



Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial

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Summary

Background Switching from therapy based on a boosted protease inhibitor to bictegravir, emtricitabine, and tenofovir alafenamide could avoid drug interactions and unwanted side-effects in virologically suppressed adults with HIV-1 infection, while maintaining a high barrier to resistance and providing a simplified once-daily, single-tablet regimen. Here, we report 48 week results of a phase 3 study investigating this switch.

Methods In this multicentre, randomised, open-label, active-controlled, non-inferiority, phase 3 trial, adults with HIV-1 infection were enrolled at 121 outpatient centres in ten countries. Eligible participants were aged 18 years or older, had an estimated glomerular filtration rate of 50 mL per min or higher, had been virologically suppressed (plasma HIV-1 RNA <50 copies per mL) for 6 months or more before screening, and were on a regimen consisting of boosted atazanavir or darunavir plus either emtricitabine and tenofovir disoproxil fumarate or abacavir and lamivudine. We randomly assigned participants (1:1), using a computer-generated randomisation sequence, to switch to co-formulated once-daily bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg), herein known as the bictegravir group, or to remain on their baseline boosted protease inhibitor regimen, herein known as the boosted protease inhibitor group, for 48 weeks. Randomisation was stratified by use of tenofovir disoproxil fumarate or abacavir at screening. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 (by US Food and Drug Administration snapshot algorithm), with a prespecified non-inferiority margin of 4%. Efficacy and safety analyses included all participants who received at least one dose of study drug. This study is ongoing but not actively recruiting patients and is registered with ClinicalTrials.gov, number NCT02603107.

Findings Between Dec 2, 2015, and July 15, 2016, 578 participants were randomly assigned and 577 were treated (290 in the bictegravir group and 287 in the boosted protease inhibitor group). At week 48, five participants (2%) in the bictegravir group and five (2%) in the boosted protease inhibitor group had plasma HIV-1 RNA of 50 copies per mL or higher (difference 0·0%, 95·002% CI -2·5 to 2·5), thus switching to the bictegravir regimen was non-inferior to continued boosted protease inhibitor therapy. The overall incidence and severity of adverse events was similar between groups, although headache occurred more frequently in the bictegravir group than in the boosted protease inhibitor group. 233 (80%) participants in the bictegravir group and 226 (79%) in the boosted protease inhibitor group had an adverse event. Only two (1%) participants in the bictegravir group and one (<1%) in the boosted protease inhibitor group discontinued treatment because of adverse events. 54 participants (19%) in the bictegravir group had drug-related adverse events compared with six (2%) in the protease inhibitor group.

Interpretation Fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide might be a safe and efficacious alternative to continued boosted protease inhibitor therapy in adults with HIV-1 infection.

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Introduction

Boosted protease inhibitors are a component of antiretroviral regimens in a sizeable proportion of the treated population with HIV-1 infection and have a high barrier to resistance.¹ Regimens based on boosted darunavir or atazanavir are widely prescribed but

have disadvantages, including the potential for drug interactions and side-effects (eg, hyperbilirubinaemia, gastrointestinal adverse events, and lipohypertrophy).²⁻⁴

Bictegravir is a potent, unboosted integrase strand transfer inhibitor (INSTI) with a high barrier to resistance and low potential for drug interactions.^{5,6} In two large

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Research in Context

Evidence before this study

We searched PubMed for randomised clinical trials of bicitegravir (GS-9883) in patients with HIV-1 using the title or abstract search terms “bicitegravir”, “randomised”, or “randomized”. Searches were limited to articles published in English between Jan 1, 1997, and Oct 1, 2017. Our search yielded three articles investigating bicitegravir in treatment-naïve adults with HIV-1 infection. All three summarised results from phase 2 or 3 studies comparing bicitegravir with dolutegravir, each given with the guideline-recommended combination of the nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) emtricitabine and tenofovir alafenamide. Both treatments showed good efficacy and were well tolerated through 48 weeks.

Added value of this study

Integrase strand transfer inhibitors (INSTIs), in combination with two NRTIs, are recommended for first-line antiretroviral treatment of HIV infection. HIV-1-infected individuals who are virologically suppressed on their existing regimen might choose to switch regimens because of safety or tolerability concerns or for regimen simplification. In this study, we co-formulated bicitegravir, a novel, potent INSTI with high in-vitro activity against most INSTI-resistant viruses, with

emtricitabine and tenofovir alafenamide into a fixed-dose combination. This NRTI backbone is recognised for its potency and favourable safety profile, particularly with respect to bone and renal measures, compared with regimens containing tenofovir disoproxil fumarate. To our knowledge, this study is the first phase 3 clinical trial to investigate switching to the fixed-dose combination of bicitegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens.

Implications of all the available evidence

We found that co-formulated bicitegravir, emtricitabine, and tenofovir alafenamide was non-inferior to remaining on boosted protease inhibitor regimens, with high rates of virological suppression observed in both groups. These results complement results from phase 2 and 3 studies of bicitegravir, emtricitabine, and tenofovir alafenamide in treatment-naïve adults with HIV-1 infection. Co-formulated bicitegravir, emtricitabine, and tenofovir alafenamide is a potent, novel, unboosted regimen with a high barrier to resistance and a favourable tolerability profile that can be administered once daily, thereby providing a safe and efficacious option for initial or ongoing treatment of adults with HIV-1 infection.

phase 3 studies^{7,8} in HIV-1-infected adults previously untreated with antiretroviral therapy, bicitegravir was compared with dolutegravir, a guideline-recommended INSTI. When co-formulated with emtricitabine and tenofovir alafenamide—two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) that are used in combination according to guideline recommendations—bicitegravir was well tolerated and showed high rates of HIV-1 suppression, without development of resistance. Switching to this regimen might also avoid the potential toxic effects of tenofovir disoproxil fumarate and abacavir, and some patients might benefit from a once daily, fixed-dose combination regimen, which can improve adherence and clinical and virological outcomes.^{9–11} Thus, the fixed-dose combination of bicitegravir, emtricitabine, and tenofovir alafenamide might prove to be a potent, tolerable, and simple regimen suitable for a wide variety of patients with HIV-1.

In this study, we investigated the efficacy and safety of switching to a fixed-dose, once-daily combination of bicitegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor therapy in virologically suppressed adults with HIV-1 infection.

Methods

Study design and participants

GS-US-380-1878 is a randomised, open-label, multicentre, active-controlled, non-inferiority, phase 3 trial at 121 out-patient centres in ten countries: Australia, Belgium, Canada, the Dominican Republic, France, Germany, Italy, Spain, the UK, and the USA. Investigators enrolled

adults (aged ≥ 18 years) with HIV-1 infection who had been virologically suppressed (plasma HIV-1 RNA of < 50 copies per mL) for 6 months or more before screening and were on a stable, once-daily antiretroviral regimen consisting of ritonavir-boosted or cobicistat-boosted atazanavir or darunavir, plus either emtricitabine and tenofovir disoproxil fumarate or abacavir and lamivudine, with no previous use of an INSTI. Unconfirmed elevations of HIV-1 RNA to 50 copies per mL or higher before screening were acceptable. Additionally, participants had to have an estimated glomerular filtration rate of 50 mL per min or higher and no documented resistance to emtricitabine, tenofovir, abacavir, or lamivudine. Individuals with chronic hepatitis B infection (unless receiving a regimen that did not contain tenofovir disoproxil fumarate) or chronic hepatitis C infection were permitted to enrol.

This study was done in accordance with the Declaration of Helsinki and was approved by central or site-specific review boards or ethics committees. All participants gave written informed consent.

Randomisation and masking

We randomly assigned participants (1:1), using a computer-generated randomised allocation sequence (block size 4) that was created by Bracket (San Francisco, CA, USA), to either switch to fixed-dose, combination bicitegravir, emtricitabine, and tenofovir alafenamide (bicitegravir group) or to continue boosted protease inhibitor therapy. Randomisation was stratified by use of tenofovir disoproxil fumarate or abacavir at screening.

Investigators established participant eligibility, obtained participant numbers, and received automated treatment assignment on the basis of a randomisation sequence. Neither investigators nor participants were masked to treatment assignment.

Procedures

Participants received co-formulated oral bicitegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) or their regimen at baseline once a day for 48 weeks. After week 48, participants in the UK continued their randomised treatment, while all other participants had the option to continue or to switch to open-label bicitegravir, emtricitabine, and tenofovir alafenamide for an additional 96 weeks.

Study visits were scheduled at week 4, 8, 12, 24, 36, and 48, and then every 12 weeks thereafter. Blood and urine samples were collected at baseline, at week 4, 8, and 12, and then every 12 weeks thereafter. Plasma viral loads were measured by the central laboratory (Covance Laboratories, Indianapolis, IN, USA) with Roche TaqMan 2.0 (Roche Diagnostics, Rotkreuz, Switzerland). Laboratory tests were done by Covance Laboratories and included haematological analysis, serum chemistry tests, and measurement of fasting lipid parameters (total cholesterol, LDL and HDL cholesterol, ratio of total cholesterol to HDL cholesterol, and triglycerides), CD4 counts (absolute and percentage), and renal function parameters (estimated glomerular filtration rate, calculated with the Cockcroft-Gault equation, and ratios of albumin to creatinine, retinol binding protein to creatinine, and β 2-microglobulin to creatinine in urine). Resistance testing consisted of genotyping and phenotyping of integrase, protease, and reverse transcriptase in participants with confirmed HIV-1 RNA of 50 copies per mL or higher whose confirmation sample (taken 2–3 weeks after the date of the original test indicating HIV-1 RNA \geq 50 copies per mL) had HIV-1 RNA of at least 200 copies per mL or in those with HIV-1 RNA of 50 copies per mL or higher at study drug discontinuation or week 48. Retrospective HIV-1 proviral DNA genotyping of baseline samples was also done in participants who qualified for resistance testing. All resistance testing was done by Monogram Biosciences (South San Francisco, CA, USA).

Safety was assessed by physical examinations, laboratory tests, 12-lead electrocardiograms, and recording of concomitant drugs and adverse events coded with the Medical Dictionary for Regulatory Activities version 19.1. Study treatment was discontinued if requested by the participant and in cases of unacceptable toxic effects, pregnancy, or development of active tuberculosis infection.

We did a prespecified, intensive pharmacokinetic analysis in a subset of participants who provided consent in the bicitegravir group. From these participants we obtained blood samples at the week 4 or 8 visit at 20–28 h

after the last dose of study drug (trough blood sample), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 h after an observed dose at the clinic (post-dose blood sample). We measured plasma concentrations of bicitegravir, emtricitabine, and tenofovir alafenamide by use of validated high-performance liquid chromatography tandem mass spectroscopy (LC-MS/MS) bioanalytical methods, which were performed and validated by QPS Holdings (Newark, DE, USA).

Outcomes

The primary outcome was the proportion of participants with plasma HIV-1 RNA 50 copies per mL or higher at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm.¹² Other prespecified secondary or tertiary efficacy endpoints were proportions of participants with plasma HIV-1 RNA less than 50 copies per mL and less than 20 copies per mL at week 48 and change in CD4 cell count (absolute and percentage) from baseline to week 48.

Safety outcomes were incidence of adverse events and laboratory abnormalities, and change from baseline to week 48 in serum creatinine, renal function parameters, and fasting lipid parameters. We also summarised the number of participants who initiated lipid-modifying drugs during the study.

Statistical analysis

Assuming that 2% of participants in each treatment group would have HIV-1 RNA of 50 copies per mL or higher at week 48, a sample size of 520 participants would achieve at least 90% power to detect non-inferiority at a one-sided α of 0.025. Non-inferiority for the primary efficacy endpoint was established if the upper bound of the 95% CI for the difference in proportion of participants with HIV-1 RNA of 50 copies per mL or higher between the groups was less than 4%.

We did the primary analysis after all enrolled participants had completed their week 48 study visit or had prematurely discontinued the study drug. The primary efficacy analysis used the full analysis set, which was defined as all randomised participants who had received at least one dose of study drug. We also analysed the primary efficacy endpoint using the per-protocol analysis set, which excluded participants who did not have plasma HIV-1 RNA values in the week 48 analysis window (days 295–378 inclusive) because of study drug discontinuation for reasons other than lack of efficacy, and those who violated key entry criteria.

We did two planned interim analyses, which were approved by the independent data monitoring committee. The first analysis was done after about 30% of enrolled participants had completed their week 12 study visit or had prematurely discontinued study drugs, and the second was done when all participants had completed their week 24 study visit or had prematurely discontinued study drugs. Both of these analyses concluded that efficacy

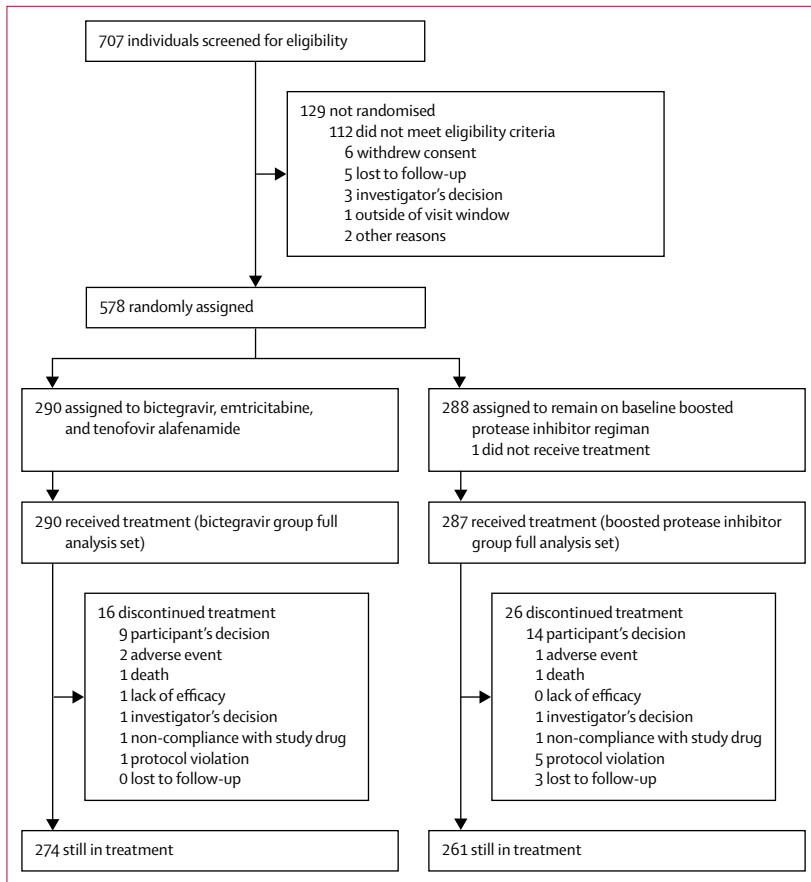


Figure: Trial profile

and safety findings warranted continuation of the trial. An α penalty of 0.0001 was applied for each planned interim analysis. As a result, the significance level for the two-sided non-inferiority test at week 48 was 0.04998, corresponding to a 95.002% CI.

We constructed the point estimate of treatment difference in the proportion of participants with HIV-1 RNA of 50 copies per mL or higher, and the associated two-sided 95.002% CI, using an unconditional exact method with two inverted one-sided tests. In the snapshot analysis, participants were classified according to three outcomes: those with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 or at the last visit before discontinuation of study drug because of low efficacy, adverse events, death, or other reasons; those with plasma HIV-1 RNA of less than 50 copies per mL at week 48; and those with no virological data in the week 48 window, including those who discontinued study drug before 48 weeks whose last available HIV-1 RNA was less than 50 copies per mL, and those who were still on study drug but were missing data in the week 48 window. The difference in response rates for the primary outcome was calculated based on these three outcomes: plasma HIV-1 RNA of 50 copies per mL

or higher versus less than 50 copies per mL at week 48 or no virological data in the week 48 window.

The proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48, according to the US FDA-defined snapshot algorithm, was analysed similarly to the primary efficacy endpoint, except that non-inferiority was defined if the lower bound of the 95.002% CI of the difference between the groups was greater than -10%. We analysed the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 in the overall population and according to subgroups of age, sex, race, and geographic region. Additionally, we assessed the proportion of participants with this outcome when imputing missing data as treatment failures or participant exclusions. The FDA snapshot approach was also used to assess the proportion of participants with plasma HIV-1 RNA of less than 20 copies per mL at week 48.

Change from baseline in CD4 cell count (absolute and percentage) at week 48 in the full analysis and per-protocol sets was summarised by treatment group with descriptive statistics. We calculated the differences between the groups in changes from baseline to week 48 in CD4 cell counts (absolute and percentage), and the corresponding 95% CIs, using ANOVA, with treatment group included as a fixed covariate in the model.

Study drug adherence, which was assessed for the bicitgravir group only, was estimated as number of pills taken divided by number of pills prescribed, where number of pills taken was number dispensed minus number returned.

We summarised baseline characteristics with descriptive statistics for the safety analysis set, which included all randomly assigned participants who received at least one dose of study drug. Safety data are described in summary form using all data collected up to either the data cutoff date (May 18, 2017) or, for participants who discontinued treatment early, up to 30 days after the last dose of study drug. Treatment differences in changes in renal biomarkers and fasting lipid parameters were assessed overall and by NRTI-containing regimen at baseline (post-hoc for lipids). For categorical data, we calculated p values using the Cochran-Mantel-Haenszel test (the general association statistic was used for nominal data, and the row mean scores differ statistic was used for ordinal data). For continuous data, we used the two-sided Wilcoxon rank-sum test, unless otherwise specified.

We used SAS software version 9.4 for all statistical analyses. Pharmacokinetic parameters were calculated with a non-linear model using standard non-compartmental analysis in WinNonlin version 6.4.

This study is registered with ClinicalTrials.gov, number NCT02603107.

Role of the funding source

The funder of the study had the lead role in study design, data collection, data analysis, data interpretation, and,

along with the first author, writing of the manuscript. All authors had access to the data. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Nov 20, 2015, and July 15, 2016, 707 individuals were screened for eligibility and 578 were randomly assigned to the bicitegravir group (n=290) or to the boosted protease inhibitor group (n=288; figure). 290 participants received at least one dose of bicitegravir, emtricitabine, and tenofovir alafenamide and 287 received at least one dose of their boosted protease inhibitor-based regimen. One individual assigned to the boosted protease inhibitor group did not receive the study drug because of consent withdrawal. The median duration of treatment for both groups was 46.7 weeks (IQR 44.0–48.0). Demographic and baseline characteristics were balanced for the two treatment groups (table 1)

At week 48, an equal number of participants in the bicitegravir and protease inhibitor groups had HIV-1 RNA of 50 copies per mL or higher (table 2). Based on the upper bound of the 95.002% CI, the fixed-dose combination of bicitegravir, emtricitabine, and tenofovir alafenamide was non-inferior to continued boosted protease inhibitor-based therapy in maintaining virological suppression. This finding was replicated in the per-protocol analysis set: three (1%) of 269 participants in the bicitegravir group had an HIV-1 RNA of 50 copies per mL or higher at 48 weeks compared with two (1%) of 250 participants in the boosted protease inhibitor group (difference 0.3%, 95.002% CI –1.9 to 2.5).

The small differences in proportions of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 were not significant (table 2), which was also true in subgroup analyses (appendix p 1) and when data were treated as treatment failure or participant exclusion (table 2). 249 (86%) participants in the bicitegravir group had plasma HIV-1 RNA of less than 20 copies per mL at week 48 compared with 243 (85%) participants in the boosted protease inhibitor group (difference 1.2%, 95% CI –4.7 to 7.1; p=0.73).

The mean change from baseline to week 48 in absolute CD4 cell count (observed data, on-treatment values) was similar between the groups (25 cells per μL [SD 151] in the bicitegravir group vs 0 cells per μL [159] in the boosted protease inhibitor group; p=0.068), as was the mean change from baseline to week 48 in CD4 percentage (0.5% [SD 3.56] in the bicitegravir group vs 0.5% [3.53] in the boosted protease inhibitor group; p=0.85).

Seven participants met protocol-defined criteria for resistance testing (two in the bicitegravir group and five in the boosted protease inhibitor group), of whom three were resuppressed to a plasma HIV-1 RNA of less than 50 copies per mL without a change in regimen (one in the bicitegravir group and two in the boosted protease inhibitor group). Resistance testing in

| | Bicitegravir group (n=290) | Boosted protease inhibitor group (n=287) |
|--|-------------------------------|--|
| Age (years)* | 48 (20–74) | 47 (21–79) |
| Sex | | |
| Men | 243 (84%) | 234 (82%) |
| Women | 47 (16%) | 53 (18%) |
| Race | | |
| White | 188 (65%) | 190 (66%) |
| Black | 79 (27%) | 72 (25%) |
| Asian | 6 (2%) | 10 (3%) |
| Native American or Alaska Native | 3 (1%) | 3 (1%) |
| Other | 14 (5%) | 12 (4%) |
| Ethnicity | | |
| Hispanic or Latino | 60 (21%) | 47 (16%) |
| HBV co-infection | 8 (3%) | 6 (2%) |
| HCV co-infection | 5 (2%) | 5 (2%) |
| eGFR (mL per min) | 106.7 (87.0–124.2) | 104.9 (87.1–125.3) |
| Body-mass index (kg/m ²) | 26.1 (23.6–29.2) | 25.9 (23.3–29.5) |
| HIV-1 RNA <50 copies per mL | 285 (98%) | 277 (97%) |
| Median CD4 count (cells per μL) | 617 (469–809) | 626 (437–821) |
| CD4 count (cells per μL) | | |
| <50 | 0 | 0 |
| 50–199 | 4 (1%) | 8 (3%) |
| 200–349 | 26 (9%) | 30 (10%) |
| 350–499 | 62 (21%) | 60 (21%) |
| \geq 500 | 198 (68%) | 189 (66%) |
| HIV disease status | | |
| Asymptomatic | 240 (83%) | 234 (82%) |
| Symptomatic HIV infection | 16 (6%) | 20 (7%) |
| AIDS | 34 (12%) | 33 (11%) |
| Baseline antiretroviral regimen | | |
| Boosted ATV plus ABC/3TC | 21 (7%) | 23 (8%) |
| Boosted DRV plus ABC/3TC | 24 (8%) | 21 (7%) |
| Boosted ATV plus FTC/TDF | 105 (36%) | 110 (38%) |
| Boosted DRV plus FTC/TDF | 140 (48%) | 133 (46%) |
| Time on boosted PI regimen (years) | 5.4 (3.2–8.5) | 5.5 (3.0–8.3) |
| Baseline protease inhibitor and boosting agent | | |
| ATV plus cobicistat | 12 (4%) | 13 (5%) |
| DRV plus cobicistat | 36 (12%) | 23 (8%) |
| ATV plus ritonavir | 114 (39%) | 120 (42%) |
| DRV plus ritonavir | 128 (44%) | 131 (46%) |

Data are median (IQR) or n (%), unless otherwise stated. HBV=hepatitis B virus. HCV=hepatitis C virus. eGFR=estimated glomerular filtration rate (by Cockcroft Gault equation). ATV=atazanavir. ABC/3TC=abacavir and lamivudine. DRV=darunavir. FTC/TDF=emtricitabine and tenofovir disoproxil fumarate.
*Data are median (range).

Table 1: Baseline demographic and clinical characteristics

See Online for appendix

one participant in the bicitegravir group who had poor study drug adherence (76% by pill count), undetectable bicitegravir plasma concentrations at the time of resistance testing, and previous treatment with NRTI-only regimens revealed a substitution mutation

| | Bictegravir group (n=290) | Boosted protease inhibitor group (n=287) | Difference (95-002% CI); p value |
|---|---------------------------|--|----------------------------------|
| HIV-1 RNA ≥50 copies per mL | 5 (2%) | 5 (2%) | -0.0% (-2.5 to 2.5); 1.00 |
| HIV-1 RNA ≥50 copies per mL in week 48 window | 2 (1%) | 2 (1%) | .. |
| Treatment discontinued before week 48 because of lack of efficacy | 1 (<1%) | 0 | .. |
| Treatment discontinued before week 48 because of adverse event or death with last available HIV-1 RNA ≥50 copies per mL | 0 | 0 | .. |
| Treatment discontinued before week 48 for other reasons* with last available HIV-1 RNA ≥50 copies per mL | 2 (1%) | 3 (1%) | .. |
| No virological data available | 18 (6%) | 27 (9%) | .. |
| Discontinued study because of adverse event or death with last available HIV-1 RNA <50 copies per mL | 3 (1%) | 2 (1%) | .. |
| Discontinued study because of other reasons* with last available HIV-1 RNA <50 copies per mL | 10 (3%) | 19 (7%) | .. |
| On study drug but missing data in the week 48 window | 5 (2%) | 6 (2%) | .. |
| HIV-1 RNA <50 copies per mL | 267 (92%) | 255 (89%) | 3.2% (-1.6 to 8.2); 0.20 |
| Missing data treated as treatment failure | 269/290 (93%) | 261/287 (91%) | 1.8% (-2.8 to 6.5); 0.45† |
| Missing data treated as participant exclusion | 269/272 (99%) | 261/264 (99%) | 0.0% (-2.2 to 2.4); 1.00† |

Data are n (%) or n/N (%), unless otherwise stated. *Other reasons include investigator's decision, participant's decision, loss to follow-up, non-compliance with study drug, protocol violation, pregnancy, and study terminated by sponsor. †Data are difference (95% CI); p value.

Table 2: Virological outcomes at week 48

| | Bictegravir group (n=290) | Boosted protease inhibitor group (n=287) |
|--|---------------------------|--|
| Any adverse event | 233 (80%) | 226 (79%) |
| Grade 3 or 4 adverse event | 13 (4%) | 18 (6%) |
| Serious adverse event | 17 (6%) | 20 (7%) |
| Treatment-related adverse event | 54 (19%) | 6 (2%) |
| Treatment-related serious adverse event | 1 (<1%) | 0 |
| Adverse event leading to study drug discontinuation* | 2 (1%) | 1 (<1%) |
| Death† | 1 (<1%) | 1 (<1%) |
| Most common adverse events‡ | | |
| Headache | 35 (12%) | 12 (4%) |
| Diarrhoea | 24 (8%) | 18 (6%) |
| Nasopharyngitis | 21 (7%) | 34 (12%) |
| Upper respiratory tract infection | 21 (7%) | 22 (8%) |
| Back pain | 13 (4%) | 17 (6%) |
| Arthralgia | 12 (4%) | 15 (5%) |

Data are n (%). *Included rash (n=1) and schizophrenia (n=1) in the bictegravir group and acetabulum fracture and acute kidney injury (n=1) in the boosted protease inhibitor group. †Causes of death included lung cancer with metastasis to the brain (n=1) in the bictegravir group and blunt force trauma to the head (n=1) in the boosted protease inhibitor group. ‡Occurred in ≥5% of participants in either group.

Table 3: Summary of adverse events

(Met184Val) in reverse transcriptase, which was found to be pre-existing in the baseline sample. No participant developed treatment-emergent resistance to any component of the bictegravir regimen. In the boosted protease inhibitor group, one participant on cobicistat-boosted darunavir, given emtricitabine plus tenofovir

disoproxil fumarate, experienced virological failure with Met184Ile in reverse transcriptase that was found to be pre-existing in the baseline sample. Another participant in the boosted protease inhibitor group who was on ritonavir-boosted darunavir, given with abacavir plus lamivudine, developed virological failure with treatment-emergent Leu74Val in reverse transcriptase at week 24; this substitution was not present in the baseline sample.

In the 28 participants in the bictegravir group who were included in the intensive pharmacokinetic sub-study, the mean trough concentration of bictegravir was 2038.2 ng/mL (coefficient of variation 36%; appendix p 2), which is more than 12 times higher than the protein-adjusted 95% effective concentration (162 ng/mL) against wildtype HIV-1 virus.⁶ This finding was consistent with pharmacokinetic results reported in studies of treatment-naive individuals.^{10,11} The pharmacokinetics of emtricitabine and tenofovir alafenamide were also consistent with historical data in HIV-1-infected people.^{13,14}

Both treatments were well tolerated, and most adverse events were mild or moderate in severity (table 3). Overall, 233 (80%) of 290 participants in the bictegravir group and 226 (79%) of 287 participants in the boosted protease inhibitor group had an adverse event. Headache was reported more frequently in the bictegravir group than in the boosted protease inhibitor group (table 3), although most headache events were mild, and none led to study drug discontinuation. The initial onset of headache occurred primarily within the first 8 weeks of switching to bictegravir, emtricitabine, and tenofovir alafenamide, with a similar prevalence in both groups reported at week 48 (2% in the bictegravir

group vs 1% in the boosted protease inhibitor group; data not shown).

Incidence of serious adverse events was similar between groups (table 3). Adverse events leading to study drug discontinuation in the bicittegravir group were rash (n=1) and schizophrenia (n=1); the event of schizophrenia was considered by the investigator to be related to treatment. Adverse events leading to study drug discontinuation in the boosted protease inhibitor group were traumatic acetabulum fracture and acute kidney injury, which occurred in a single participant; neither event was considered to be treatment related, and they were resolved after treatment discontinuation. This participant eventually entered the extension phase of the study.

Treatment-related adverse events were more common in participants who switched (bicittegravir group) than in those who did not (table 3). Treatment-related adverse events were predominantly mild or moderate in severity, with grade 3 or 4 drug-related adverse events occurring in two (1%) participants in the bicittegravir group and in no participants in the boosted protease inhibitor group. The difference between groups in the incidence of treatment-related adverse events was mainly driven by differences in the incidence of treatment-related headache (14 [5%] of 290 participants in the bicittegravir group vs no participants in the boosted protease inhibitor group), flatulence (seven [2%] vs none), nausea (seven [2%] vs none), and diarrhoea (six [2%] vs none).

Two participants (one in each group) died during the study. Neither death was thought to be related to study drugs (lung cancer with metastasis to the brain in the bicittegravir group and blunt force trauma to the head in the boosted protease inhibitor group). No pregnancies occurred during the randomised phase of the study.

Grade 3 or 4 laboratory abnormalities were reported in 45 (16%) of 290 participants in the bicittegravir group and in 83 (29%) of 285 participants in the boosted protease inhibitor group (two individuals in the boosted protease inhibitor group did not have post-baseline laboratory data for this analysis; appendix p 3). The difference between the groups was mainly a result of the higher incidence of increased total bilirubin, a known side-effect of atazanavir,¹⁵ in the boosted protease inhibitor group than in the bicittegravir group (43 of the 44 participants with increased total bilirubin in the boosted protease inhibitor group were on an atazanavir-containing regimen); otherwise the incidence of grade 3 or 4 laboratory abnormalities was balanced between groups. No consistent, clinically significant new ECG findings were observed in either group.

No cases of proximal tubulopathy or Fanconi syndrome were reported in either group. The median estimated glomerular filtration rate decreased from baseline to week 48 in the bicittegravir group (median change was -4.3 mL per min [IQR -12.6 to 4.8]) and remained stable (median change was 0.2 mL per min [-6.6 to 7.6])

in the boosted protease inhibitor group ($p=0.0005$). These differences were observed by week 4 and were generally stable through week 48. At 48 weeks, percentage changes in quantitative proteinuria (ratio of albumin to creatinine in urine) and tubular proteinuria (ratios of retinol binding protein or β 2-microglobulin to creatinine in urine) remained stable or had decreased in the bicittegravir group, whereas they had increased in the boosted protease inhibitor group (appendix p 4). Decreases in the tubular markers in the bicittegravir group were driven by individuals switching from a boosted protease inhibitor regimen that contained tenofovir disoproxil fumarate (appendix p 5).

Changes from baseline to week 48 in concentrations of total cholesterol, LDL cholesterol, and HDL cholesterol were similar between the groups (appendix p 6). Significant differences were observed for changes in fasting triglyceride concentrations and the ratio of total cholesterol to HDL (appendix p 6). In participants who were on boosted protease inhibitor regimens containing emtricitabine and tenofovir disoproxil fumarate at baseline, changes from baseline at week 48 in all lipid fasting parameters were similar between the treatment groups (appendix p 7). For those participants on boosted protease inhibitor regimens containing abacavir and lamivudine at baseline, switching to bicittegravir, emtricitabine, and tenofovir alafenamide resulted in significant decreases in concentrations of fasting total cholesterol, LDL cholesterol, and triglycerides, and in the total cholesterol to HDL ratio at week 48 compared with participants who remained on boosted protease inhibitor therapy (appendix p 7). No difference between the groups in change in concentrations of HDL cholesterol between baseline and week 48 was noted ($p=0.40$ after adjusting for the baseline HDL value). Eight (3%) of 290 participants in the bicittegravir group started lipid-modifying drugs during the study versus ten (3%) of 287 participants in the boosted protease inhibitor group ($p=0.64$).

Discussion

Switching to bicittegravir, emtricitabine, and tenofovir alafenamide was non-inferior to remaining on a boosted protease inhibitor regimen, with an equal number of participants in each group having plasma HIV-1 RNA of 50 copies per mL or higher at week 48. The primary endpoint was confirmed in multiple secondary analyses. Both regimens were well tolerated, with few participants discontinuing the study because of adverse events. The adverse event profiles were similar between groups, except that mild headache was more frequently reported in the bicittegravir group. Headache has been reported in other studies^{7,8} comparing bicittegravir, emtricitabine, and tenofovir alafenamide with dolutegravir-containing regimens, but without a difference between groups. Treatment-related adverse events were more common in the bicittegravir group than in the boosted protease inhibitor group, which has been seen in other open-label

studies^{16–18} comparing a switch to a new drug with continuing a previously well tolerated baseline regimen. No renal adverse events, with or without leading to treatment discontinuation, were reported in the bicittegravir group. Switching to bicittegravir, emtricitabine, and tenofovir alafenamide was associated with a decreased estimated glomerular filtration rate, probably due to bicittegravir-mediated inhibition of OCT2 or MATE1, without affecting the actual glomerular filtration rate.^{19,20} Improvements in tubular proteinuria after switching to bicittegravir, emtricitabine, and tenofovir alafenamide were observed, with greater effects seen in those who were on regimens containing tenofovir disoproxil fumarate at baseline. This finding is consistent with those of other studies^{21–26} in which tenofovir disoproxil fumarate or abacavir were switched to tenofovir alafenamide.

In previous studies,^{17,27–29} switching from boosted protease inhibitors has been associated with improvements in fasting lipids. In this study, participants switching to bicittegravir, emtricitabine, and tenofovir alafenamide experienced a change in multiple components of their regimens: all NRTIs were switched to emtricitabine and tenofovir alafenamide, and all boosted protease inhibitors were switched to bicittegravir. Because tenofovir disoproxil fumarate decreases total cholesterol and LDL cholesterol, and increases HDL cholesterol, whereas abacavir generally does not, changes in fasting lipids through week 48 in our study were dependent on whether participants were taking regimens containing tenofovir disoproxil fumarate or abacavir plus lamivudine at baseline. The effect of switching emtricitabine plus tenofovir disoproxil fumarate and a boosted protease inhibitor to bicittegravir, emtricitabine, and tenofovir alafenamide resulted in no change in any fasting lipid parameter at week 48, indicating that the effect of switching away from tenofovir disoproxil fumarate was balanced by switching from a boosted protease inhibitor to bicittegravir. Notably, participants who were on regimens containing abacavir plus lamivudine at baseline had significant improvements in total cholesterol, LDL cholesterol, triglycerides, and total cholesterol to HDL ratio 48 weeks after switching to bicittegravir, emtricitabine, and tenofovir alafenamide. The mechanism behind the observed treatment differences is not known, but our results reinforce findings from previous studies^{7,8,25} showing that tenofovir alafenamide does not significantly affect lipid parameters. Overall, our results suggest that switching from boosted protease inhibitors to bicittegravir leads to improvements in lipid parameters.

The main limitation of this study is the open-label design, which means that between-group differences in adverse events, particularly those that occurred more frequently in the bicittegravir group than in the boosted protease inhibitor group, should be interpreted with caution. Participants in the bicittegravir group were aware of the change in their treatment and might have been more likely than individuals who remained on their well

tolerated boosted protease inhibitor regimen to attribute emerging symptoms to their new medications. Other limitations include the small proportions of study participants who had advanced HIV-1 disease or were female, co-infected with chronic hepatitis C virus, or taking cobicistat at baseline. Additionally, we only assessed treatment adherence in the bicittegravir group. The trial was also not powered for secondary objectives because the sample size calculation was based on the primary efficacy endpoint. Lastly, the study findings might not be generalisable to all patients who are switching HIV treatment because our population was reasonably healthy, had good renal function, and were stably suppressed and tolerating their antiretroviral regimen.

Our results complement those from two large randomised clinical trials^{7,8} that showed high efficacy and good tolerability for bicittegravir, emtricitabine, and tenofovir alafenamide compared with dolutegravir in treatment-naïve adults with HIV-1 infection. Co-formulated bicittegravir, emtricitabine, and tenofovir alafenamide was non-inferior to dolutegravir, abacavir, and lamivudine in both trials, and showed high rates of HIV-1 suppression, without development of resistance. In this study, switching from a boosted protease inhibitor regimen to bicittegravir, emtricitabine, and tenofovir alafenamide maintained virological suppression without development of resistance or unmanageable toxic effects. Thus, the fixed-dose combination of bicittegravir, emtricitabine, and tenofovir alafenamide is an efficacious and well tolerated regimen for the initial and ongoing treatment of HIV-1 infection, offering the potential for reduced drug interactions and regimen simplification (from a multi-tablet to a single-tablet regimen, with one of the smallest tablet sizes among available single-tablet regimens^{30–36}).

Contributors

All authors were involved in the development of the primary manuscript and interpretation of data, and have read and approved the final version. ESD, EDJ, PR, GC, GO, CC, JKR, J-MM, and EK enrolled participants, analysed data, independently interpreted the results, and edited and approved the report. HG, AC, HM, and EQ designed the study. Y-PL did the data analyses, which were reviewed and interpreted by JC, KA, HG, AC, HM, and EQ. The first draft was written by ESD and HG. All authors contributed to edits of the final report.

Declaration of interests

ESD reports grants from Gilead Sciences, Merck, and ViiV Healthcare, and serves as a consultant or an adviser for Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Theratechnologies, Teva, and ViiV Healthcare. EDJ reports research grants from Abbott Laboratories, Achillion Pharmaceuticals, Avexa, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix, Janssen, Merck, Sangamo, Taimed, and Tobira, and consulting fees as a member of advisory boards for Gilead Sciences and Janssen. PR reports grants from Gilead Sciences, AbbVie, Janssen, Bristol-Myers Squibb, and ViiV Healthcare; has acted as a consultant for Gilead Sciences, AbbVie, and Idenix; has given sponsored lectures for Gilead Sciences, AbbVie, and Janssen; and is a stockholder of Gilead Sciences. GC reports grants from Gilead Sciences, ViiV Healthcare, Merck, and Janssen, and advisory honoraria from Gilead Sciences and ViiV Healthcare. JKR reports personal fees from Abbott, Hexal, Merck, Gilead Sciences, AbbVie, Janssen, Merck, Bristol-Myers Squibb, ViiV Healthcare, Cipla, and Bionor. J-MM reports serving on advisory boards for Gilead Sciences, Merck, ViiV Healthcare, Janssen, Bristol-Myers Squibb, and Teva, and has received research grants from Gilead Sciences. Y-PL, JC, KA,

HG, AC, HM, and EQ are employees of Gilead Sciences and hold stock interest in the company. All other authors declare no competing interests.

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