



Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial

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Summary

Background In the primary analysis of SPRING-2 at week 48, dolutegravir showed non-inferior efficacy to and similar tolerability to raltegravir in adults infected with HIV-1 and naive for antiretroviral treatment. We present the 96 week results.

Methods SPRING-2 is an ongoing phase 3, randomised, double-blind, active-controlled, non-inferiority study in treatment-naive adults infected with HIV-1 that started in Oct 19, 2010. We present results for the safety cutoff date of Jan 30, 2013. Patients had to be aged 18 years or older and have HIV-1 RNA concentrations of 1000 copies per mL or more. Patients were randomly assigned (1:1) to receive either dolutegravir (50 mg once daily) or raltegravir (400 mg twice daily), plus investigator-selected tenofovir–emtricitabine or abacavir–lamivudine. Prespecified 96 week secondary endpoints included proportion of patients with HIV-1 RNA less than 50 copies per mL, CD4 cell count changes from baseline, safety, tolerability, and genotypic or phenotypic resistance. We used an intention-to-treat exposed population (received at least one dose of study drug) for the analyses. Sponsor staff were masked to treatment assignment until primary analysis at week 48; investigators, site staff, and patients were masked until week 96. This study is registered with ClinicalTrials.gov, NCT01227824.

Findings Of 1035 patients screened, 827 were randomly assigned to study group, and 822 received at least one dose of the study drug (411 patients in each group). At week 96, 332 (81%) of 411 patients in the dolutegravir group and 314 (76%) of 411 patients in the raltegravir group had HIV-1 RNA less than 50 copies per mL (adjusted difference 4·5%, 95% CI –1·1% to 10·0%) confirming non-inferiority. Secondary analyses of efficacy such as per protocol (HIV RNA <50 copies per mL: 83% for dolutegravir and 80% for raltegravir) and treatment-related discontinuation equals failure (93% without failure for dolutegravir; 91% for raltegravir) supported non-inferiority. Virological non-response occurred less frequently in the dolutegravir group (22 [5%] patients for dolutegravir vs 43 [10%] patients for raltegravir). Median increases in CD4 cell count from baseline were similar between groups (276 cells per μ L for dolutegravir and 264 cells per μ L for raltegravir). Ten patients (2%) in each group discontinued because of adverse events, with few such events between weeks 48 and 96 (zero in the dolutegravir group and one in the raltegravir group). No study-related serious adverse events occurred between week 48 and week 96. At virological failure, no additional resistance to integrase inhibitors or nucleotide reverse transcriptase inhibitors was detected since week 48 or in any patient receiving dolutegravir.

Interpretation At week 96, once-daily dolutegravir was non-inferior to twice-daily raltegravir in treatment-naive, patients with HIV-1. Once-daily dosing without requirement for a pharmacokinetic booster makes dolutegravir-based therapy an attractive treatment option for HIV-1-infected treatment-naive patients.

Funding ViiV Healthcare.

Introduction

HIV integrase inhibitors are a promising new class of antiretroviral drugs with reported potency and a favourable safety profile. The first two approved integrase inhibitors, raltegravir (Isentress; Merck & Co, Inc, Whitehouse Station, NJ, USA) and elvitegravir are effective but have some limitations. Although well tolerated, raltegravir requires twice-daily doses and has a low genetic barrier to resistance compared with ritonavir-boosted protease inhibitors.^{1–3} Elvitegravir (as coformulated with cobicistat,

tenofovir, and emtricitabine; Stribild; Gilead Sciences, Inc, Foster City, CA, USA) must be taken with food, requires pharmacological boosting that can lead to substantial drug interactions, has a low genetic barrier to resistance compared with ritonavir-boosted protease inhibitors, and is available only as a fixed-dose combination of tenofovir, emtricitabine, elvitegravir, and cobicistat with a possible increased risk of proximal renal tubulopathy.^{4–6}

Dolutegravir is a next-generation integrase inhibitor with a plasma half-life of 14 h, which supports once-daily

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See [Comment](#) page 908

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dosing without pharmacological boosting.⁷⁻⁹ No relevant inhibition or induction of cytochrome P450 or food effect has been reported, suggesting low potential for interactions.^{7,10}

Results from the week 48 primary analysis for SPRING-2¹¹ showed that dolutegravir provides non-inferior efficacy compared with raltegravir in antiretroviral-naïve patients, with a similar safety profile.¹¹ Here, we provide longer-term efficacy and safety data from the week 96 analysis of SPRING-2, the first phase 3 study in treatment-naïve patients assessing dolutegravir versus raltegravir in combination with the two most widely recommended nucleoside reverse transcriptase inhibitor (NRTI) backbones.

Methods

Study design and participants

SPRING-2 (ING113086) is an ongoing phase 3, randomised, double-blind, active-controlled, double-placebo, multicentre, parallel-group, non-inferiority study that started on Oct 19, 2010. Adults (aged ≥ 18 years) naïve for antiretroviral therapy with HIV-1 infection and HIV-1 RNA of 1000 copies per mL or more were recruited from 100 sites in Australia, Europe, Canada, and the USA. Study methods and eligibility criteria have been published previously.¹¹ Results presented here are through the safety cutoff date of Jan 30, 2013.

We obtained ethics committee approval at all participating centres in accordance with the principles of the 2008 Declaration of Helsinki. All patients provided written informed consent before undergoing any protocol-specified procedures.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily and matching placebo. The study drugs were given with an investigator-selected NRTI backbone of coformulated tenofovir-emtricitabine (Truvada; Gilead Sciences) or abacavir-lamivudine (Epzicom-Kivexa; ViiV Healthcare, Research Triangle Park, NC, USA).

Centralised computer-generated randomisation included stratification by HIV-1 RNA ($\leq 100\,000$ copies per mL and $>100\,000$ copies per mL) and NRTI backbone (tenofovir/emtricitabine or abacavir/lamivudine). Investigators had knowledge of screening HIV-1 RNA results before randomisation. Through week 96, matching placebo was given with masked dolutegravir or raltegravir. Placebo for dolutegravir was formulated to visually match the active tablets. Raltegravir was provided as overcoated 400 mg tablets; placebo for raltegravir was formulated to visually match the overcoated raltegravir active tablets. Sponsor staff were masked to treatment assignment until the week 48 primary analysis; investigators, site staff, and patients were masked until week 96.

Procedures

As a prespecified secondary objective of SPRING-2, the endpoint analyses done at week 48 were repeated at week 96. The main week 96 endpoint was the proportion of participants with HIV-1 RNA less than 50 copies per mL, with a 10% non-inferiority margin. Additional week 96 endpoints included changes from baseline in CD4 cell count, incidence and severity of adverse events, changes in laboratory variables, and genotypic or phenotypic evidence of resistance.

Study visits occurred at baseline, weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter. We assessed treatment compliance by pill count at every visit. We measured plasma HIV-1 RNA concentration with the Abbott RealTime HIV-1 PCR assay (Abbott Molecular, Inc., Des Plaines, IL, USA). Protocol-defined virological failure (PDVF) consisted of two consecutive plasma HIV-1 RNA values of 50 copies per mL or greater, on or after week 24 through to week 48; these patients were withdrawn from the study. After week 48, patients whose plasma HIV-1 RNA was 50 to less than 200 copies per mL could remain on study at the investigator's discretion, and withdrawal was mandatory for HIV-1 RNA of 200 copies per mL or greater. We measured CD4 cell count and percentage at every study visit (except week 2).

We analysed viral genotype (reverse transcriptase and protease) by Quest Diagnostics (Valencia, CA, USA) at screening. For patients with PDVF, we analysed plasma samples stored at baseline and taken at the time of confirmed virological failure for reverse transcriptase and integrase genotype and phenotype with GenoSure, Standard Phenosense, GeneSeq Integrase, and PhenoSense Integrase assays (Monogram Biosciences, San Francisco, CA, USA).

We assessed safety as described previously¹¹ and continued to week 96. We took electrocardiographs (ECGs) at baseline and week 96 (or at withdrawal for patients who discontinued prematurely). To assure patient safety, we implemented safety stopping criteria.

Statistical analyses

The analysis for the primary endpoint was described previously.¹¹ Assuming a 75% response rate in the raltegravir group, the study required 394 patients per group to have 90% power with a 10% non-inferiority margin and a one-sided 2.5% significance level. This response rate assumption also yielded 90% power or more with a 10% non-inferiority margin for the week 96 timepoint.

Efficacy and safety analyses were based on the intention-to-treat exposed or safety populations, which both included all randomised patients who received at least one dose of study medication.

For the snapshot algorithm, as codified by the US Food and Drug Administration (FDA), we counted as responders those patients whose last HIV-1 RNA result was lower than 50 copies per mL in the analysis window

(ie, 96±6 weeks); we counted patients who were not suppressed or did not have data at the analysis timepoint as non-responders. Of note, after the week 48 analysis was completed, the sponsor became aware of issues of non-compliance to good clinical practice at one site in Russia, where 14 patients (eight assigned to dolutegravir, six assigned to raltegravir) were enrolled. Because of these findings, the site subsequently closed, and these patients were counted as non-responders in the week 96 analysis. Non-compliance to good clinical practice was site-specific and did not affect study conduct at other participating sites. ViiV Healthcare, the sponsor of the study, used a robust auditing and monitoring programme to manage the trial and correct issues in real time.

The protocol permitted one switch in backbone NRTI for the management of toxic effects; the snapshot algorithm recorded patients switching NRTIs after week 4 as non-responders. We based the adjusted difference (between dolutegravir and raltegravir) in the proportions on a stratified analysis using Cochran-Mantel-Haenszel weights for baseline HIV-1 RNA and investigator-selected NRTIs.

We compared antiviral activity over time using summaries of the proportions of responders and summaries of plasma HIV-1 RNA values, presented by treatment group and visit. We based the proportions of responders on thresholds of 50 copies per mL and 400 copies per mL (snapshot algorithm) and summarised by visit.

Prespecified secondary efficacy analyses included per-protocol analysis and Kaplan-Meier estimates of the proportion of patients without failure related to treatment or efficacy by week 96.

For the analysis of treatment-related discontinuation equals failure, we calculated the time to PDVF or discontinuation as a result of treatment-related reasons (ie, drug-related adverse events, protocol-defined safety stopping criteria, or lack of efficacy). Patients who discontinued for reasons other than those related to treatment were censored at the time of discontinuation. For the analysis of efficacy-related discontinuation equals failure, we calculated the time to PDVF or discontinuation because of lack of efficacy. We censored patients who discontinued for reasons other than no efficacy at the time of discontinuation. The per-protocol population consisted of patients in the intention-to-treat exposed population with the exception of those with a protocol deviation who met prespecified criteria, such as non-compliance with study medication. We used the data of per-protocol population and assessments of treatment-related discontinuation equals failure and efficacy-related discontinuation equals failure as supporting analyses for the primary endpoint at week 48 and for a secondary endpoint at week 96.

We compared immunological activity over time by use of summaries of CD4 cell counts and changes from baseline at every visit. We assessed tolerability and safety of dolutegravir compared with raltegravir over 96 weeks

by prevalence of adverse events and serious adverse events and graded laboratory toxic effects.

We compared the proportions of patients with both PDVF and treatment-emergent genotypic or phenotypic evidence of resistance to integrase inhibitors to assess the development of resistance. This study is registered with ClinicalTrials.gov, number NCT01227824.

Role of funding source

ViiV Healthcare and GlaxoSmithKline participated in the study design, data collection, analysis and interpretation, and writing of this report. All authors had full access to all the data in the study and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility to submit for publication.

Results

Of the 1035 patients screened, 827 were randomly assigned to treatment, and 822 received at least one dose of study medication (411 in each group; figure 1). Baseline demographics and disease characteristics were balanced across treatment groups and were presented previously.¹¹ Patients predominantly had HIV-1 subtype B, with A1 being the next most common.¹¹ In other patients, various subtypes were noted in small numbers, including AG, BF, C, F1, and G. HIV-1 subtype did not affect treatment response to dolutegravir or raltegravir over time (data not shown).

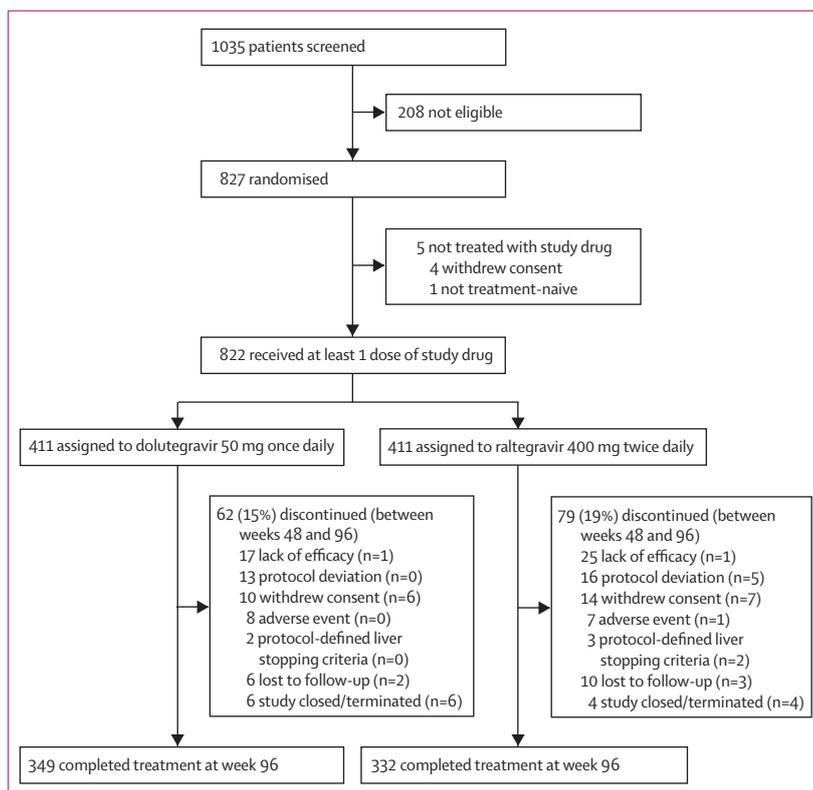


Figure 1: Trial profile at week 96

At week 48, we noted non-inferior virological response of dolutegravir.¹¹ The proportion of patients achieving the primary endpoint of HIV-1 RNA lower than 50 copies per mL (FDA snapshot) by week 48 in the dolutegravir group was similar to that in the raltegravir group (table 1; adjusted treatment difference 2.4%, 95% CI -2.2 to 7.1), which confirmed non-inferiority because the lower end of the 95% CI was greater than -10%.¹¹ We reached the same non-inferiority conclusion at week 96, with 332 (81%) of 411 patients in the dolutegravir group and 314 (76%) of 411 patients in the raltegravir group with HIV-1 RNA of less than

50 copies per mL and an adjusted difference of 4.5% (95% CI -1.1 to 10.0; figure 2, table 1). The difference between week 48 and week 96 responses was driven mainly by discontinuations for reasons other than adverse events (table 1); the proportion of virological non-response was unchanged for dolutegravir from week 48 to week 96, whereas it rose by 2% for raltegravir from week 48 to week 96 (table 1).

Secondary efficacy analyses were supportive of the primary results (table 2). Analyses of virological outcomes by baseline viral load or NRTI backbone also support non-inferiority of dolutegravir versus raltegravir (table 2). Virological responses (snapshot) by NRTI were affected by discontinuations for other reasons; all 14 patients at the closed site were on abacavir-lamivudine (because tenofovir-emtricitabine was not available in Russia when the study started) and were included in the discontinued for other reason category by week 96 (table 1). Subgroup analyses of virological non-responders (snapshot) that combine baseline viral load strata and backbone NRTI, however, showed similar numbers of virological non-responders between groups (table 3).

Median CD4 cell counts increased from baseline to week 96 (increase of 276 cells per μ L for dolutegravir and 264 cells per μ L for raltegravir). The proportions of patients with virological response were much the same across CD4 cell count subgroups. Although in patients with baseline CD4 cell counts lower than 350 cells per μ L, 155 (78%) of 199 in the dolutegravir group had virological responses compared with 131 (69%) of 189 in the raltegravir group; and in those with CD4 cell counts lower than 200 cells per μ L, 39 (71%) of 55 and 28 (56%) of 50 had virological response.

| | Dolutegravir group (n=411) | | Raltegravir group (n=411) | |
|---------------------------------------------------------------------|----------------------------|-----------|---------------------------|-----------|
| | Week 48 | Week 96 | Week 48 | Week 96 |
| Virological success | 361 (88%) | 332 (81%) | 351 (85%) | 314 (76%) |
| Virological non-response† | 20 (5%) | 22 (5%) | 31 (8%) | 43 (10%) |
| Data in window not <50 copies per mL | 8 (2%) | 6 (1%) | 5 (1%) | 12 (3%) |
| Discontinued for lack of efficacy | 5 (1%) | 9 (2%) | 13 (3%) | 14 (3%) |
| Discontinued for other reason while HIV-1 RNA not <50 copies per mL | 2 (<1%) | 2 (<1%) | 11 (3%) | 14 (3%) |
| Change in antiretroviral therapy | 5 (1%) | 5 (1%) | 2 (<1%) | 3 (<1%) |
| No virological data at week 96 | 30 (7%) | 57 (14%) | 29 (7%) | 54 (13%) |
| Discontinued because of adverse event or death | 9 (2%) | 10 (2%) | 6 (1%) | 10 (2%) |
| Discontinued for other reason‡ while HIV-1 RNA <50 copies per mL | 21 (5%) | 40 (10%) | 23 (6%) | 41 (10%) |
| Missing data during window but on study | 0 | 7 (2%) | 0 | 3 (<1%) |

Data are number of participants (%). *Week 48 data were previously reported.¹¹ †Virological failure. ‡Other reasons include protocol deviation, lost to follow-up, and withdrawal of consent.

Table 1: Snapshot outcomes for plasma HIV-1 RNA <50 copies per mL at weeks 48* and 96

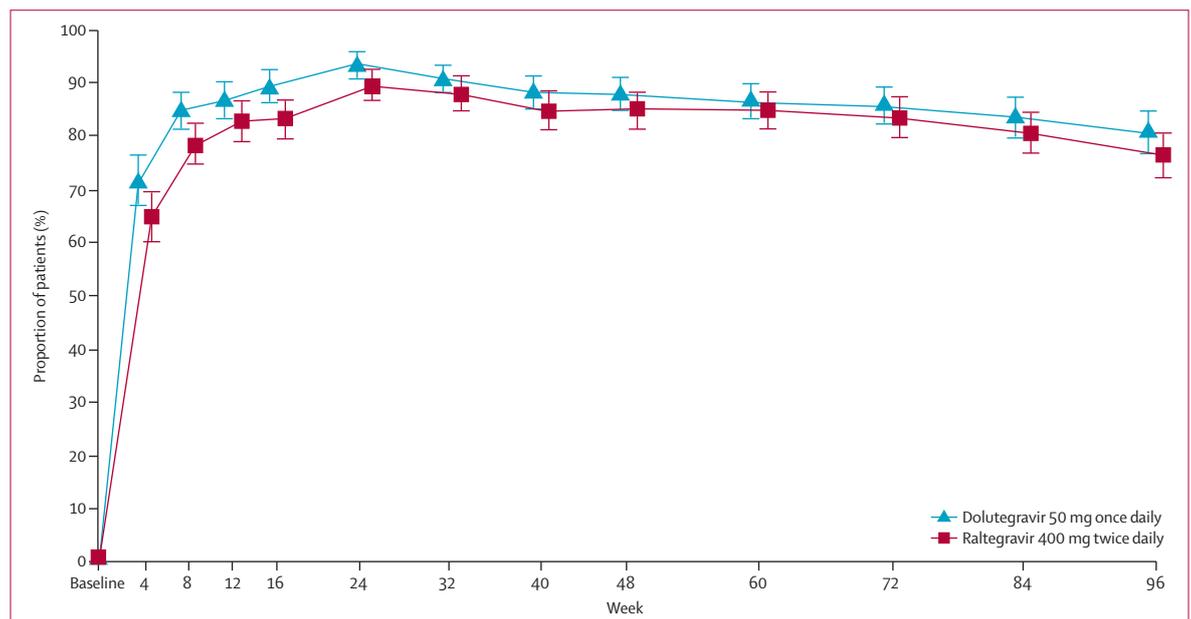


Figure 2: Proportion of patients with less than 50 copies of HIV-1 RNA per mL, by visit
Data are % (95% CI). Snapshot (missing, switch, discontinuation=failure) analysis.

As noted at week 48, the dolutegravir group had fewer PDVFs than did the raltegravir group (table 4). Most patients who met criteria for PDVF had low viraemia. All 22 PDVFs in the dolutegravir group were in patients who had viral loads less than 1000 copies per mL, of whom 17 (77%) had less than 200 copies per mL at confirmed failure. In the raltegravir group, three (10%) of the 29 patients who had PDVFs had more than 10 000 copies per mL at confirmed failure, and 22 (76%) had less than 200 copies per mL. No dolutegravir patients had treatment-emergent integrase or NRTI resistance compared with one patient (5%) resistant to integrase and four patients (20%) resistant to NRTIs in the raltegravir group (table 4). Resistance in these raltegravir PDVFs all occurred during the first 48 weeks.¹¹

Tolerability and safety of dolutegravir versus raltegravir continued to be similar to 96 weeks, with comparable rates of adverse events of all grades across treatment groups, and equivalent low occurrence of adverse events leading to discontinuation in both groups (ten patients [2%] in each group). The number of patients discontinuing for adverse events between weeks 48 and 96 were zero for dolutegravir and three for raltegravir (figure 1). The adverse event profile at week 96 was similar to that reported at week 48;¹¹ the most common clinical adverse events were nausea (dolutegravir 15% and raltegravir 14%), nasopharyngitis (13% and 14%), diarrhoea (14% and 13%), and headache (14% and 13%; appendix). A high proportion of events reported in both treatment groups were classified as grade 1 or 2 in intensity (74% [303/411] in the dolutegravir group, 73% [302/411] in the raltegravir group). No deaths or serious adverse events related to study drug occurred between the week 48 and week 96 analyses.

Rates of graded laboratory toxic effects were similar between treatment groups. We noted no evidence of clinically significant changes over time in the fasting lipid profile in either group. Patients receiving dolutegravir had small mean increases in serum creatinine that were evident by week 2 and remained stable through week 96; the raltegravir group showed smaller increases in creatinine that also remained stable (figure 3). The mean change from baseline in serum creatinine was 12.3 µmol/L at week 48 and 14.6 µmol/L at week 96 for dolutegravir versus 4.7 µmol/L at week 48 and 8.2 µmol/L at week 96 for raltegravir. Few treatment-emergent creatinine toxic effects of grade 1 (14 patients in the dolutegravir group, eight patients in the raltegravir group), grade 2 (one patient in the dolutegravir group), and grade 4 (one patient in the raltegravir group) were noted. Mean change in estimated creatinine clearance calculated by the Cockcroft-Gault formula at week 96 was -19.6 mL/min in the dolutegravir group and -9.3 mL/min in the raltegravir group.

Median change from baseline in urine albumin to creatinine ratio was no different between groups:

| | Dolutegravir group (n=411) | Raltegravir group (n=411) | Difference in proportion (95% CI) |
|------------------------------------------------------|----------------------------|---------------------------|-----------------------------------|
| Per protocol, HIV-1 RNA <50 copies per mL at week 96 | 328/393 (83%) | 311/387 (80%) | 3.2 (-2.1 to 8.6)* |
| Kaplan-Meier proportion without failure (%) | | | |
| TRDF† | 92.9% (89.9 to 95.0) | 90.6% (87.2 to 93.1) | 2.3 (-1.5 to 6.2) |
| ERDF‡ | 94.1% (91.2 to 96.0) | 92.3% (89.1 to 94.5) | 1.8 (-1.7 to 5.4) |
| Baseline plasma HIV-1 RNA (snapshot) | | | |
| ≤100 000 copies per mL | 243/297 (82%) | 241/295 (82%) | 0.1 (-6.1 to 6.3) |
| >100 000 copies per mL | 89/114 (78%) | 73/116 (63%) | 15.1 (3.5 to 26.8) |
| Backbone dual NRTI¶ (snapshot) | | | |
| Abacavir-lamivudine | 125/169 (74%) | 124/164 (76%) | -1.6 (-11.0 to 7.7) |
| Tenofovir-emtricitabine | 207/242 (86%) | 190/247 (77%) | 8.6 (1.7 to 15.5) |

Data are % (95% CI) or n/N (%). TRDF=treatment-related discontinuation equals failure. ERDF=efficacy-related discontinuation equals failure. NRTI=nucleotide reverse transcriptase inhibitor. *Adjusted difference, based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background NRTI. †Protocol-defined virological failure or withdrawal because of drug-related adverse event, safety stopping criteria, or lack of efficacy. ‡Protocol-defined virological failure or withdrawal because of lack of efficacy. §Unadjusted difference in proportion, p-value test for homogeneity. ¶NRTI group based on initial treatment assignment.

Table 2: Treatment differences at week 96, by sensitivity analyses and strata

| | Dolutegravir group (n=411) | Raltegravir group (n=411) |
|-------------------------------------------|----------------------------|---------------------------|
| Baseline HIV-1 RNA ≤100 000 copies per mL | 10/297 (3%) | 17/295 (6%) |
| Baseline HIV-1 RNA >100 000 copies per mL | 12/114 (11%) | 26/116 (22%) |
| Abacavir-lamivudine | 10/169 (6%) | 16/164 (10%) |
| Tenofovir-emtricitabine | 12/242 (5%) | 27/247 (11%) |
| Baseline HIV-1 RNA ≤100 000 copies per mL | | |
| Abacavir-lamivudine | 6/132 (5%) | 8/125 (6%) |
| Tenofovir-emtricitabine | 4/165 (2%) | 9/170 (5%) |
| Baseline HIV-1 RNA >100 000 copies per mL | | |
| Abacavir-lamivudine | 4/37 (11%) | 8/39 (21%) |
| Tenofovir-emtricitabine | 8/77 (10%) | 18/77 (23%) |

Data are number of participants (%). NRTI=nucleotide reverse transcriptase inhibitor.

Table 3: Virological non-responders (snapshot) at week 96

See Online for appendix

0.00 mg/mmol (IQR -0.30 to 0.20) for dolutegravir and 0.00 mg/mmol (-0.20 to 0.20) for raltegravir. Overall, no discontinuations were due to renal events through 96 weeks.

Similar numbers of patients in every treatment group had maximum treatment-emergent rises in alanine transaminase three times or more the upper limit of normal (ULN; appendix). Details of clinically relevant liver chemistry rises were previously described;¹¹ no new events of alanine transaminase five times or more the ULN were identified in this week 96 analysis. Two additional patients receiving raltegravir were withdrawn because they met liver stopping criteria. One patient was identified as meeting these criteria in the week 48

analysis but had not yet been withdrawn, and after week 48, one additional patient had an alanine transaminase elevation of roughly more than four times ULN with accompanying rash, which was deemed secondary to hepatitis C and alcohol use, and led to withdrawal from the study.

We identified no clinically significant patterns of changes in vital signs or ECGs in either group. One patient only in the dolutegravir group developed Fridericia's corrected QT (QTcF) values higher than 500 ms (appendix), and changes from baseline in QTcF values were low (mean changes were 6.9 ms [SD 24.55] for dolutegravir and 3.6 msec [23.18] for raltegravir).

Discussion

Supporting the week 48 primary analysis, dolutegravir 50 mg once daily was again non-inferior to raltegravir 400 mg twice daily when given in combination with coformulated tenofovir–emtricitabine or abacavir–lamivudine. The change in response rates from week 48 to week 96 mostly was due to discontinuations after week 48 for administrative reasons (ie, not related to efficacy or tolerability). SPRING-2 is to our knowledge the first randomised, double-blind trial in HIV-1-infected, treatment-naive patients to compare the efficacy and safety of two regimens containing integrase inhibitors (panel). The integrase inhibitor class offers a valuable long-term treatment option for HIV-1-infected patients, providing high antiviral potency and a favourable safety profile.

Non-inferiority of dolutegravir to raltegravir was further supported by additional secondary efficacy analyses. Within treatment groups, virological non-response was similar for abacavir–lamivudine and tenofovir–emtricitabine. Snapshot responses for the NRTI combinations varied because of differences in discontinuations for other reasons while HIV-1 RNA was less than 50 copies per mL, some of which were driven by the site closure in Russia, where all patients were receiving abacavir–lamivudine and were deemed non-responders in snapshot analysis. We did ad-hoc analyses excluding patients from this site, with no change to the non-inferiority conclusions at week 48 and week 96.

Coupled with a high response rate, the results for this study were well within the margin of non-inferiority.¹⁵ The response rates for this study were consistent with the STARTMRK trial¹² week 96 response rate for raltegravir 400 mg twice daily (81%) in treatment-naive adults.

| | Dolutegravir group (n=411) | | Raltegravir group (n=411) | |
|---------------------------------------------------------------------------------|----------------------------|-------------------------|---------------------------|-------------------------|
| | During first 48 weeks | Between weeks 48 and 96 | During first 48 weeks | Between weeks 48 and 96 |
| PDFV | 20 (5%) | 2 (<1%) | 28 (7%) | 1 (<1%) |
| Integrase genotype results at baseline and time of PDFV | 8 (40%) | 2 (100%) | 18 (64%) | 1 (100%) |
| Emergent INI-resistance mutations | 0 | 0 | 1 (6%) | 0 |
| Protease or reverse transcriptase genotype results at baseline and time of PDFV | 12 (60%) | 2 (100%) | 19 (68%) | 1 (100%) |
| NRTI-resistance mutations | 0 | 0 | 4 (21%)* | 0 |

INI=integrase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PR=protease. PDFV=protocol-defined virological failure. RT=reverse transcriptase. *One participant had INI-resistance mutations T97T/A, E138E/D, V151V/I, and N155H, and NRTI-resistance mutations A62A/V, K65K/R, K70K/E, and M184V; one participant had NRTI-resistance mutation M184M/I; one participant had NRTI-resistance mutation A62A/V; and one participant had NRTI-resistance mutation M184M/V.

Table 4: Genotype analysis at PDFV

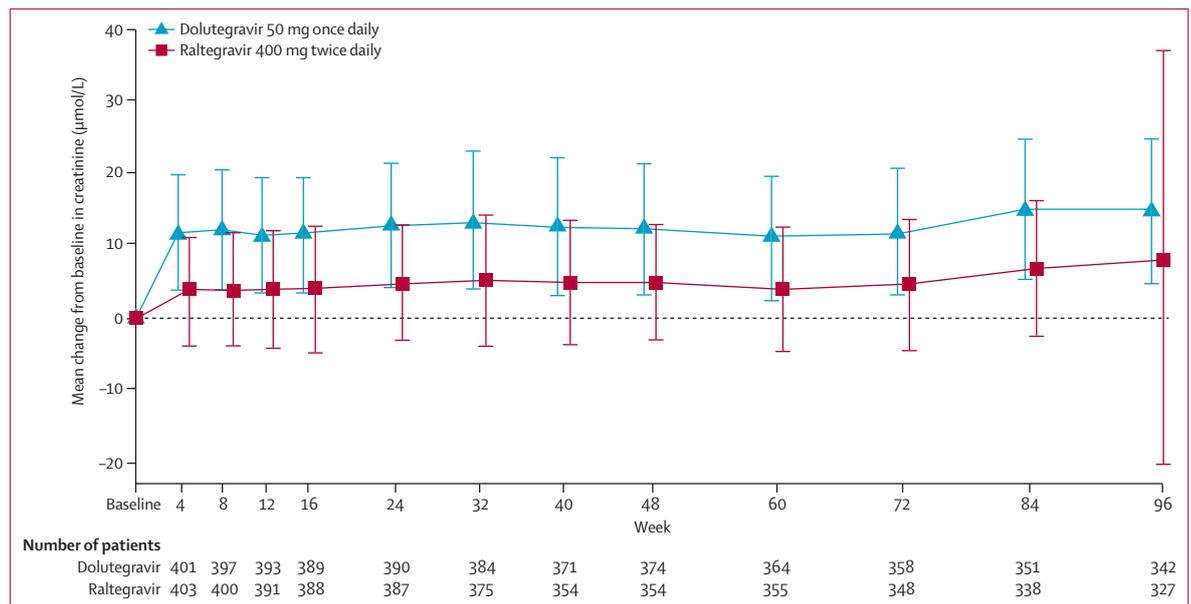


Figure 3: Mean change in serum creatinine over time
Error bars indicate standard deviations.

CD4 cell count increases were similar between groups. The proportion of patients with clinically optimum CD4 cell counts (ie, greater than 500 cells per μL) at week 96 was high and similar in both groups, providing further benefit of this integrase inhibitor-containing regimen strategy. We noted at week 96 that exploratory analysis of efficacy in patients with low baseline CD4 cell count showed a higher response rate for dolutegravir than for raltegravir, confirming the trend observed at week 48.

After week 48, there were only three additional PDVFs (two dolutegravir, one raltegravir), with no integrase inhibitor or NRTI resistance detected in any of these three. Thus, the resistance results from week 96 confirm absence of resistance to integrase inhibitors or the NRTI backbone in patients from the dolutegravir group. This is consistent with *in vitro* studies¹⁶ wherein highly resistant mutants were not selected when virus was passaged in the presence of dolutegravir, and single mutations in the integrase gene were associated with only low-level resistance to dolutegravir. Similarly, at week 96 in the phase 2b SPRING-1 study,^{17,18} no patients receiving dolutegravir 50 mg once daily experienced PDVF or resistance to integrase inhibitors or NRTIs. The lower viral loads (eg, between 50 copies per mL and 200 copies per mL) at PDVF in SPRING-2 could have affected the ability of resistance assays to detect clinically relevant genotypic or phenotypic changes. Additionally, the level of residual viraemia at failure, lower with dolutegravir than with raltegravir, theoretically could affect the emergence of resistance. From a clinical standpoint, however, the robustness of dolutegravir in the prevention of virological resistance is unique to the integrase inhibitor class and confers a specific advantage to this molecule.

The tolerability and safety of dolutegravir and raltegravir were similar in terms of frequency and nature of adverse events through 96 weeks, including changes in key laboratory variables. Between weeks 48 and 96, incidence of alanine transaminase three times higher than ULN, or more, was low in both groups, and only two additional patients, both in the raltegravir group, discontinued therapy for toxic effects on the liver. Overall, the risk of drug-induced liver injury over 96 weeks was similar for dolutegravir and raltegravir.¹⁹ Both raltegravir and dolutegravir had a favourable effect on lipids. The absence of cardiovascular events in the study, and more specifically, in the abacavir–lamivudine subgroup, does not allow conclusions to be made, because of the small sample size and duration of follow-up. Although the D:A:D cohort study²⁰ suggested a link between abacavir exposure and increased risk of myocardial infarction, the conclusions of an FDA meta-analysis²¹ showed no increased risk of cardiovascular complications with abacavir use.

Changes in serum creatinine for dolutegravir were consistent with previous findings.^{17,18} Dolutegravir inhibits the organic anion transporter OCT2, similar to

Panel: Research in context

Systematic review

We searched PubMed with the keywords “integrase strand transfer inhibitors”, “integrase inhibitors”, and “clinical trials” for papers published in English between Jan 1, 2006, and July 15, 2013. Antiretroviral therapy is now recommended for all HIV-infected individuals to reduce the risk of disease progression and for the prevention of transmission of HIV. Several antiretrovirals have been authorised for use in first-line therapy on the basis of 48 week data. However, as HIV treatment is lifelong, effort is still required to best select initial combination of antiretroviral drugs and to try to avoid changing the regimen too frequently. Information on longer-term follow-up on initial regimens is very useful in this regard, since it shows whether these regimens are sustainable, convenient, and free of new emerging side-effects, allowing for planning for long-term anticipated success and retention. Week 96 results of phase 3 trials comparing the first approved integrase strand transfer inhibitors, raltegravir¹² and elvitegravir,¹³ with efavirenz, the preferred first-line non-nucleoside reverse transcriptase inhibitor (NNRTI), or elvitegravir with atazanavir–ritonavir,¹⁴ one of the preferred first-line ritonavir-boosted protease inhibitors, showed that although both integrase strand transfer inhibitors showed sustainable antiviral efficacy, similar to the comparator, there was occurrence of new virological failures and serious adverse events occurred during the second year of therapy. Furthermore, raltegravir and elvitegravir regimens were not convenient since raltegravir required twice-daily dosing and elvitegravir required food intake and pharmacological boosting. Dolutegravir, a new once-daily integrase strand transfer inhibitor, had similar efficacy and safety to raltegravir at 48 weeks, when dosed with either tenofovir–emtricitabine or abacavir–lamivudine for first-line antiretroviral therapy.¹¹ In combination with up to two other antiretroviral drugs, dolutegravir was well tolerated with greater virological effect compared with twice-daily raltegravir in treatment-experienced patients.

Interpretation

We report the 96 week assessment of a phase 3 study of dolutegravir that compared, in a double-blind double-dummy design, two integrase strand transfer inhibitors, raltegravir and dolutegravir, in combination with two fixed-dose NNRTIs tenofovir–emtricitabine or abacavir–lamivudine, for first-line antiretroviral treatment. Proportion of virological success remains high in both groups and similar across stratification subgroups. Furthermore, the most important practical findings were that discontinuation for adverse events and rate of new virological failure were very low between week 48 and week 96, with no new serious adverse events or higher than grade 2 laboratory toxic effects. None of the patients in the dolutegravir group developed emergence of resistance mutations to integrase strand transfer inhibitors or nucleos(t)ide reverse transcriptase inhibitors over the 96 week period. Taken together, the 96 week results of this head-to-head phase 3 study of raltegravir versus dolutegravir suggest that once-daily 50 mg dolutegravir, in combination with either tenofovir–emtricitabine or abacavir–lamivudine, is well tolerated and has sustained antiviral efficacy as initial therapy for treatment of adults with HIV infection and is an alternative to the twice-daily raltegravir regimen.

other drugs such as trimethoprim or cimetidine,^{22,23} which decrease tubular secretion of creatinine and therefore increase serum creatinine concentrations without affecting glomerular filtration.^{24,25} In SPRING-2, we noted small elevations in serum creatinine and small decreases in creatinine clearance early in treatment with dolutegravir (about weeks 2–4) and these values remained stable to week 96. No patients in the dolutegravir group had grade 3 or 4 creatinine elevations, and no patients in either treatment group discontinued the study because of renal adverse events.

One limitation of SPRING-2 is that it enrolled low numbers of non-white or female patients, which limits our understanding of efficacy and safety in some groups of patients. However, it is improbable that generalisation of SPRING-2 findings would be biased, since meta-analyses from previous clinical trials did not show any differences related to sex or ethnic origin in treatment outcome.²⁶ This finding is further supported by an analysis from a study¹² of a first-line raltegravir-containing regimen in which outcome did not differ with regard to ethnic origin or sex. Additional data will be available for dolutegravir from other phase 3 studies in patients naive for antiretroviral treatment and in those who are ART-experienced, which have enrolled higher percentages of women and non-white patients than this study.^{27,28} Furthermore, a phase 3b study designed specifically to assess the safety and efficacy of dolutegravir–abacavir–lamivudine in 474 HIV-1-infected and antiretroviral treatment-naive women (ARIA; NCT0191040) is enrolling.

Another limitation of SPRING-2 is that the design of the study (ie, double-blind, double-placebo) precludes assessing the effect of a once-daily versus twice-daily treatment on response.

In summary, the SPRING-2 week 96 results confirm the durable antiviral potency and favourable resistance and safety profile of dolutegravir. Once-daily dosing without food restrictions or any requirement for a pharmacokinetic booster makes dolutegravir-based therapy an attractive treatment option for HIV-1-infected, treatment-naive patients.

Contributors

SA, JG, and SM contributed to protocol concept and design. J-GB and CB provided clinical oversight of the study. HA, J-GB, EB, JG, and FR enrolled patients in the study. HA, J-GB, CB, PD, SM, EQ-R, and FR collected data. SA, CB, PD, SM, and FR analyzed data. SA, CB, PD, JG, SM, EQ-R, and FR interpreted data. SA provided statistical expertise. HA, SA, J-GB, EB, CB, PD, JG, HJ, SM, EQ-R, and FR participated in the drafting and revision of the report.

SPRING-2 investigators

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Conflicts of interest

SA and CB are employees of GlaxoSmithKline and own stock in the company. J-GB has served as a consultant or speaker at conferences

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