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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

This online publication has been corrected. The corrected version first appeared at thelancet.com on Nov 28, 2018.

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SUPPORTING MATERIAL

Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, double-blind, non-inferiority, phase 3 trials

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SUPPORTING METHODS

Participants

Prior use of pre- and post-exposure prophylaxis for HIV-1 infection was allowed if the last dose was >1 year before diagnosis or the participant was confirmed as being seronegative between last dose and diagnosis. Exclusion criteria included severe hepatic impairment or unstable liver disease; evidence of hepatitis B virus infection at screening; anticipated need for hepatitis C virus therapy in the first 48 weeks; untreated syphilis; certain ongoing malignancies; suicidality risk, as assessed by the investigator; exposure to certain therapies within stipulated timeframes before screening (ie, HIV-1 immunotherapeutic vaccines, radiotherapy, cytotoxic chemotherapy, systemic immunosuppressants, any investigational drug or vaccine); or certain clinical laboratory assessments (eg, verified Grade 4 abnormalities, creatinine clearance <50 mL/min).

Outcomes

Secondary endpoints were

- Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Weeks 24, 96, and 144 using the FDA Snapshot algorithm (Missing, Switch, or Discontinuation = Failure [MSD = F]) for the ITT-E population
- Time to viral suppression (HIV-1 RNA <50 copies/mL)
- Absolute values and changes from baseline in CD4+ cell counts at Weeks 24, 48, 96, and 144
- Incidence of disease progression (HIV-associated conditions, AIDS, and death)
- Incidence of treatment-emergent genotypic and phenotypic resistance to dolutegravir and lamivudine or tenofovir disoproxil fumarate and emtricitabine in participants meeting confirmed virologic withdrawal criteria
- Incidence and severity of adverse events (AEs) and laboratory abnormalities
- Proportion of participants who discontinued treatment due to AEs over 24, 48, 96, and 144 weeks
- Change from baseline in renal and bone biomarkers at Weeks 24, 48, 96, and 144
- Change from baseline in fasting lipids at Weeks 24, 48, 96, and 144
- Incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144
- Proportion of participants by patient subgroups (eg, by age, gender, baseline CD4+ cell count) with plasma HIV-1 RNA <50 copies/mL at Weeks 24, 48, 96, and 144 using the Snapshot algorithm for the ITT-E population
- Change from baseline in CD4+ cell counts at Weeks 24, 48, 96, and 144 by patient subgroups
- Change from baseline in health-related quality of life using the EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or withdrawal from the study)

Statistical analysis

Change from baseline at Week 48 in serum or plasma lipids, renal biomarkers, and bone biomarkers was also analysed using an ANCOVA based on a data set where multiple imputations have been drawn from a multivariate normal model with a Markov chain Monte Carlo approach to impute missing observations. For serum or plasma lipids, the statistical model was adjusted for treatment, baseline lipid value, randomisation strata term baseline plasma HIV-1 RNA, and baseline CD4+ cell count and age as a continuous covariate. For renal biomarkers, the statistical model was adjusted for treatment, baseline biomarker value, randomisation strata term baseline plasma HIV-1 and baseline CD4+ cell count, age, sex (female vs male), race (white, African American/African heritage, Asian, other), presence of diabetes mellitus, and presence of hypertension. For bone biomarkers, the statistical model was adjusted for treatment, baseline biomarker value, randomisation strata term baseline plasma HIV-1 RNA and baseline CD4+ cell count, age, sex, race, BMI (<25 vs \geq 25 kg/m²), smoking status (never vs former vs current smoker), and current vitamin D use (yes vs no). If the distribution of a particular biomarker was not normal, the data were log-transformed and the log ratio of Week 48 over baseline was used in the statistical analyses. In the summaries, geometric means replaced arithmetic means, 95% CIs replaced standard deviations, and mean changes from baseline were presented as geometric mean ratios.

Change from baseline in EQ-5D-5L utility score at Week 48 and change from baseline in EQ VAS at Week 48 was analysed using a mixed-effect model repeat measurement (MMRM) adjusted for treatment, randomisation strata terms baseline plasma HIV-1 RNA (\leq 100,000 vs >100,000 copies/mL) and baseline CD4+ cell count (\leq 200 vs >200 cells/mm³), and baseline value as a covariate, with visit as the repeated factor. Treatment-by-visit and baseline score-by-visit interaction terms were also included in the MMRM model. All data analysis was performed using SAS (version 9.4).

SUPPORTING TABLES

Supporting Table 1. Randomized Participants by Country

Countries, n (%) ^a	2DR (N=719)	3DR (N=722)	Total (N=1441)
United States	129 (18)	119 (16)	248 (17)
Argentina	91 (13)	91 (13)	182 (13)
Spain	78 (11)	88 (12)	166 (12)
Russia	79 (11)	83 (11)	162 (11)
Italy	67 (9)	63 (9)	130 (9)
Taiwan	57 (8)	60 (8)	117 (8)
Mexico	51 (7)	52 (7)	103 (7)
Canada	21 (3)	25 (3)	46 (3)
France	12 (2)	25 (3)	37 (3)
United Kingdom	21 (3)	16 (2)	37 (3)
Portugal	24 (3)	12 (2)	36 (2)
Germany	14 (2)	21 (3)	35 (2)
Belgium	13 (2)	17 (2)	30 (2)
Romania	18 (3)	11 (2)	29 (2)
Peru	11 (2)	12 (2)	23 (2)
Australia	14 (2)	6 (<1)	20 (1)
Switzerland	8 (1)	5 (<1)	13 (1)
Poland	3 (<1)	6 (<1)	9 (<1)
Republic of Korea	3 (<1)	4 (<1)	7 (<1)
South Africa	4 (<1)	3 (<1)	7 (<1)
The Netherlands	1 (<1)	3 (<1)	4 (<1)

2DR, 2-drug regimen; 3DR, 3-drug regimen.

^aPercentages may not sum to 100 due to rounding.

Supporting Table 2. Participants With AEs in GEMINI-1 and GEMINI-2^a

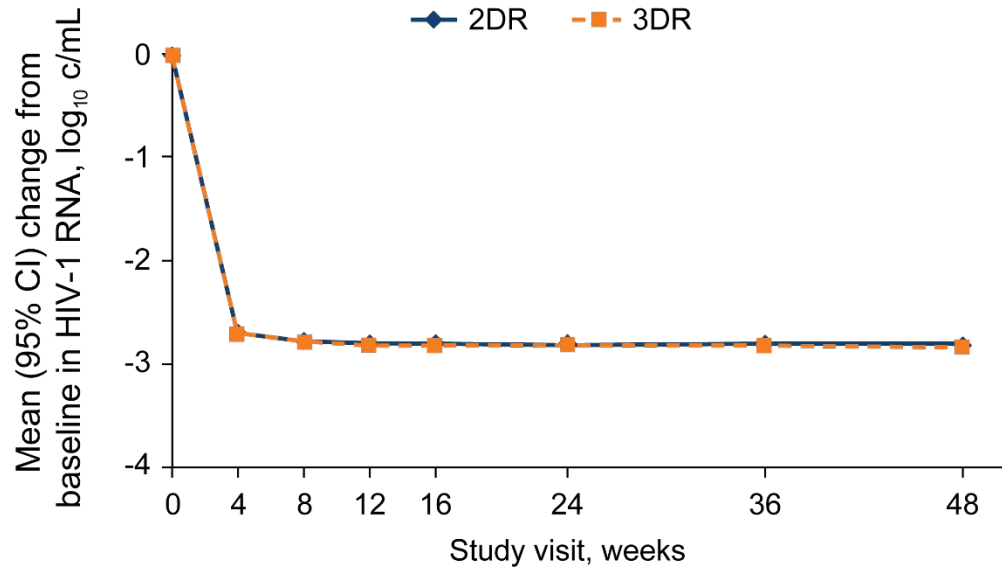
n (%)	GEMINI-1		GEMINI-2	
	2DR (N=356)	3DR (N=358)	2DR (N=360)	3DR (N=359)
Any AE	276 (78)	295 (82)	267 (74)	284 (79)
AEs occurring in ≥5% of participants in either group of either trial				
Headache	40 (11)	44 (12)	31 (9)	31 (9)
Diarrhea	33 (9)	42 (12)	35 (10)	35 (10)
Nasopharyngitis	33 (9)	37 (10)	22 (6)	41 (11)
Upper respiratory tract infection	24 (7)	22 (6)	32 (9)	22 (6)
Insomnia	16 (4)	29 (8)	11 (3)	16 (4)
Nausea	12 (3)	30 (8)	15 (4)	23 (6)
Back pain	19 (5)	19 (5)	16 (4)	12 (3)
Pharyngitis	23 (6)	13 (4)	13 (4)	19 (5)
Syphilis	17 (5)	15 (4)	10 (3)	12 (3)
Bronchitis	20 (6)	11 (3)	8 (2)	10 (3)
Fatal AEs	0	0	2 (<1) ^b	0
Serious AEs	21 (6)	22 (6)	29 (8)	33 (9)
Drug-related AEs	71 (20)	94 (26)	55 (15)	75 (21)
Drug-related AEs occurring in ≥2% of participants in either group of either trial				
Headache	14 (4)	19 (5)	7 (2)	11 (3)
Nausea	8 (2)	23 (6)	6 (2)	16 (4)
Diarrhoea	6 (2)	14 (4)	8 (2)	5 (1)
Insomnia	7 (2)	12 (3)	6 (2)	6 (2)
Somnolence	7 (2)	5 (1)	1 (<1)	2 (<1)
Dizziness	5 (1)	6 (2)	3 (<1)	7 (2)
Fatigue	6 (2)	3 (<1)	4 (1)	3 (<1)
Grade 2-5	21 (6)	25 (7)	21 (6)	22 (6)
Grade 2-5 occurring in ≥1% of participants in either group of either trial				
Headache	4 (1)	7 (2)	4 (1)	1 (<1)
Diarrhoea	2 (<1)	4 (1)	1 (<1)	0
Insomnia	0	4 (1)	2 (<1)	2 (<1)
AEs leading to permanent discontinuation of treatment/withdrawal from study	7 (2)	8 (2)	8 (2)	8 (2)

AE, adverse event; 2DR, 2-drug regimen; 3DR, 3-drug regimen.

^aData cutoff was May 22, 2018. ^bIncludes one event due to Burkitt's lymphoma and the other due to acute myocardial infarction with possible association with drug abuse; neither was considered by the investigators to be related to study medication; both participants had HIV-1 RNA <40 copies/mL at last study visit.

SUPPORTING FIGURE

Supporting Figure. Change from baseline in plasma HIV-1 RNA by visit. Error bars are too small to be seen for some data points. 2DR, two-drug regimen; 3DR, three-drug regimen.



2DR, n	716	708	704	686	681	688	674	664
3DR, n	717	706	699	699	688	688	681	675