Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study

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Summary

Background Dolutegravir has been shown to be non-inferior to an integrase inhibitor and superior to a non-nucleoside reverse transcriptase inhibitor (NNRTI). In FLAMINGO, we compared dolutegravir with darunavir plus ritonavir in individuals naive for antiretroviral therapy.

Methods In this multicentre, open-label, phase 3b, non-inferiority study, HIV-1-infected antiretroviral therapy-naive adults with HIV-1 RNA concentration of 1000 copies per mL or more and no resistance at screening were randomly assigned (1:1) to receive either dolutegravir 50 mg once daily or darunavir 800 mg plus ritonavir 100 mg once daily, with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine. Randomisation was stratified by screening HIV-1 RNA (≤100 000 or >100 000 copies per mL) and nucleoside reverse transcriptase inhibitor (NRTI) selection. The primary endpoint was the proportion of patients with HIV-1 RNA concentration lower than 50 copies per mL (Food and Drug Administration [FDA] snapshot algorithm) at week 48 with a 12% non-inferiority margin. This trial is registered with ClinicalTrials.gov, NCT01449929.

Findings Recruitment began on Oct 31, 2011, and was completed on May 24, 2012, in 64 research centres in nine countries worldwide. Of 595 patients screened, 484 patients were included in the analysis (242 in each group). At week 48, 217 (90%) patients receiving dolutegravir and 200 (83%) patients receiving darunavir plus ritonavir had HIV-1 RNA of less than 50 copies per mL (adjusted difference 7·1%, 95% CI 0·9–13·2), non-inferiority and on pre-specified secondary analysis dolutegravir was superior (p=0·025). Confirmed virological failure occurred in two (<1%) patients in each group; we recorded no treatment-emergent resistance in either group. Discontinuation due to adverse events or stopping criteria was less frequent for dolutegravir (four [2%] patients) than for darunavir plus ritonavir (ten [4%] patients) and contributed to the difference in response rates. The most commonly reported (≥10%) adverse events were diarrhoea (dolutegravir 41 [17%] patients vs darunavir plus ritonavir 70 [29%] patients), nausea (39 [16%] *vs* 43 [18%]), and headache (37 [15%] *vs* 24 [10%]). Patients receiving dolutegravir had significantly fewer low-density lipoprotein values of grade 2 or higher (11 [2%] *vs* 36 [7%]; p=0·0001).

Interpretation Once-daily dolutegravir was superior to once-daily darunavir plus ritonavir. Once-daily dolutegravir in combination with fixed-dose NRTIs represents an effective new treatment option for HIV-1-infected, treatment-naive patients.

Funding ViiV Healthcare and Shionogi & Co.

Introduction

For almost two decades, HIV treatment guidelines have recommended the use of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third antiretroviral drug for treatment-naive patients with HIV/AIDS.[1–4] Recommended drugs for use with NRTIs include the non-nucleoside reverse transcriptase inhibitors (NNRTIs; eg, efavirenz), ritonavir-boosted protease inhibitors (eg, darunavir, atazanavir), and integrase inhibitors (eg, raltegravir).

Boosted protease inhibitor regimens are often preferred as a first-line treatment because of their antiviral potency.[3] Boosted protease inhibitors also offer the advantage of infrequent selection for resistance-associated mutations with treatment failure, thus preserving future treatment options.[5] These attributes can be especially important for patients with suboptimum adherence.

The first approved HIV integrase inhibitor, raltegravir, is effective and well tolerated, but requires twice-daily dosing.[6] Elvitegravir, another HIV integrase inhibitor,[7] must be taken with food and needs pharmacological boosting, which can lead to clinically important drug interactions.[8,9]

Dolutegravir is an integrase inhibitor approved in the USA, Europe, Australia, and Canada for once-daily dosing without pharmacokinetic boosters in patients naive to antiretrovirals.[10] Dolutegravir has a profile that reduces the potential for frequent drug interactions or

Published **Online**
April 1, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60084-2

See **Online/Comment**
http://dx.doi.org/10.1016/S0140-6736(14)60447-5

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food effect.[10,11] Two phase 3 studies compared dolutegravir with an integrase inhibitor or NNRTI in therapy-naive patients. In SPRING-2,[12] once-daily dolutegravir showed non-inferiority to twice-daily raltegravir with respect to the primary endpoint (proportion of participants with HIV-1 RNA of less than 50 copies per mL at 48 weeks) and showed similar tolerability and safety to 96 weeks.[13] In SINGLE,[14] dolutegravir plus abacavir–lamivudine showed significant superiority over combination therapy with tenofovir–emtricitabine–efavirenz at 48 weeks for the primary endpoint (also proportion of participants with an HIV-1 RNA of less than 50 copies per mL), due to improved tolerability on the dolutegravir regimen. Importantly, treatment-naive patients treated with dolutegravir did not develop any resistance-associated mutations in integrase or reverse transcriptase, whereas the comparator treatment groups (ie, raltegravir and the combination tenofovir–emtricitabine–efavirenz) had patients who developed resistance-associated mutations to both the NRTI backbone drugs and integrase inhibitors or NNRTIs. Regimens based on protease inhibitors are less likely to lead to the development of resistance-associated mutations;[5] thus, direct comparison of dolutegravir with protease inhibitors can be important to further understand the efficacy and barrier to resistance of dolutegravir. We therefore undertook this phase 3b study to assess the efficacy, safety, and tolerability of dolutegravir versus a guideline-recommended boosted protease inhibitor-based regimen (darunavir plus ritonavir), in combination with two widely recommended NRTI backbones, as first-line treatment for adults with HIV-1 who were naive for antiretroviral therapy.

Methods

Study design and patients

FLAMINGO is a 96-week, phase 3b, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study conducted at 64 research centres in France, Germany, Italy, Puerto Rico, Romania, Russia, Spain, Switzerland, and the USA. Recruitment began on Oct 31, 2011, and was completed on May 24, 2012; the date of the last finding for this week-48 analysis was April 22, 2013.

Eligible patients (aged ≥18 years) had a concentration of plasma HIV-1 RNA of 1000 copies per mL or higher, no previous treatment with antiretroviral therapy, and no primary resistance to NRTIs or protease inhibitors. We excluded patients with active disease of category C from the Centers for Disease Control and Prevention, and defined laboratory values or medical characteristics such as pregnancy, moderate or severe hepatic impairment, an anticipated need for hepatitis C treatment during the study, estimated creatinine clearance of less than 50 mL/min (due to use of fixed-dose NRTI combinations), recent (within the past 5 years) or ongoing malignancy, or treatment with an HIV-1 vaccine within 90 days of screening or with any immunomodulator within 28 days. Patients could receive abacavir–lamivudine only after screening negative for the *HLA-B57*01* allele.

Ethics committee approval was obtained at all participating centres in accordance with the principles of the 2008 Declaration of Helsinki. Every patient gave written informed consent before undergoing study procedures.

Randomisation and masking

Patients were randomly assigned (1:1) via a central interface to receive either dolutegravir 50 mg once daily or darunavir 800 mg plus ritonavir 100 mg once daily. The study statistician generated the list using validated randomisation software. At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir–emtricitabine or abacavir–lamivudine. Randomisation was stratified by HIV-1 RNA (>100 000 copies per mL or ≤100 000 copies per mL) and NRTI backbone. No masking was done in this study.

Procedures

The pre-specified primary endpoint was the proportion of patients with a concentration of HIV-1 RNA lower than 50 copies per mL at week 48, using the US Food and Drug Administration (FDA) snapshot (missing, switch, or discontinuation equals failure; MSDF) algorithm. Secondary endpoints included changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory variables (such as fasting low-density lipoprotein [LDL] cholesterol), time to virological suppression, and treatment-emergent genotypic or phenotypic evidence of resistance. Other secondary endpoints were disease progression, proportion of patients who discontinued treatment because of adverse events, and health outcomes measures, including the EuroQol five dimension (EQ-5D),[15] HIV Treatment Satisfaction Questionnaire,[16,17] and Symptom Distress Module.[18]

Study visits were done at baseline and weeks 2, 4, 8, 12, 16, 24, and every 12 weeks thereafter. We measured plasma HIV-1 RNA using the Abbott Real Time HIV-1 PCR assay (Abbott Molecular, Des Plaines, IL, USA). We used a protocol-defined virological failure of two consecutive plasma HIV-1 RNA values of more than 200 copies per mL on or after week 24 (testing was repeated within 2–4 weeks for patients with HIV RNA of more than 200 copies per mL after week 24). Patients meeting this criterion were withdrawn from the study; no other follow-up was done. After week 24, patients with confirmed HIV-1 RNA between 50 and 200 copies per mL could continue in the study on the basis of investigator discretion and local guidelines. We measured CD4 cell count and percentage at every study visit (apart from week 2) to assess immunological response. We analysed viral genotype (reverse transcriptase and protease) centrally by Quest

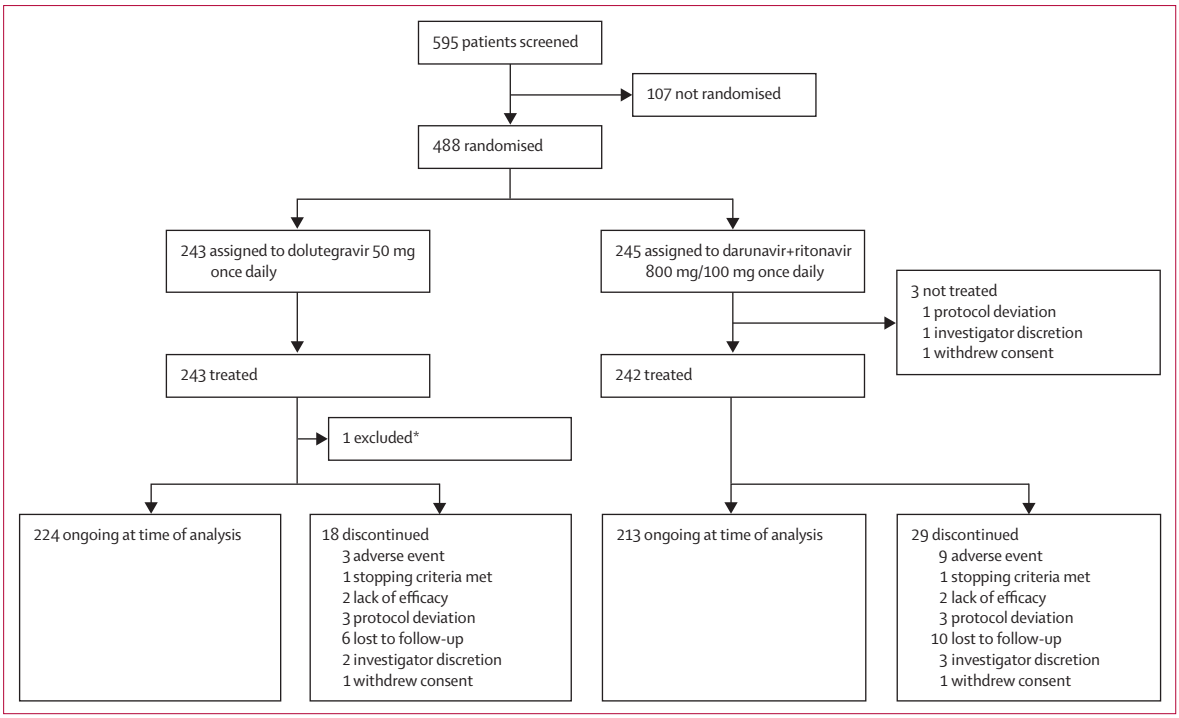

Figure 1: **Patient disposition to week 48**
Reason for discontinuation was at the discretion of the investigator. *One patient excluded at one site due to good clinical practice violations.

Diagnostics (Valencia, CA, USA) at screening. At time of confirmed virological failure we did genotypic and phenotypic analyses (reverse transcriptase, protease, and integrase) of plasma samples from baseline and suspected virological failure for all patients with protocol-defined virological failure. We used GenoSure, Standard Phenosense, GeneSeq Integrase, and PhenoSense Integrase assays (Monogram Biosciences, San Francisco, CA, USA).

We assessed safety at all study visits and recorded all adverse events and serious adverse events, laboratory variables (including haematology, fasting lipid profile, clinical chemistry, and urinalysis), and intermittent vital signs and electrocardiographs. We graded adverse events according to the Division of AIDS toxicity scales. Stopping criteria were in place to assure patient safety. Health outcomes assessments were given at baseline and weeks 4 (except EQ-5D), 24, 48, and 96.

Statistical analyses

We set the non-inferiority margin as 12%. The endpoint for the primary comparison was response rate—ie, the proportion of patients with plasma HIV-1 RNA of less than 50 copies per mL at week 48. Review of response rates of dual-NRTI therapy and dual-NRTI plus third agent therapy in earlier studies showed response rates to be similar between dual-NRTI therapy and dual-NRTI plus third agent. These response rates ranged from 34% to 49%, and all of the lower bounds of 95% CI were no less than 0%, which showed that the additional effect of third agent therapy in each study was significant. Moreover, the pooled difference (the 95% CI) of these

	Dolutegravir 50 mg once daily (n=242)	Darunavir 800 mg plus ritonavir 100 mg once daily (n=242)
Median age (range), years	34 (18–67)	34 (19–67)
Male sex	211 (87%)	201 (83%)
Race		
White	173 (71%)	176 (73%)
African American or African heritage	60 (25%)	53 (22%)
Other	8 (3%)	13 (5%)
Baseline HIV-1 RNA		
Median (IQR), $\log_{10}$ copies per mL	4·49 (4·02–5·02)	4·48 (4·01–5·01)
>100 000 copies per mL	61 (25%)	61 (25%)
Baseline CD4 cell count		
Median (IQR), cells per µL	390 (290–500)	400 (300–530)
<200 cells per µL	23 (10%)	24 (10%)
Hepatitis co-infection		
Hepatitis B only	9 (4%)	4 (2%)
Hepatitis C only	17 (7%)	15 (6%)
Hepatitis B and C	0	1 (<1%)
Dual NRTI on day 1		
Tenofovir/emtricitabine	163 (67%)	162 (67%)
Abacavir/lamivudine	79 (33%)	80 (33%)

Data are number of patients (%) unless otherwise stated. NRTI=nucleoside reverse transcriptase inhibitor.

Table 1: **Baseline demographics and disease characteristics**

response rates was 39% (95% CI 33–45). A non-inferiority margin of 12% was small enough compared with the additional effect of third agent therapy, because the non-inferiority margin was much lower than the half of the lower bound of 95% CI for the pooled difference. Also, the non-inferiority margin of 12% was in the midrange of the margins described in a review of non-inferiority trials in HIV conducted between 2000 and 2007 in which the margins varied between 10% and 15%.[19]

Non-inferiority of dolutegravir to darunavir plus ritonavir was to be concluded if the lower bound of a two-sided 95% CI for the difference in proportions (dolutegravir−[darunavir+ritonavir]) of patients with plasma HIV-1 RNA of less than 50 copies per mL at week 48 was greater than –12%. With an assumed 80% response rate in the darunavir plus ritonavir group, we needed to enrol 234 evaluable patients per group to have 90% power with a 12% non-inferiority margin and a one-sided 2·5% significance level. We did the analyses on the modified intention-to-treat exposed or modified safety populations, which consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug, excluding one patient at one study site in Russia that was closed early after the sponsor became aware of issues of non-compliance to good clinical practice in another ViiV Healthcare-sponsored study.

See Online for appendix

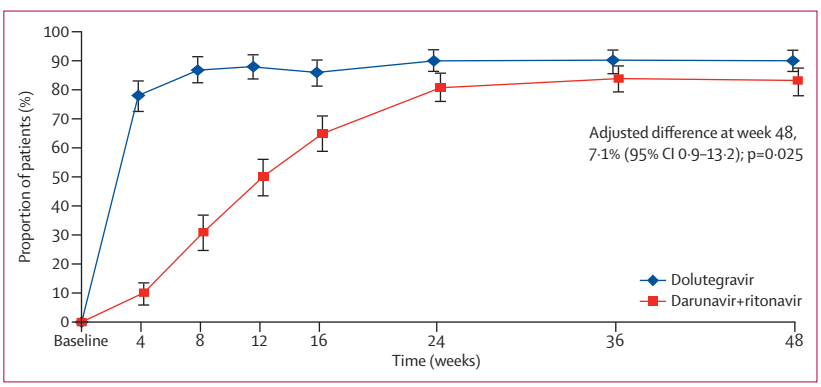

Figure 2: **Proportion of patients (95% CI) with HIV-1 RNA of less than 50 copies per mL by visit**
Error bars indicate 95% CIs.

	Dolutegravir 50 mg once daily (n=242)	Darunavir 800 mg plus ritonavir 100 mg once daily (n=242)
Virological success	217 (90%)	200 (83%)
Virological non-response*	15 (6%)	18 (7%)
Data in window outside <50 copies per mL	6 (2%)	11 (5%)
Discontinued for lack of efficacy	1 (<1%)	1 (<1%)
Discontinued for other reason while HIV-1 RNA not <50 copies per mL	3 (1%)	5 (2%)
Change in antiretroviral therapy	5 (2%)	1 (<1%)
No virological data at week 48	10 (4%)	24 (10%)
Discontinued because of adverse event or death	3 (1%)	9 (4%)
Discontinued for other reasons†	6 (2%)	11 (5%)
Missing data during window but on study	1 (<1%)	4 (2%)

Data are number of patients (%). *Virological failure. †Other reasons include protocol deviation, lost to follow-up, and withdrawal of consent.

Table 2: **Outcomes for plasma HIV-1 RNA of less than 50 copies per mL at week 48**

We used the FDA snapshot algorithm for the primary analysis. We based the adjusted difference in proportions on a stratified analysis with Cochran-Mantel-Haenszel weights for baseline HIV-1 RNA and investigator-selected backbone dual NRTIs. We assessed the tests for homogeneity for stratification factors at the one-sided 10% level.

Pre-specified secondary efficacy analyses done to support the primary endpoint analysis included a per-protocol sensitivity analysis and Kaplan-Meier estimates of the proportion of patients without virological failure by week 48. The per-protocol population consisted of the modified intention-to-treat exposed population, excluding patients with a protocol deviation that met pre-specified criteria, such as non-compliance with the study drug. If both the per-protocol and modified intention-to-treat exposed analyses showed non-inferiority, then testing for superiority was to be done. For the analyses of treatment-related discontinuation equals failure, we calculated the time to protocol-defined virological failure or discontinuation for treatment-related reasons, such as drug-related adverse events, protocol-defined safety stopping criteria, or lack of efficacy. We did a similar efficacy-related discontinuation equals failure analysis, based on the time to protocol-defined virological failure or discontinuation because of lack of efficacy.

Additionally, if the primary efficacy comparison showed non-inferiority for the modified intention-to-treat exposed population, then the following superiority comparisons were also pre-specified to be tested, with the general multistage gate keeping procedure[20,21] to adjust for the risk of false positives: change from baseline in fasting LDL cholesterol at week 48 (with repeated measures ANCOVA), incidence of abnormalities in fasting LDL cholesterol of grade 2 or higher by week 48 (with χ^2 test), time to viral suppression (with generalised Wilcoxon text), and change from baseline in overall symptom bother score at week 48 (with ANCOVA; appendix).

We analysed change from baseline in utility and thermometer scores of the EQ-5D and in symptom bother score for the comparison between dolutegravir and darunavir plus ritonavir using an ANCOVA model adjusting for the same categorical covariates as used in the primary endpoint analysis, as well as sex, race, baseline score, and age as continuous variables, regardless of their significance.

We compared the HIV Treatment Satisfaction Questionnaire total scores, lifestyle or ease subscores, and convenience item scores between the dolutegravir and darunavir plus ritonavir treatment groups using Wilcoxon rank sum tests.

This trial is registered with ClinicalTrials.gov, number NCT01449929.

Role of funding source

The sponsors of the study participated in the study design, data collection, data analysis, and data interpretation. All authors had full access to the data and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of the 595 patients screened, 488 were randomly assigned to treatment, of which 485 received at least one dose of study drug and 484 patients were included in the analysis (figure 1). Baseline demographics and disease characteristics were similar between treatment groups (table 1). At week 8, 211 (87%) of 242 patients in the dolutegravir group and 74 (31%) of 242 in the darunavir plus ritonavir group had achieved plasma HIV-1 RNA of less than 50 copies per mL. For the primary analysis at week 48, 217 (90%) patients in the dolutegravir group and 200 (83%) in the darunavir plus ritonavir group had reached this threshold (figure 2, table 2). The adjusted treatment difference between groups was 7·1% (95% CI 0·9–13·2), which met non-inferiority and was supported by the per-protocol analysis (appendix). Additionally, dolutegravir was significantly superior to darunavir plus ritonavir (p=0·025).

Treatment difference across high and low baseline HIV-1 RNA strata showed a significantly higher treatment difference in patients with high baseline viral load (p=0·005; appendix). In patients with baseline HIV RNA of greater than 100 000 copies per mL in the darunavir plus ritonavir group, FDA snapshot non-response was split between virological (11 [18%] of 61 patients) and non-virological (seven [11%] of 61 patients) reasons, with the non-virological reasons predominantly driven by adverse event-related discontinuations. In patients with high viral load at baseline, the response rate was higher for patients in the dolutegravir treatment group than for patients in the

	Dolutegravir 50 mg once daily (n=242)	Darunavir 800 mg plus ritonavir 100 mg once daily (n=242)
Any event	206 (85%)	205 (85%)
Diarrhoea	41 (17%)	70 (29%)
Nausea	39 (16%)	43 (18%)
Headache	37 (15%)	24 (10%)
Nasopharyngitis	22 (9%)	19 (8%)
Upper respiratory tract infection	13 (5%)	23 (10%)
Insomnia	18 (7%)	15 (6%)
Cough	13 (5%)	17 (7%)
Vomiting	14 (6%)	15 (6%)
Fatigue	15 (6%)	12 (5%)
Pyrexia	13 (5%)	14 (6%)
Dizziness	14 (6%)	11 (5%)
Rash	9 (4%)	15 (6%)
Back pain	9 (4%)	12 (5%)
Pharyngitis	7 (3%)	12 (5%)
Bronchitis	5 (2%)	13 (5%)
Sinusitis	6 (2%)	12 (5%)
Depression	11 (5%)	6 (2%)
Arthralgia	5 (2%)	11 (5%)

Data are number of patients (%) reporting an event.

Table 3: **Common adverse events (≥5% incidence in either treatment group)**

	Dolutegravir 50 mg once daily (n=242)	Darunavir 800 mg plus ritonavir 100 mg once daily (n=242)
Patients with serious adverse events	26 (11%)	13 (5%)
Infections and infestations	5 (2%)	8 (3%)
Acute hepatitis C	0	1 (<1%)
Acute sinusitis	0	1 (<1%)
Appendicitis	1 (<1%)	0
Bronchitis	0	1 (<1%)
Herpes zoster disseminated	0	1 (<1%)
Perineal abscess	1 (<1%)	0
Pneumonia	0	1 (<1%)
Pneumonia bacterial	0	1 (<1%)
Pulmonary tuberculosis	0	1 (<1%)
Pyelonephritis	1 (<1%)	0
Staphylococcal infection	0	1 (<1%)
Subcutaneous abscess	0	1 (<1%)
Tonsillitis	1 (<1%)	0
Urinary tract infection	1 (<1%)	0
Gastrointestinal disorders	6 (2%)	2 (<1%)
Abdominal adhesions	1 (<1%)	0
Anal fistula	1 (<1%)	0
Constipation	0	1 (<1%)
Diarrhoea haemorrhagic	0	1 (<1%)
Haematemesis	1 (<1%)	0
Haemorrhoids	1 (<1%)	0
Odynophagia	1 (<1%)	0
Pancreatitis acute	1 (<1%)	0
Small intestinal obstruction	1 (<1%)	0
Psychiatric disorders	4 (2%)	1 (<1%)
Depression	1 (<1%)	1 (<1%)
Suicide attempt	2 (<1%)	0
Drug abuse	1 (<1%)	0
Injury, poisoning, and procedural complications	4 (2%)	0
Overdose	2 (<1%)	0
Postoperative ileus	1 (<1%)	0
Stab wound	1 (<1%)	0
Nervous system disorders	4 (2%)	0
Cerebrovascular accident	1 (<1%)	0
Epilepsy	1 (<1%)	0
Grand mal convulsion	1 (<1%)	0
Syncope	1 (<1%)	0

(Table 4 continues on next page)

	Dolutegravir 50 mg once daily (n=242)	Darunavir 800 mg plus ritonavir 100 mg once daily (n=242)
(Continued from previous page)		
Cardiac disorders	1 (<1%)	1 (<1%)
Congestive cardiomyopathy	1 (<1%)	0
Myocardial infarction	0	1 (<1%)
Musculoskeletal and connective tissue disorders	2 (<1%)	0
Arthralgia	1 (<1%)	0
Polyarthritis	1 (<1%)	0
Renal and urinary disorders	1 (<1%)	1 (<1%)
Calculus urinary	0	1 (<1%)
Renal failure acute	1 (<1%)	0
Hepatobiliary disorders	1 (<1%)	0
Cholelithiasis	1 (<1%)	0
Immune system disorders	0	1 (<1%)
Drug hypersensitivity	0	1 (<1%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (<1%)	0
Hodgkin's disease	1 (<1%)	0
Respiratory, thoracic, and mediastinal disorders	1 (<1%)	0
Asthma	1 (<1%)	0

Data are number of patients (%) reporting an event.

Table 4: **Summary of serious adverse events by system organ class**

darunavir plus ritonavir treatment group, irrespective of the background dual NRTI given (appendix).

CD4 cell counts increased from baseline to week 48 by a median of 210 cells per µL in both groups (IQR 120–350 for dolutegravir; 110–290 for darunavir plus ritonavir).

Four patients had protocol-defined virological failure; two in the dolutegravir group (HIV-1 RNA at protocol-defined virological failure 2270 and 668 copies per mL, week 24 for each) and two in the darunavir plus ritonavir group (HIV-1 RNA of 218 copies per mL at protocol-defined virological failure, week 48; and HIV-1 RNA of 61754 copies per mL at protocol-defined virological failure, week 36). Both patients in the dolutegravir group received tenofovir–emtricitabine as the NRTI backbone, whereas the two patients in the darunavir plus ritonavir group received abacavir–lamivudine as the NRTI backbone. None of these patients had treatment-emergent primary integrase inhibitor, protease inhibitor, or NRTI resistance.

Over 48 weeks, both groups had similar rates of adverse events (tables 3, 4) and low rates of adverse events leading to discontinuation (dolutegravir [2%] *vs* darunavir plus ritonavir [4%]), although the differences in discontinuations because of adverse events contributed to the differences in efficacy. The most frequently reported adverse events were diarrhoea, nausea, headache, and nasopharyngitis (table 3), with most events reported as grade 1 or grade 2. Serious adverse events were reported more frequently in the dolutegravir group (11%) than in the darunavir plus ritonavir group (5%). We noted no discernible patterns of serious adverse events, since each individual serious adverse event was reported in less than 1% of patients in each treatment group (table 4). One serious adverse event was deemed drug-related, a suicide attempt in a patient in the dolutegravir group who had previous history of suicidal ideation. No deaths occurred in this study.

The changes in lipid profile through week 48 were favourable for dolutegravir compared with darunavir plus ritonavir. The mean increase in fasting LDL cholesterol at week 48 was significantly lower in the dolutegravir group than in the darunavir plus ritonavir group (adjusted mean difference, –0·30; 95% CI –0·42 to –0·19; p<0·0001), against a pre-specified p value threshold of 0·025 (two-sided). The dolutegravir group had significantly fewer LDL values of grade 2 or higher than did the darunavir plus ritonavir group (2% *vs* 7%; p=0·0001), against a pre-specified p value threshold of 0·045 (two-sided; appendix).

Increases in serum creatinine were evident in the dolutegravir group by week 2, but remained stable to week 48 (appendix). The change from baseline values ranged from –24·8 to 48·6 µmol/L for dolutegravir and from –240·6 to 37·1 µmol/L for darunavir plus ritonavir. Post-baseline emergent grade 1 creatinine toxic effects were reported infrequently (dolutegravir, 10 patients [4%]; darunavir plus ritonavir, two patients [<1%]); two (<1%) patients in the dolutegravir group had grade 2 toxic effects, and no patients had grade 3 or 4 toxic effects. No patient in either group discontinued because of renal events during the 48 weeks. The median change from baseline in urine albumin/creatinine ratios was 0·0 for both treatment groups at week 48. Nine (4%) patients receiving dolutegravir and six (2%) patients receiving darunavir plus ritonavir had maximum treatment-emergent increases in alanine aminotransferase three times or more the upper limit of normal (appendix). One patient (<1%) receiving dolutegravir and four patients (2%) receiving darunavir plus ritonavir met the protocol liver stopping criteria, with all cases related to other causes (ie, barbiturate use for the patient given dolutegravir; chronic hepatitis B and acute hepatitis C infection for the patients given darunavir plus ritonavir).

No significant differences were noted between the dolutegravir and darunavir plus ritonavir treatment groups in the EQ-5D utility and thermometer scores or the Symptom Distress Module bother score. However, for the HIV Treatment Satisfaction Questionnaire, patients in the dolutegravir group had significantly higher mean total scores at week 24 than did patients in the darunavir plus ritonavir group, as well as significantly higher scores in the lifestyle or ease subscore at weeks 24 and 48, and for the convenience item score at weeks 4, 24, and 48 (table 5).

Discussion

FLAMINGO is a head-to-head, open-label comparison of a once-daily integrase inhibitor and a boosted protease

	Dolutegravir 50 mg once daily (n=214)	Darunavir 800 mg plus ritonavir 100 mg once daily (n=206)	p value*
	Median (range)	Median (range)	
Total score by week			
Week 4 (dolutegravir, n=206; darunavir plus ritonavir, n=192)	56·0 (21–60)	54·0 (22–60)	0·050
Week 24 (dolutegravir, n=211; darunavir plus ritonavir, n=200)	58·0 (29–60)	57·0 (21–60)	0·005
Week 48 (dolutegravir, n=212; darunavir plus ritonavir, n=201)	58·0 (40–60)	57·0 (29–60)	0·060
Lifestyle/ease subscore by week			
Week 4 (dolutegravir, n=202; darunavir plus ritonavir, n=190)	28·0 (9–30)	27·0 (8–30)	0·167
Week 24 (dolutegravir, n=210; darunavir plus ritonavir, n=199)	29·0 (14–30)	28·0 (8–30)	0·017
Week 48 (dolutegravir, n=211; darunavir plus ritonavir, n=201)	29·0 (19–30)	28·0 (13–30)	0·044
Convenience item score by week			
Week 4 (dolutegravir, n=204; darunavir plus ritonavir, n=190)	6·0 (3–6)	6·0 (1–6)	0·0003
Week 24 (dolutegravir, n=211; darunavir plus ritonavir, n=200)	6·0 (3–6)	6·0 (0–6)	0·002
Week 48 (dolutegravir, n=212; darunavir plus ritonavir, n=201)	6·0 (3–6)	6·0 (2–6)	0·003

Individual item scores ranged from 6 (very satisfied) to 0 (very dissatisfied). The treatment satisfaction total score (range 0–60) was the sum of the individual items. The lifestyle or ease subscore was the sum of items 4, 5, 6, 7, and 8 (range 0–30). This table includes patients from France, Germany, Italy, Spain, and the USA, for whom valid questionnaire translations were available. *Dolutegravir *vs* darunavir plus ritonavir p values at each timepoint based on Wilcoxon rank sum test.

Table 5: **Summary and statistical analysis of HIV Treatment Satisfaction Questionnaire scores by week**

inhibitor for first-line antiretroviral therapy (panel). At week 48, once-daily dolutegravir 50 mg was better than once-daily darunavir 800 mg plus ritonavir 100 mg, both in combination with coformulated tenofovir–emtricitabine or abacavir–lamivudine, with 90% of patients in the dolutegravir group and 83% in the darunavir plus ritonavir group achieving plasma HIV-1 RNA concentrations of less than 50 copies per mL. Differences in efficacy were driven primarily by lower rates of treatment withdrawal and a higher rate of virological response in patients treated with dolutegravir than in those treated with darunavir plus ritonavir, particularly in patients with high baseline viral load (HIV-1 RNA of more than 100 000 copies per mL). Based on study outcomes for the snapshot analysis, the primary drivers for the larger treatment difference between dolutegravir and darunavir plus ritonavir in the high viral load stratum were absence of virological suppression and discontinuations due to adverse events in the darunavir plus ritonavir treatment group. This finding was supported by secondary efficacy and safety analyses, which showed similar numbers and types of safety events in both groups.

The 83% response rate for darunavir plus ritonavir in our study is similar to the response rate in the ARTEMIS study,[22] in which 84% of antiretroviral therapy-naive patients receiving darunavir 800 mg plus ritonavir 100 mg once daily achieved HIV-1 RNA concentration of less than 50 copies per mL at week 48 (time to loss of virological response). Compared with our study, the population included in ARTEMIS[22] was at a more advanced stage of disease with baseline CD4 count of 225 cells per μL and 34% of patients with HIV-1 RNA of more than 100 000 copies per mL. The response rates were similar for patients receiving darunavir plus ritonavir irrespective of baseline HIV-1 RNA (86% for those with less than 100 000 HIV-1 RNA copies per mL, and 79% for those with ≥100 000 copies). In our study, response rates for patients with HIV-1 RNA of more than 100 000 copies per mL receiving darunavir plus ritonavir were lower (70%). In participants with high viral load at baseline, the response rate was higher in the dolutegravir group than in the darunavir plus ritonavir group, irrespective of the background dual NRTI. However, the number of participants is too small to draw definitive conclusions and is the subject of further research.

This open-label design enabled assessment of the effect of pill burden on patient satisfaction and virological outcome for patients who received two versus four pills per day. FLAMINGO[23] was designed as an open-label study because of the difficulty in blinding a study that contains ritonavir, in view of its well described side-effects and lipid profile. Additionally, a double-blind and double-dummy design would have increased the pill burden in this study, which has an effect on adherence and subject attrition. Lastly, the use of a double-blind, double-dummy design would have precluded the assessment of the health outcomes measures included in FLAMINGO.

Although we examined all patients with protocol-defined virological failure irrespective of HIV-1 RNA value at failure, we did not detect antiviral resistance to integrase inhibitors or the NRTI backbone in those who received dolutegravir or to protease inhibitors or the NRTI backbone in those who received darunavir plus ritonavir.

These data are consistent with findings from a study of in-vitro passage,[24] which showed that resistance was difficult to select for, and with two other large, randomised, blinded studies in treatment-naive patients.[12–14] As neither treatment group showed resistance mutations, this study further supports that dolutegravir has a high barrier to the development of virological resistance, similar to the profile shown by protease inhibitors.

One major limitation of the open-label design was the assessment of safety. Since the safety profile for both drugs was consistent with current labelling,[10,25] the safety assessments still provide valuable information. No specific trends in adverse events were noted. Only one serious adverse event was deemed related to dolutegravir, but this event (attempted suicide) was noted in a patient with a previous history of depression and suicide attempts. With the exception of two patients reporting suicide attempt and overdose in the dolutegravir group, both of whom had relevant past medical histories for depression or suicide attempt, serious adverse events occurred in individual patients, with no discernible pattern. To date, other large phase 3 clinical trials have not shown a similar pattern for dolutegravir; this will be assessed further at the week 96 analysis.

Changes in serum creatinine for dolutegravir were consistent with previous findings and not regarded as clinically significant.[26,27] Dolutegravir inhibits the organic cation transporter 2, similar to other drugs such as trimethoprim or cimetidine,[28,29] which decrease tubular secretion of creatinine and therefore increase concentrations of serum creatinine without affecting glomerular filtration.[30,31] No patients had grade 3 or 4 creatinine elevations, and no patients in either group discontinued the study because of a renal adverse event.

A limitation of this study is the low number of non-white, female, and co-infected (HIV and hepatitis B or HIV and hepatitis C) patients enrolled, which is not fully representative of the HIV global epidemic. ARIA is an ongoing open-label, randomised, phase 3b clinical trial in treatment-naive HIV-1–infected women, studying the safety and efficacy of a once-daily regimen of dolutegravir–abacavir–lamivudine (Clinicaltrials.gov, NCT01910402). ARIA is being done in 13 countries and will provide more data on the efficacy and safety of dolutegravir in this population. Similar to other studies in antiretroviral therapy-naive patients, fewer patients with advanced disease were enrolled in FLAMINGO, probably because of current treatment guidelines that support early initiation of therapy.[32–34] Another limitation is the open-label nature of the study. Potential sources of bias are considered here. Part of the difference in the virological response rates was driven by a higher percentage of discontinuations for other reasons (eg, lost to follow-up) in the darunavir plus ritonavir group than in the dolutegravir group, but we found no evidence that the process for tracking missed study visits was implemented differently for each treatment group. Sensitivity analyses all showed treatment differences in favour of the dolutegravir treatment group. This difference was not significant for sensitivity analyses that excluded discontinuations for other reasons (treatment-related discontinuation, efficacy-related discontinuation), but it was significant for the per-protocol analysis. Further, analyses by stratification factors and key subgroups supported the primary endpoint results. Few patients (six patients) receiving darunavir plus ritonavir and one patient receiving dolutegravir withdrew within 14 days after randomisation (shortly after knowledge of treatment assignment); in some cases, these patients withdrew because of reasons clearly unrelated to study drug assignment (eg, incarceration). For potential bias in virological retesting for blips (HIV-1 RNA between 50 and 200 copies per mL), investigators received the same instructions for following up virological blips and doing viral load retests in both groups. Proportionally, more retests were done in the darunavir plus ritonavir group than in the dolutegravir group, although the numbers are small. Therefore, we noted no evidence for strong bias on virological retests for either treatment group in this open-label study.

On the basis of our findings, dolutegravir is expected to be an appealing new treatment option for treatment-naive patients with HIV.

Panel: Research in context

Systematic review

We searched PubMed with combinations of the keywords "integrase strand transfer inhibitor," "integrase inhibitor," "protease inhibitor," "ritonavir," "darunavir," "superior," "noninferior," "boosted," with no restrictions on language or date published. The integrase inhibitor class has provided the opportunity to construct potent and well tolerated first-line regimens. The US Department of Health and Human Services recently updated their guidelines to include dolutegravir with either abacavir–lamivudine or tenofovir–emtricitabine as recommended options for HIV-infected, treatment-naive individuals.[34] The Panel now recommends the following four integrase inhibitor-based regimens as preferred regimens for antiretroviral therapy-naive patients (listed in order of drug approval): (1) raltegravir 400 mg twice daily plus tenofovir 300 mg–emtricitabine 200 mg once daily; (2) elvitegravir 150 mg–cobicistat 150 mg–tenofovir 300 mg–emtricitabine 200 mg once daily in patients with estimated creatinine clearance ≥70 mL/min; (3) dolutegravir 50 mg once daily plus abacavir 600 mg–lamivudine 300 mg once daily in patients who are *HLA-B57*01* negative; and (4) dolutegravir 50 mg once daily plus tenofovir 300 mg–emtricitabine 200 mg once daily.

Interpretation

Data from the FLAMINGO study provide additional data in the treatment-naive population. This study demonstrated higher virological potency of dolutegravir over the boosted protease inhibitor, darunavir, in an HIV-1–infected, treatment-naive population. This difference between the regimens was due to differences in tolerability and bigger treatment differences noted in the high viral load stratum. Both groups showed low rates of virological failure, and there was no evidence of treatment-emergent resistant mutations. Taken together, the results of this head-to-head phase 3 study of dolutegravir versus darunavir boosted by ritonavir suggest that once-daily dolutegravir 50 mg, in combination with two other antiretroviral drugs, is a well tolerated and effective therapy for antiretroviral therapy-naive adults, and is an alternative to the darunavir-containing regimen.

Contributors

BC was involved in data interpretation and writing and reviewing the report. JF was involved in data analysis and interpretation and report preparation. JvL contributed to the literature search, data collection, data analysis, data interpretation, and writing for the report. M-AK-J participated in the acquisition of data and drafting/revising of the report. AA enrolled patients in the study and was involved in the acquisition of data, collected and analysed data, participated in data interpretation, and provided input to the report. ID participated in patient recruitment, data collection, and reviewing the report. VP contributed to the data collection and critical review of the report. JF was involved in data collection and interpretation and writing of the report. RO enrolled patients in the trial. MS participated in the study design, data collection and interpretation, and review of the report. JH was the study statistician, was involved in data analysis and interpretation, and contributed to writing and reviewing the report. CB contributed to the acquisition of data and clinical oversight of the study, analysis and interpretation of data for the report, and drafted the report and revised it critically for content. TF contributed to the study design, data interpretation, and report review. SM contributed to the study design, data collection, data analysis and interpretation, and writing/editing of the report. All authors have provided input to the report and approved the final version.

Declaration of interests

BC has served as a consultant on advisory boards, participated in speakers' bureaus, or consulted on clinical trials with Bristol-Myers Squibb, Abbott, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. JF has received research grants from Bristol-Myers Squibb, ViiV Healthcare, Tobira Therapeutics, and Pfizer; has received speaker's honoraria from Bristol-Myers Squibb, ViiV Healthcare, Janssen, and Merck; has been a consultant or adviser for Janssen, Merck, and GlaxoSmithKline/ViiV Healthcare; and has received travel grants from Bristol-Myers Squibb, ViiV Healthcare, Janssen, Merck, and Tobira Therapeutics. JvL has received honoraria, educational, and travel grants from ViiV Healthcare and Janssen-Cilag. M-AK-J has received travel grants from MSD, ViiV Healthcare, and Tibotec, and has received payment for development of educational presentations from Gilead Sciences and MSD. AA has received honoraria for consultancy from Bristol-Myers Squibb, Gilead Sciences, Merck, Janssen-Cilag, AbbVie, and ViiV Healthcare, and has received research funding from Bristol-Myers Squibb, Gilead Sciences, and ViiV Healthcare. JF has received travel grants and unrestricted grants from Abbot, Bristol-Myers Squibb, Gilead Sciences, Merck, Janssen, and ViiV Healthcare. MS has served as a scientific adviser for Bristol-Myers Squibb and Gilead Sciences and as a research investigator for ViiV Healthcare, GlaxoSmithKline, Merck, Ardea, Bristol-Myers Squibb, Gilead Sciences, BIPI, and AbbVie. JH, CB, and SM are employees of GlaxoSmithKline and own GlaxoSmithKline stock. TF is an employee of Shionogi & Co, Ltd. ID, VP, and RO declare that they have no competing interests.

Acknowledgments

Funding for this work was provided by ViiV Healthcare LLC and Shionogi & Co. We thank the FLAMINGO study patients and their families and caregivers for participation in the study. We thank the following FLAMINGO investigators and their staff. France: M-A Khuong-Josses, J-M Molina, G Pialoux, F Raffi, J Reynes, P Yeni. Germany: W Kern, C Stephan, J Van Lunzen. Italy: A Antinori, A D'Arminio Monforte, G Di Perri, G Guaraldi, A Lazzarin. Puerto Rico: I Melendez-Rivera, J Morales Ramirez, J Santana-Bagur. Romania: D Duiculescu, L Preotescu, S Rugina. Russia: O Kozyrev, V Kulagin, V Pokrovskiy, A Shuldyakov, E Voronin. Spain: B Clotet, J Gatell, D Podzamczer, R Rubio, P Viciana. Switzerland: M Cavassini, J Fehr, H Furrer. USA: N Bellos, G Blick, I Brar, C Dietz, R Dretler, R Elion, J Eron, J Feinberg, G Georgescu/A Scribner, D Hagins, W Henry, C Martorell, C Mayer, L McCurdy, A Mills, M Murphy, C Newman, R Ortiz, G Pierone, A Rana, M Saag, P Shalit, G Simon, L Sloan, J Stephens, P Tebas, W Towner, M Tribble, D Warner, A Wilkin, B Young. The authors also wish to acknowledge the following individuals for editorial assistance during the development of this report: Susan Porter-Atkinson, J Louise Martin-Carpenter, and Gina Uhlenbrauck.

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