors.

The objective of our phase 2b study was to assess the efficacy, safety, and pharmacokinetics of three doses of dolutegravir and a standard-care efavirenz-based regimen in adults not previously treated with antiretroviral drugs to select a dose for phase 3 development. Long-term follow-up of these participants will further characterise the risk to benefit ratio of the compound, including assessment of the emergence of drug-resistance isolates in the clinic.

Methods

Participants

On July 9, 2009, we started a 96 week, randomised, dose-ranging study in adults infected with HIV who had not previously received treatment, at 34 sites in France, Germany, Italy, Russia, Spain, and the USA. Eligible participants were seropositive for HIV-1, aged 18 years or older, and had a plasma HIV RNA viral load of 1000 copies per mL or greater, and a CD4 count of 200 cells per μL or greater at screening. We excluded any patients that had received more than 10 days of previous treatment with antiretroviral drugs, evidence of primary resistance mutations to antiretroviral drugs, or defined exclusionary laboratory values or medical characteristics, including pregnancy, active US Centers for Disease Control and Prevention category C disease, electrocardiographic abnormalities, and recent pancreatitis or hepatitis. Patients could receive abacavir only after exclusion of the *HLA-B*5701* haplotype.

Written informed consent was obtained from each patient before screening procedures. Our study was approved by the respective national regulatory authorities and ethics review committees for each site.

Randomisation and masking

Randomisation was by a central integrated voice-response system according to a computer-generated code and was stratified by viral load at screening (≤100 000 copies per mL or >100 000 copies per mL) and baseline nucleoside reverse transcriptase inhibitor (NRTI) selection. Eligible participants were randomly assigned (1:1:1:1) to receive one of three doses of dolutegravir (10 mg, 25 mg, or 50 mg once daily) or efavirenz. The dose of dolutegravir was masked with matched placebo tablets. Dose but not drug allocation was masked from participants and investigators. Each participant was started on an open-label dual NRTI background regimen of either abacavir plus lamivudine or tenofovir plus emtricitabine at the investigator's discretion as fixed-dose combination tablets give once daily.

Procedures

Dolutegravir and matching placebo, as appropriate, were given once daily without regard to food. Open-label efavirenz and the selected dual-NRTI fixed-dose combination tablets (either tenofovir plus emtricitabine or abacavir plus lamivudine) were given in accordance with the product labels. Participants recorded dates and times of doses before pharmacokinetic sampling and returned unused study drugs for collection and counting by clinic staff.

Clinical assessments and samples of blood, urine, or both were collected at baseline and weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 and planned every 12 weeks thereafter. Laboratory analyses were done centrally by Quest Diagnostic Laboratories (Van Nuys, CA, USA, and Heston, Middlesex, UK). Viral load was quantified with the Abbott RealTime HIV-1 assay (lower limit of detection 40 copies per mL). Blood samples for dolutegravir pharmacokinetic assessments were collected from 142 participants equally distributed across the dolutegravir groups at weeks 2, 12, and 24. Dolutegravir pharmacokinetic parameters were estimated with a non-compartmental data analysis approach from participants providing intensive samples at week 2.

We anticipated that all doses of dolutegravir that we assessed would provide desirable long-term efficacy in combination therapy and were based on a pharmacokinetic and pharmacodynamic analysis from phase 2a monotherapy data in treatment-naive participants.[9] With a maximum effect pharmacokinetic and pharmacodynamic model we assessed the relation between exposure to dolutegravir and change in viral load from baseline. For the 50 mg once daily dose, the recorded changes in viral load were on the plateau of the concentration versus effect curve, showing that a minimum additional change in effect would be predicted with increasing dose. Therefore, 50 mg once daily was anticipated to have a maximum antiviral effect in this population. Because we intended to select one dose for patients not previously treated with integrase inhibitors, to compensate for slight drug–drug interactions in the treatment-experienced population, we adopted an a-priori dose selection strategy to select the highest maximum tolerated dose for further investigation in phase 3 trials.

Statistical analysis

We designed our study to select a dose primarily on the basis of antiviral activity and tolerability together with immunological response and safety and pharmacokinetic measures, and not to assess formal statistical hypotheses. We chose the sample size of 50 participants per group to ensure a high probability (>95%) that a dose with a truly poor response (ie, >10% worse than another dose) relative to others would not be selected on the basis of an analysis of the primary endpoint, while allowing for the formal consideration of other measures of antiviral activity.

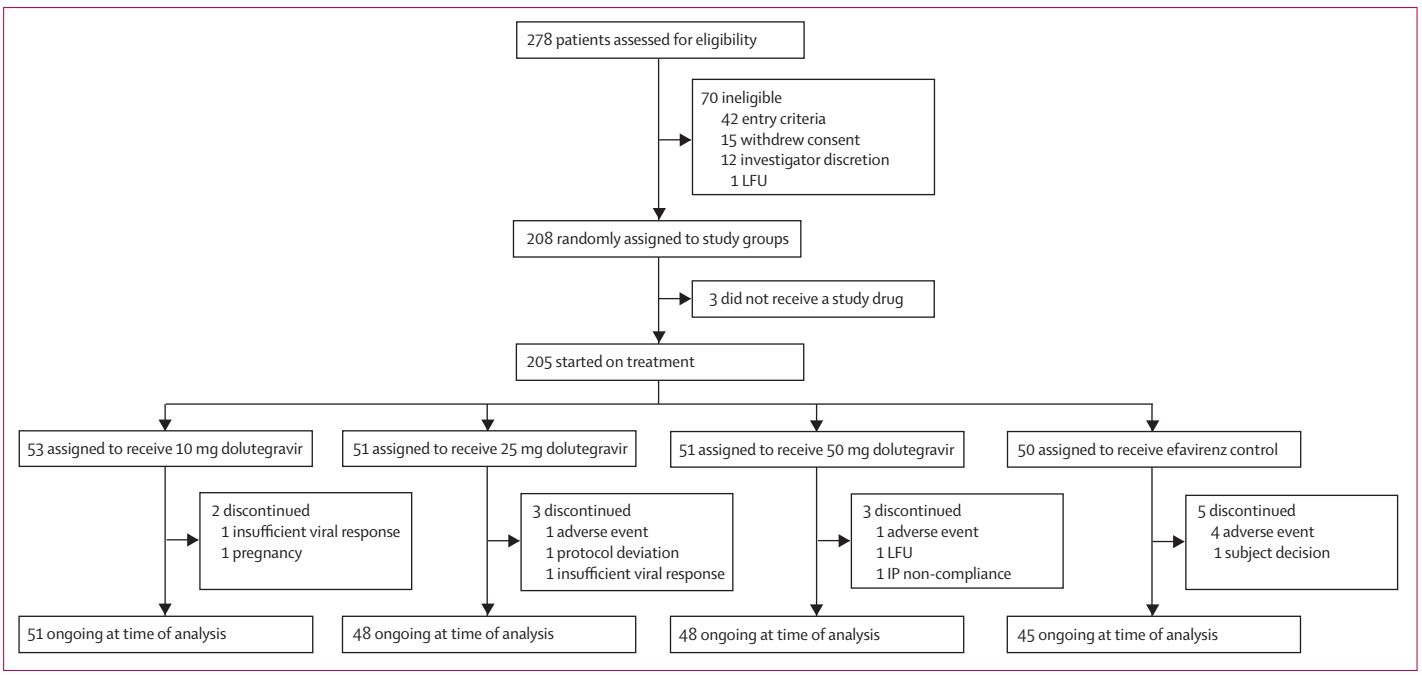

Figure 1: **Trial profile to week 48**
LFU=lost to follow-up. IP=investigational product.

Our primary endpoint was the proportion of participants in each treatment group that achieved viral load lower than 50 copies per mL at week 16, established with the US Food and Drug Administration time to loss of virological response (TLOVR) algorithm.[14] We repeated this analysis at weeks 24 and 48. We based our analyses on the intention-to-treat exposed (ITT-E) population, comprising all participants randomly assigned to receive treatment who received at least one dose of study drug assessed on the basis of treatment allocation.

Virological failure was defined as a less than 1·0 $\log_{10}$ copy per mL decrease in plasma HIV RNA by week 4 unless the measure was lower than 400 copies per mL, failure to suppress plasma HIV RNA to less than 400 copies per mL on or after week 24, rebound to 400 copies per mL or more after suppression to less than 400 copies per mL, or rebound to greater than 0·5 $\log_{10}$ above nadir if 400 copies per mL or greater. Participants with confirmed virological failure (two consecutive samples 1–4 weeks apart) were assessed for study discontinuation and had samples analysed for genotypic and phenotypic resistance (Monogram Biosciences, South San Francisco, CA, USA).

Our statistical algorithm calculated non-responders as participants without a confirmed plasma HIV RNA of 50 copies per mL at analysis timepoints. We allowed participants judged to be non-responders but who did not meet our definition of virological failure to remain in our study. Non-responders were assessed as virological or non-virological. Subgroups included baseline viral load and background NRTI. Further efficacy analyses, based on the ITT-E population, included increases from baseline in CD4 cell counts and HIV disease progression.

Summaries of safety data (eg, incidences of adverse events and graded laboratory abnormalities) were based on the safety population, consisting of all participants who received at least one dose of study drug, and were assessed according to the treatment actually received.

In addition to planned analyses, stopping rules based on events recorded during preclinical assessment were agreed a priori to rule out unacceptable doses on the basis of efficacy and safety. Our dose-selection approach was to select the maximum tolerated dose to allow for maximum potency and exposure coverage while maintaining good safety and tolerability. This study is registered with ClinicalTrials.gov, number NCT00951015.

Role of the funding source

Initially sponsored by GlaxoSmithKline (GSK), this study is now sponsored by ViiV Healthcare. Shionogi-GSK Pharmaceuticals LLC, now Shionogi-ViiV Healthcare LLC, provided funding. The study was designed by GSK, Shionogi & Co Ltd, and external consultants. Data were collected by site investigators and monitored by GSK, and GSK did the data analysis. All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors, had access to the study data, and agreed to the submission of this article for publication.

	10 mg dolutegravir (n=53)	25 mg dolutegravir (n=51)	50 mg dolutegravir (n=51)	600 mg efavirenz (n=50)	Total (n=205)
Age (years), median (range)	32 (21–61)	38 (20–64)	37 (22–55)	40 (20–79)	37 (20–79)
Number of men	42 (79%)	46 (90%)	45 (88%)	44 (88%)	177 (86%)
Ethnic origin					
Black	7 (13%)	6 (12%)	8 (16%)	4 (8%)	25 (12%)
White	41 (77%)	42 (82%)	38 (75%)	43 (86%)	164 (80%)
Other*	5 (9%)	3 (6%)	5 (10%)	3 (6%)	16 (8%)
Baseline viral load (HIV-1 RNA)					
Number with >100 000 copies per mL	11 (21%)	10 (20%)	12 (24%)	11 (22%)	44 (21%)
Mean concentration, $\log_{10}$ copies per mL (SD; range)	4·4 (0·66; 3·3–6·2)	4·4 (0·68; 2·9–5·6)	4·6 (0·68; 2·9–6·0)	4·5 (0·68; 3·2–6·0)	4·5 (0·68; 2·9–6·2)
Baseline CD4 count (cells per μL)					
Mean	309	334	327	328	324
Median	289	330	305	308	305
CDC category A or B	53 (100%)	50 (98%)	51 (100%)	49 (98%)	203 (99%)
Background NRTI selection					
Tenofovir plus emtricitabine	36 (68%)	34 (67%)	34 (67%)	34 (68%)	138 (67%)
Abacavir plus lamivudine	17 (32%)	17 (33%)	17 (33%)	16 (32%)	67 (33%)

Data are n (%) unless otherwise stated. CDC=US Centers for Disease Control and Prevention. NRTI=nucleoside reverse transcriptase inhibitor. *Includes Asian, Native American, Native Alaskan, Native Hawaiian, or other Pacific Islander. Overall, 16% of participants reported Hispanic ethnicity.

Table 1: **Baseline characteristics**

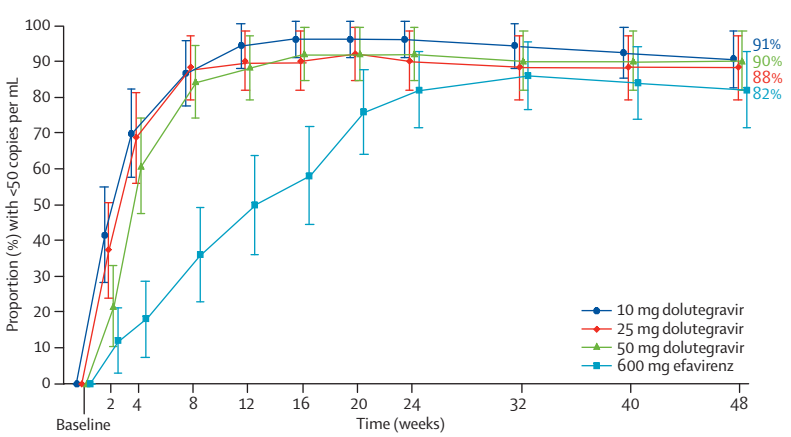

Figure 2: **Proportion of participants with viral load less than 50 copies per mL**
Viral load measured as HIV-1 RNA copies per mL. Endpoint established with time to loss of virological response algorithm. 95% CIs derived with the normal approximation.

Results

205 individuals were given at least one dose of study drug and comprise both the ITT-E and the safety populations (figure 1). Baseline characteristics were balanced across the study groups with the exception that a larger proportion of patients had baseline HIV RNA greater than 100 000 copies per mL, in the dolutegravir 50 mg once daily group than in the others (table 1). More participants were started on tenofovir plus emtricitabine than abacavir plus lamivudine as the dual-NRTI backbone. Of participants with an HIV RNA concentration greater than 100 000 copies per mL at screening, 69% were started on tenofovir plus emtricitabine and 31% on abacavir plus lamivudine. 18 participants (9%) had hepatitis C virus, as detected with serology. We did not exclude any participants from our ITT-E analyses.

We recorded a rapid and sustained response across all dolutegravir groups, with most participants achieving a viral load of less than 50 copies per mL at week 16, which was generally sustained to week 48 (figure 2).

At week 2, the absolute change in viral load was a decrease of about 2·38 $\log_{10}$ copies per mL in the dolutegravir groups and 1·93 $\log_{10}$ copies per mL in the efavirenz group. The response rates for the dolutegravir groups were much higher by week 4 (66% of participants receiving dolutegravir compared with 18% receiving efavirenz; figure 2).

We did not identify differences across the dolutegravir groups or a pattern across predefined baseline strata in reasons for non-response (TLOVR algorithm) up to week 48 (table 2). Because our study was not powered to do so, we did not do formal statistical testing on baseline strata.

Four participants met protocol-defined virological failure, two in the 10 mg dolutegravir group, one in the 25 mg dolutegravir group, and one in the efavirenz group. One participant receiving 10 mg dolutegravir had Met184Met/Val reverse transcriptase; the other participant had no changes in reverse transcriptase, protease, or integrase. No genotypic results were available for the participant receiving 25 mg dolutegravir with low copy number at the time of analysis (483 copies per mL; 2·68 $\log_{10}$ copies per mL). The participant in the efavirenz group achieved a 1·0 $\log_{10}$ copies per mL decrease in plasma viral load by week 4 with no treatment-emergent mutations. The participant continued to respond and remained in our study. So far we have not identified integrase mutations in our study.

Median CD4 counts increased from baseline to week 48 in all groups and were higher with the dolutegravir doses than with the efavirenz control (231 cells per μL *vs* 174 cells per μL; p=0·076 by post-hoc Wilcoxon two-sample test).

Three participants developed HIV-associated disorders: two had herpes zoster (10 mg and 50 mg dolutegravir groups) and one had Burkitt's lymphoma (50 mg dolutegravir group).

Most patients experienced at least one adverse event over the first 48 weeks of study (table 3). We did not identify any dose-related patterns in type, frequency, or severity of adverse events across dolutegravir doses, and most events reported in the dolutegravir groups were of mild (48%) or moderate (34%) intensity. Six participants withdrew from our study because of adverse events: two receiving dolutegravir (grade 2 dyspepsia in the 25 mg group and grade 4 Burkitt's lymphoma in the 50 mg group) and four receiving efavirenz (one each of drug intolerance, drug hypersensitivity, abnormal dreams, and

suicide attempt). We judged that no serious adverse events were related to dolutegravir and the one serious adverse event, suicide attempt, was related to efavirenz.

A larger proportion of participants in the efavirenz group had drug-related adverse events of moderate or higher severity (ten [20%] of 50) than those in the combined dolutegravir groups (13 [8%] of 155). Table 3 lists the most common drug-related adverse events of any intensity.

We identified few grade 3 or 4 laboratory abnormalities in the dolutegravir (19 [12%] of 155) or efavirenz (seven [14%] of 50) groups. We did not record a dose–response relation within the dolutegravir groups for graded laboratory abnormalities. Grade 3 or 4 laboratory abnormalities reported for participants receiving dolutegravir included raised concentrations of lipase (four participants), creatine phosphokinase (seven), aspartate aminotransferase (one), and LDL cholesterol (one), decreased concentrations of phosphorus (three), raised activated partial thromboplastin time (two), raised international normalised ratio (four), raised prothrombin time (four), and decreased neutrophil count (one). Grade 3 or 4 laboratory abnormalities reported for efavirenz included increased lipase (two), decreased phosphorus, hyperkalaemia, raised alkaline phosphatase, raised prothrombin time, and decreased neutrophil count (one each). Increases in creatine phosphokinase and lipase were asymptomatic, transient, and associated with physical activity, and mean and median changes from baseline in both were similar across all treatment groups.

Across all dolutegravir doses, but not efavirenz, small non-progressive mean increases from baseline in creatinine concentrations at week 1 remained constant to about week 16 (0·10 mg/dL [SD 0·108] dolutegravir overall *vs* 0·01 [0·079] efavirenz; p<0·0001 with post-hoc *t* test); values gradually returned to baseline over 48 weeks. The increases happened across both NRTI backbones (0·11 mg/dL [0·099] for the tenofovir plus emtricitabine subgroup and 0·08 mg/dL [0·123] for abacavir plus lamivudine). Four participants who received 25 mg dolutegravir had treatment-emergent grade 1 increases in creatinine concentration, and one had a grade 2 increase; we did not identify any other graded creatinine abnormalities. More participants in the dolutegravir groups (21 participants; 14%) than in the efavirenz group (one; 2%) had treatment-emergent increases in dipstick urine protein (≥1), which were neither time nor dose dependent. Since these results are semiquantitative, to better define this effect, a more definitive quantitative assessment (urine albumin-to-creatinine ratio) is now being done in our study and for ongoing phase 3 studies. Participants with the higher levels of proteinuria (ie, ≥2; four participants [2·6%]) had confounding medical disorders such as hepatitis C, hypertension, and diabetes. None of the patients receiving dolutegravir discontinued because of renal toxicity.

	10 mg dolutegravir (n=53)	25 mg dolutegravir (n=51)	50 mg dolutegravir (n=51)	600 mg efavirenz (n=50)
Overall number of responders at week 16	51 (96%)	47 (92%)	46 (90%)	30 (60%)
Overall number of responders at week 48	48 (91%)	45 (88%)	46 (90%)	41 (82%)
Non-response (virological reason) by week 48				
Rebound or protocol-defined virological failure	4 (8%)	3 (6%)	2 (4%)*	3 (6%)
Never suppressed by week 48	0	0	1 (2%)	1 (2%)
Non-response (non-virological reasons) by week 48				
Discontinuation because of adverse event	0	1 (2%)	0	4 (8%)
Protocol deviation or non-permitted change in ART	1 (2%)	2 (4%)	1 (2%)	0
Lost to follow-up or participant discontinued	0	0	1 (2%)	1 (2%)
By baseline viral load (HIV-1 RNA)				
Non-response (virological reason)				
≤100 000 copies per mL subgroup (n=161)	3	2	0	2
>100 000 copies per mL subgroup (n=44)	1	1	3*	2
By background NRTI selection				
Non-response (virological reason)				
Tenofovir plus emtricitabine (n=138)	2	0	1	3
Abacavir plus lamivudine (n=67)	2	3	2*	1

Data are n (%). ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. *Includes one participant who discontinued the study drug because of Burkitt's lymphoma and therefore had detectable viral load at the time of discontinuation.

Table 2: **Summary of study outcomes at weeks 16 and 48—overall and by baseline strata**

	10 mg dolutegravir (n=53)	25 mg dolutegravir (n=51)	50 mg dolutegravir (n=51)	Subtotal (n=155)	600 mg efavirenz (n=50)
Any event	47 (89%)	41 (80%)	44 (86%)	132 (85%)	44 (88%)
Serious adverse events*	3 (6%)	1 (2%)	4 (8%)	8 (5%)	4 (8%)
Any drug-related event (all grades)†	25 (47%)	18 (35%)	23 (45%)	66 (43%)	29 (58%)
Nausea	7 (13%)	6 (12%)	6 (12%)	19 (12%)	3 (6%)
Diarrhoea	4 (8%)	3 (6%)	5 (10%)	12 (8%)	3 (6%)
Dizziness	2 (4%)	0	3 (6%)	5 (3%)	9 (18%)
Headache	2 (4%)	4 (8%)	4 (8%)	10 (6%)	1 (2%)
Fatigue	1 (2%)	3 (6%)	1 (2%)	5 (3%)	4 (8%)
Asthenia	3 (6%)	0	1 (2%)	4 (3%)	0
Insomnia	0	0	3 (6%)	3 (2%)	4 (8%)
Abnormal dreams	1 (2%)	0	0	1 (<1%)	3 (6%)
Rash	2 (4%)	0	0	2 (1%)	4 (8%)

Data are n (%). *For 10 mg dolutegravir were abscess, dysmenorrhoea, and joint dislocation; for 25 mg was headache after lumbar puncture; for 50 mg were herpes zoster, fracture (foot and wrist), pyrexia, and Burkitt's lymphoma; and for efavirenz were bronchitis, neurosyphilis, epididymitis, and suicide attempt. †Adverse events in at least 5% of participants in one or more treatment groups.

Table 3: **Adverse events**

Participants receiving dolutegravir had more favourable changes in lipids than did those receiving efavirenz (figure 3); mean change from baseline in fasting LDL cholesterol was lower for participants in the dolutegravir groups (0·55 mg/dL increase) than for those in the efavirenz group (15·88 mg/dL increase).

Summary dolutegravir pharmacokinetic parameters at week 2 are listed in table 4. Dolutegravir exposure

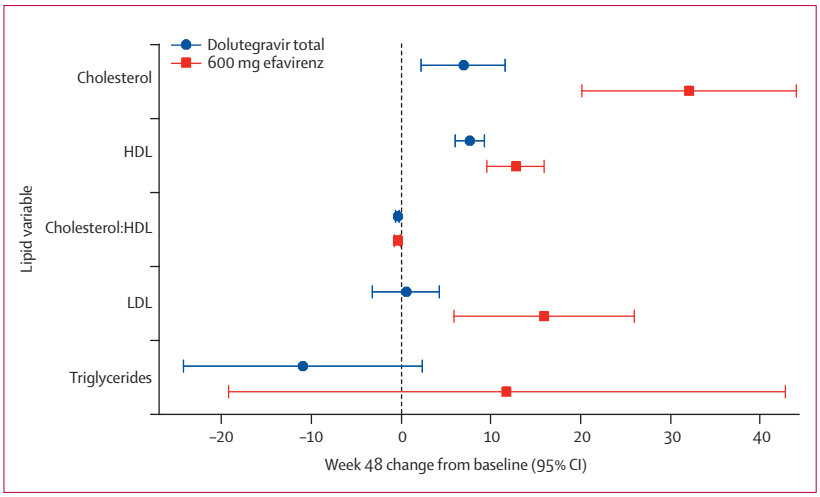

Figure 3: **Changes in lipid variables to week 48**
Individual lipids are expressed in mg/dL. Cholesterol:HDL is a unitless ratio.

	$AUC_{(0-\tau)}$ μg.h/mL	C_{max} μg/mL	C_{τ} μg/mL*	Inhibitory quotient (C_{τ}/protein-adjusted IC_{90})†
10 mg (n=15)	16·0 (40%)	1·10 (37%)	0·30 (71%)	4·7
25 mg (n=15)	23·1 (48%)	1·71 (43%)	0·54 (67%)	8·4
50 mg (n=15)	48·1 (40%)	3·40 (27%)	1·20 (62%)	19

Data are geometric means (coefficient of variance, %). $AUC_{(0-\tau)}$=area under the concentration–time curve from zero to the end of dosing interval. C_{max}=maximum observed plasma concentration. C_{τ}=concentration at the end of the dosing interval. IC_{90}=90% inhibitory concentration. *Total number of samples assessed for the 10 mg group were 47, for the 25 mg group were 44, and for the 50 mg group were 44. †Protein-adjusted IC_{90}=0·064 μg/mL.

Table 4: **Summary of dolutegravir pharmacokinetic parameters by dose at week 2**

increased proportionally from 25 mg to 50 mg (where the same tablet strength was used) and less-than-dose proportionally from 10 mg to 25 mg (where different tablet strengths were used). Over the dosing interval, dolutegravir exposures were well above the protein-adjusted 90% inhibitory concentration (IC_{90}). Dolutegravir showed moderately low pharmacokinetic variability (coefficient of variation 30–70%). Because virological responses at week 24 were greater than 90% across all dolutegravir groups, we did not identify a relation between dolutegravir exposure (minimum drug concentration [Cτ] or area under the curve) and response (data not shown).

Discussion

Dolutegravir has antiviral activity in combination with dual NRTIs in treatment-naive adults with HIV-1. All dolutegravir doses led to similarly high proportions (≥88%) of participants with plasma HIV RNA concentrations of less than 50 copies per mL by week 16, which were maintained to week 48.

The rate of viral decay was much faster in the dolutegravir groups than in the efavirenz group, and was similar to that reported for raltegravir.[2,15] The rapid antiviral response might relate to the favourable CD4 cell responses noted in the dolutegravir groups. The long-term clinical significance for rapid viral-load decline remains undefined but might have important implications in patients in whom rapid virological suppression is desirable (eg, late-presenting pregnant women infected with HIV). Our interim analysis from SPRING-1 supports in-vitro experiments that suggest the possibility of a higher barrier to resistance for dolutegravir than for raltegravir; so far, no treatment-emergent integrase mutations have been detected.[7]

All doses of dolutegravir in combination with dual NRTI were well tolerated. Drug-related adverse events that were more common with dolutegravir than efavirenz were self-limited headache and nausea (primarily grade 1; not dose limiting). More participants in the efavirenz group experienced well described neuropsychiatric adverse events and rash and discontinued because of tolerability or safety events.

The small, non-progressive increases in serum creatinine recorded across dolutegravir doses are consistent with pharmacological inhibition of tubular creatinine secretion via the organic cation transporter OCT2 (similar to cimetidine or trimethoprim).[16,17] In-vitro studies have confirmed that dolutegravir is a potent inhibitor of human OCT2 at clinically relevant concentrations, and a study of healthy participants confirmed that dolutegravir had no significant effect on glomerular filtration rate or effective renal plasma flow compared with placebo over 14 days.[18]

As expected, no relation between exposure and response was noted in our study because of our use of combination therapy and because all doses of dolutegravir were predicted to yield exposures on the plateau of the exposure–response curve.[8] Indeed, dolutegravir trough concentrations in our study were four to 19 times higher than protein-adjusted IC_{90} (64 ng/mL; table 4). The three participants with virological failure while on dolutegravir had similar drug exposure to others, and one had documented study medication non-compliance.

Our dose-selection strategy for dolutegravir was to select the maximum tolerated dose to compensate for potential reductions in exposure caused by drug interactions without the need for dose adjustment. Additionally, higher doses might ensure durability of response in patients who have not received integrase inhibitors before. Because we recorded similar efficacy, safety, and tolerability across all three dolutegravir doses at week 16 and to week 48, we selected the 50 mg once daily dose and it is currently being assessed in phase 3 clinical studies.

We carefully assessed the reporting of adverse events to understand if the partly-masked nature of our study contributed to under-reporting of adverse events for an investigational drug without an established safety profile. We noted the opposite in the reporting of headache (all grades): 14% of participants in the dolutegravir groups reported headache but only one (2%) in the efavirenz group. This finding differs from efavirenz product labels that suggest 2–8% of

Panel: Research in context

Systematic review

We searched PubMed for reports published up to Oct 12, 2011, with the MeSH terms "HIV integrase inhibitors" and "phase 2 clinical trials". We identified three studies, two of which were reports on raltegravir used in patients that had been previously treated with antiretroviral drugs,[20,21] and one that reported on the use of elvitegravir in patients with HIV with previous virological failure due to the development of drug resistance.[22] Our study is the first phase 2b trial to report on antiretroviral combination therapy with dolutegravir in populations of patients with HIV who have not been previously treated. An additional search with the MeSH terms "dolutegravir", "S/GSK1349572", or both, identified an additional 18 reports all focusing either on in-vitro data or on the pharmacology, drug resistance, or both, of dolutegravir. This additional search has been confirmed by representatives of the companies involved in the development of dolutegravir (GSK, Shinogi, ViiV Healthcare).

Interpretation

Antiretroviral combination therapy against HIV has been extended by a new drug class that inhibits the integration of proviral DNA into the host genome. So far, raltegravir is the only licensed inhibitor of HIV integrase that is approved for use in populations of patients that are both previously untreated and treated. Two other integrase inhibitors are in later stages of clinical development at present: elvitegravir and dolutegravir. All integrase inhibitors have a unique antiviral profile with a very rapid decay of viral load in previously untreated patients when combined with other antiretroviral drugs. Potential advantages of dolutegravir include once daily application as a single tablet, no need for pharmacological boosting, established dose–response characteristics, higher genetic barrier to resistance, and good tolerability. On the basis of our findings, this new compound is being carried forward into larger phase 3 studies both in previously untreated and treated patients. The toxicity profile needs to be confirmed in these larger studies. Moreover, more studies are needed to exclude major pharmacological interactions. If the favourable findings of our study are confirmed by ongoing phase 3 trials, dolutegravir has the potential to be used as a first-line option and a salvage therapy in a substantial proportion of individuals with HIV.

participants in clinical trials reported headaches of grade 2 or higher intensity.[19] Our phase 2 study enrolled a restricted number of participants and as such, does not fully characterise the safety and efficacy profile of dolutegravir, and our study was not powered to rule out all potential differences. Additionally, although consistent with other phase 2 trials (panel), the proportion of women enrolled into our trial is not representative of the general disease population. On the basis of the metabolic pathway for dolutegravir, we do not anticipate significant sex differences; however, large, fully powered phase 3 trials are needed and are underway to provide more generalisable information.

Contributors

The SPRING-1 investigators enrolled patients in the study and collected clinical data. SA and IS did the analyses. JKR and JvL contributed scientific expertise. All authors contributed to the data interpretation. The report was drafted by CB and JvL. All authors reviewed the report and have seen and approved the final version.

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Conflicts of interest

JvL has served as a consultant for and has received honoraria and travel grants from Abbott Laboratories, Boehringer Ingelheim GmbH, Bristol-Myers Squibb (BMS), GSK, Janssen-Cilag Inc, Merck Sharp & Dohme Corp, Pfizer Inc, ViiV Healthcare, Gilead Sciences Inc, and Roche. FM has served as a consultant on advisory boards for Boehringer Ingelheim GmbH, BMS, Gilead Sciences Inc, GSK, Merck Sharp & Dohme Corp, Roche, and Tibotec; he has received lecture fees from Abbott, Bayer, BMS, Gilead Sciences Inc, GSK, Merck Sharp & Dohme Corp, Pfizer, and Roche; and he has received research and educational grants from Boehringer Ingelheim GmbH, BMS, Gilead Sciences Inc, GSK, Janssen-Cilag, and Roche. JRA has received advisory and speaker fees as well as grant support from ViiV Healthcare, Tibotec, Janssen, Abbott, BMS, Gilead Sciences Inc, and Merck Sharp & Dohme Corp. AR is employed by the St Petersburg Healthcare Committee. PY has received support to travel to meetings from ViiV Healthcare, Gilead Sciences Inc, and BMS; he has been a consultant for Gilead Sciences Inc, BMS, and Merck Sharp & Dohme Corp; he has received grants from ViiV Healthcare, Gilead Sciences Inc, BMS, Merck Sharp & Dohme Corp, GSK, and Tibotec. BY is an advisory board member for BMS, Cerner Corporation, GSK, Merck & Co, and ViiV Healthcare; he has received grants or research funding from BMS Company, Cerner Corporation, Gilead Sciences, GSK, Hoffman-LaRoche, and Merck & Co; he has been on the speakers bureau for GSK, Merck & Co, ViiV Healthcare; he has received payment for the development of educational presentations from TheBody.com, Health Connections International, and ViiV Healthcare. JKR has received consultant fees from GSK, Abbott Laboratories, Bionor Laboratories AS, BMS, Boehringer Ingelheim GmbH, Gilead Sciences Inc, Merck Sharp & Dohme Corp, Novartis, Pfizer Inc, Roche, Tibotec, and ViiV Healthcare; he has received grants from Abbott Laboratories, Merck Sharp & Dohme Corp, and Roche; he has received payment for lectures and for being on the speakers bureau for GSK, Abbott Laboratories, BMS, Boehringer Ingelheim GmbH, Gilead Sciences Inc, Merck Sharp & Dohme Corp, Novartis, Pfizer Inc, Roche, Tibotec, and ViiV Healthcare; and he has received payment for development of educational presentations for Abbott Laboratories and Viral Ed. SA, IS, CB, and SM are employees of GSK and own GSK stock and stock options.

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