SUPPLEMENTAL DIGITAL CONTENT 1

Supplemental Methods

Health outcomes

Assessments of health-related quality of life using the EuroQol–5 Dimensions–5 Levels (EQ-5D-5L) Questionnaire[1] were planned for baseline; Weeks 4, 24, 48, 96, and 144; and study withdrawal. The EQ-5D-5L consists of 2 distinct scoring components: the health state utility score (potential range, −0.281 to 1) and the visual analog scale (VAS; potential range, 0-100). Higher scores on the EQ-5D-5L indicate better health.

Secondary endpoints[2]

- Proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 96 using the FDA Snapshot algorithm (Missing, Switch, or Discontinuation = Failure [MSD = F]) for the intention-to-treat–exposed (ITT-E) population
- Time to viral suppression (HIV-1 RNA <50 copies/mL)
- Absolute values and changes from baseline in CD4+ cell count at Weeks 48 and 96
- 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/emtricitabine in participants meeting confirmed virologic withdrawal criteria
- Incidence and severity of adverse events (AEs) and laboratory abnormalities
- Proportion of participants who discontinued treatment because of AEs over 48 and 96 weeks
- Change from baseline in renal and bone biomarkers at Week 96
- Change from baseline in fasting lipids at Week 96

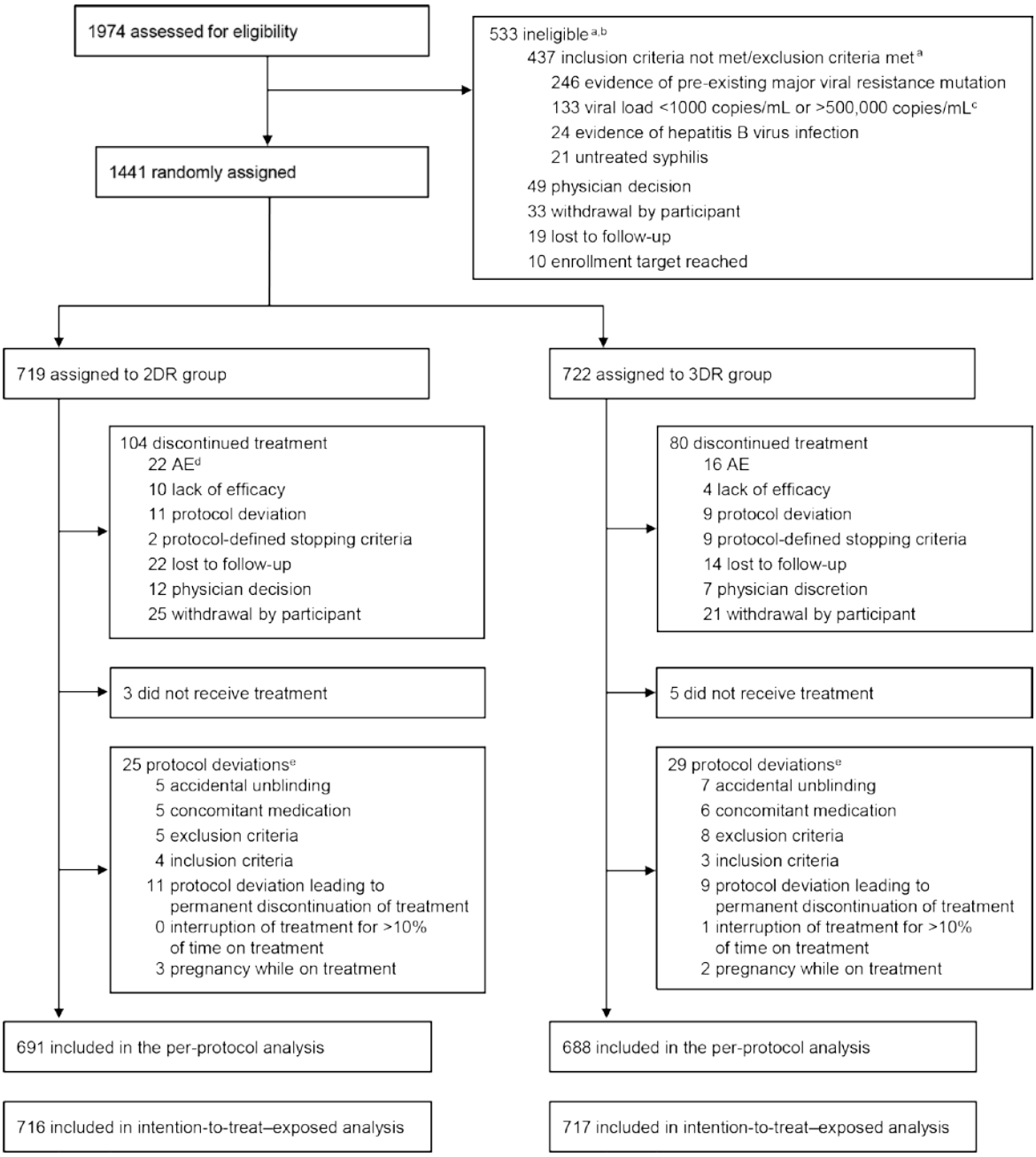
- Incidence of grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Week 96
- Proportion of participants by patient subgroups (eg, by age, sex, baseline CD4+ cell count) with plasma HIV-1 RNA <50 copies/mL at Week 96 using the Snapshot algorithm for the ITT-E population
- Change from baseline in CD4+ cell counts at Week 96 by patient subgroups
- Change from baseline in health-related quality of life using the EQ-5D-5L at Week 96 (or withdrawal from the study)

References

1. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727–1736.
2. Cahn P, Madero JS, Arribas JR, et al. 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, non-inferiority, phase 3 trials. *Lancet*. 2019;393:143–155.

SUPPLEMENTAL DIGITAL CONTENT 2

Trial profile.



AE, adverse event; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine). [a]Participants could have multiple reasons for ineligibility. [b]Most common reasons for not meeting inclusion criteria or meeting exclusion criteria listed. All other reasons occurred in <1% of participants. [c]Viral load criterion

was revised to allow enrollment of participants with plasma HIV-1 RNA of 1000-500,000 copies/mL on or after November 5, 2016. [d]Includes 1 fatal outcome in the GEMINI-1 study and 2 fatal outcomes in the GEMINI-2 study. All other AE-related withdrawals were non-fatal. [e]Protocol deviations leading to exclusion from the per-protocol population; participants could have had more than 1 reason.

SUPPLEMENTAL DIGITAL CONTENT 3

Snapshot Analysis of Participants With HIV-1 RNA <50 Copies/mL at Week 96 in the ITT-E Population From GEMINI-1 and GEMINI-2

	GEMINI-1		GEMINI-2	
Snapshot outcome, n (%)	**2DR (N=356)**	**3DR (N=358)**	**2DR (N=360)**	**3DR (N=359)**
HIV-1 RNA <50 copies/mL	300 (84.3)	320 (89.4)	316 (87.8)	322 (89.7)
HIV-1 RNA ≥50 copies/mL	11 (3.1)	5 (1.4)	11 (3.1)	9 (2.5)
Data in window and HIV-1 RNA ≥50 copies/mL	1 (0.3)	0	3 (0.8)	4 (1.1)
Discontinued for lack of efficacy	4 (1.1)	2 (0.6)	5 (1.4)	1 (0.3)
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	5 (1.4)	3 (0.8)	2 (0.6)	3 (0.8)
Change in ART	1 (0.3)	0	1 (0.3)	1 (0.3)
No virologic data at Week 96	45 (12.6)	33 (9.2)	33 (9.2)	28 (7.8)
Discontinued study because of AE or death	12 (3.4)	13 (3.6)	10 (2.8)	8 (2.2)
Discontinued study for other reasons	33 (9.3)	20 (5.6)	23 (6.4)	18 (5.0)
Withdrew consent	10 (2.8)	6 (1.7)	8 (2.2)	9 (2.5)
Lost to follow-up	10 (2.8)	6 (1.7)	8 (2.2)	4 (1.1)
Protocol deviation	6 (1.7)	5 (1.4)	4 (1.1)	3 (0.8)
Physician decision	7 (2.0)	3 (0.8)	3 (0.8)	1 (0.3)
Protocol-defined confirmed virologic withdrawal	0	0	0	1 (0.3)
On study but missing data in window	0	0	0	2 (0.6)

AE, adverse event; ART, antiretroviral therapy; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); ITT-E, intention-to-treat–exposed.

SUPPLEMENTAL DIGITAL CONTENT 4

Confirmed Virologic Withdrawals Through the Week 96 Analysis Window

Week of failure confirmation	Baseline CD4+, cells/mm^3	Time between SVW and CVW, day	Viral loads at baseline / SVW / CVW / and withdrawal, copies/mL	Resistance mutations		Fold change at baseline and CVW
				Baseline	SVW	
2DR						
Week 16	212	7	124,492 / 6648 / 56,435 / 95	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.67, 0.72 3TC, 1.13, 1.12
Week 24	284	28	50,263 / 348 / 206 / 96	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.76, 0.7 3TC, 0.98, 0.69
Week 24	19	23	368,439 / 212 / 376 / 362	NRTI: none INSTI: G193G/E	NRTI: none INSTI: none	DTG, 0.88, 0.86 3TC, 1.02, 1.43
Week 24	213	27	96,277 / 451 / 9602 / 67	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.92, 0.8 3TC, 1.16, 1.16
Week 24	529	34	17,232 / 461 / 251 / 59	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.81, 0.87 3TC, 1.17, 1.09
Week 48	414	22	37,701 / 43,908 / 38,457[a]	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.8, 0.79 3TC, 0.9, 1.74
Week 60	347	101	101,671 / 703 / 85,556[a]	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.89, 1.13 3TC, 0.95, 0.87
Week 60	567	21	7654 / 3972 / 3131 / 1513	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.7, 0.71 3TC, 0.86, 0.86
Week 72	50	14	63,817 / 422 / 2154 / 115	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.64, 0.81 3TC, 0.84, 0.69
Week 72	74	27	112,812 / 61,076 / 87,794 / 671	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.84. 0.9 3TC, 0.84, 0.73

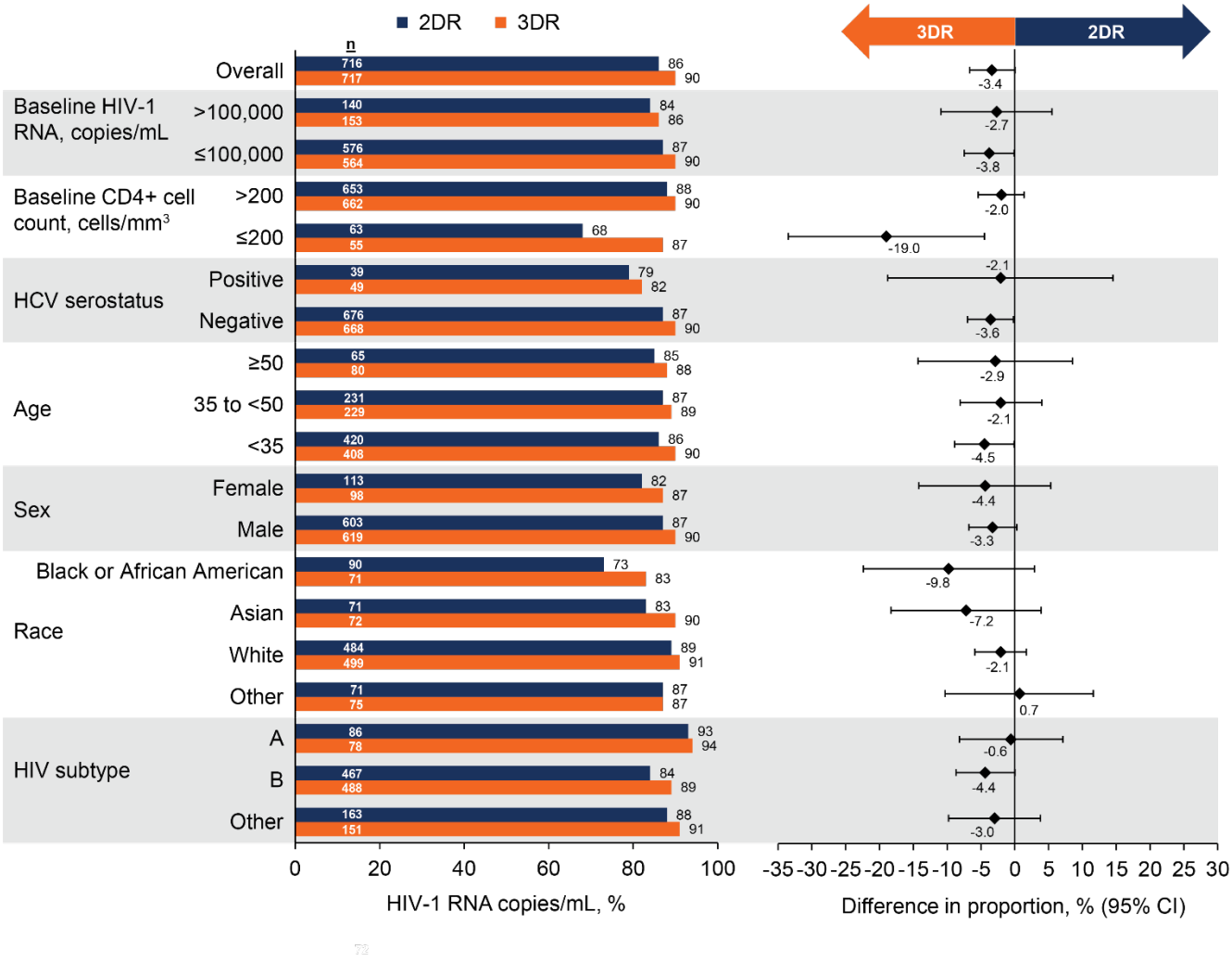
Week 108[b]	317	31	341,818 / 396 / 726 / 280	NRTI: none INSTI: L74I	NRTI: none INSTI: L74I	DTG, 0.72, 0.83 3TC, 1.09, 1.04
3DR						
Week 12	22	28	136,753 / 393 / 276[c]	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.95, 1.03 TDF, 0.98, 0.99 FTC, 0.86, 1.10
Week 24	226	27	10,930 / 1136 / 809 / 264	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.72, NR TDF, 1, 0.81 FTC, 0.92, 0.95
Week 24	251	30	76,325 / 569 / 362 / <50	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.68, 1.38 TDF, 0.95, 0.61 FTC, 1.13, 0.67
Week 24	201	28	156,701 / 213 / 1559 / 97	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 0.9, NR TDF, 1.04, 1.07 FTC, 0.97, 1.01
Week 48	602	83	1568 / 8384 / 3653 / 3011	NRTI: L70K/E INSTI: G193E	NRTI: none INSTI: G193G/E	DTG, 1.05, 1.05 TDF, 0.76, 0.77 FTC, 1.14, 1.28
Week 72	253	16	668,811 / 254 / 232 / 121	NRTI: none INSTI: none	NRTI: none INSTI: none	DTG, 1.13, NR TDF, 0.71, NR FTC, 0.68, NR
Week 96	144	40	28,905 / 30,316 / 7793[a]	NRTI: none INSTI: L74I	NRTI: none INSTI: L74I	DTG, 0.68, 0.78 TDF, 0.82, 0.95 FTC, 1.07, 0.82

CVW, confirmed virologic withdrawal; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); DTG, dolutegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NR, not reported because of assay failure; NRTI, nucleoside reverse transcriptase inhibitor; SVW, suspected virologic withdrawal; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

[a]Participant met CVW at the withdrawal visit; no subsequent visit occurred. [b]Participant met SVW criteria within the Week 96 window, with confirmatory viral load at Week 108. [c]Participant met the criteria for CVW at Week 12 but was not reported at the Week 48 analysis because of a laboratory reporting error identified after the Week 48 analysis. This participant was not withdrawn as per protocol at the time and has been allowed to continue in the study (the participant has maintained virologic suppression from Week 24 through Week 108).

SUPPLEMENTAL DIGITAL CONTENT 5

Snapshot analysis of the proportion of participants with HIV-1 RNA <50 copies/mL by subgroup in the ITT-E population at Week 96, with unadjusted treatment group differences (95% CI).



2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); HCV, hepatitis C virus; ITT-E, intention-to-treat–exposed.

SUPPLEMENTAL DIGITAL CONTENT 6

Reasons for Snapshot Non-response in the Subgroup of Participants With Baseline CD4+ Cell Count ≤200 Cells/mm^3

Participants, n (%)	**2DR (N=63)**	**3DR (N=55)**
Snapshot non-response	20 (31.7)	7 (12.7)
Protocol-defined confirmed virologic withdrawal	3 (4.8)	1 (1.8)[a]
HIV-1 RNA ≥50 copies/mL and continued in study	2 (3.2)	0
Discontinued because of treatment-related AE	1 (1.6)	0
Discontinued because of non–treatment-related AE	2 (3.2)	0
Protocol violation (eligibility criteria not met)	2 (3.2)	0
Lost to follow-up	3 (4.8)	3 (5.5)
Withdrew consent	4 (6.3)	2 (3.6)
Withdrew to start HCV treatment	1 (1.6)	0
Change in ART due to incarceration	1 (1.6)	0
Investigator discretion (incarceration)	0	1 (1.8)
Pregnancy	1 (1.6)	0

AE, adverse event; ART, antiretroviral therapy; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); HCV, hepatitis C virus. [a]One participant met the criteria for confirmed virologic withdrawal at Week 12 but was not reported at the Week 48 analysis because of a laboratory reporting error identified after the Week 48 analysis. This participant was not withdrawn as per protocol at the time and has been allowed to continue in the study (the participant has maintained virologic suppression from Week 24 and at the Week 96 Snapshot analysis and is therefore not considered a Snapshot non-responder).

SUPPLEMENTAL DIGITAL CONTENT 7

Snapshot Outcomes at Week 96 in Participants with Baseline HIV-1 RNA >500,000 Copies/mL

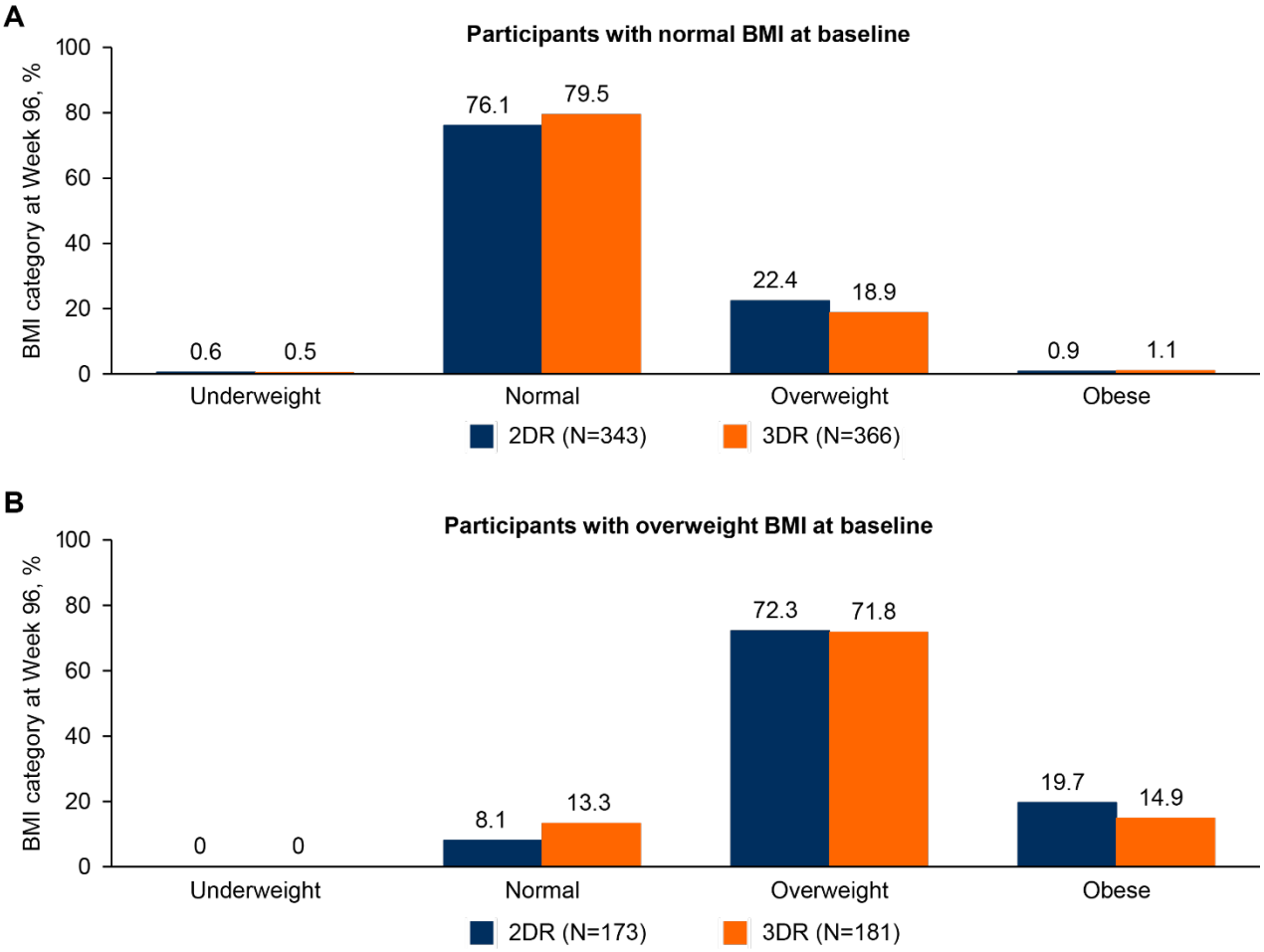
Baseline HIV-1 RNA, copies/mL	**Baseline CD4+ cell count, cells/mm^3**	**Week 96 Snapshot outcome <50 copies/mL**
2DR (n=13)		
502,915	147	≥50 copies/mL[a]
510,168	229	✓
523,934	305	✓
558,856	337	No virologic data[b]
577,561	314	✓
579,350	437	✓
582,666	454	✓
586,886	168	✓
833,905	219	No virologic data[b]
902,151	316	✓
934,790	255	✓
1,341,981	262	✓
1,848,435	22	No virologic data[c]
3DR (n=15)		
500,265	268	✓
503,837	279	✓
524,883	38	No virologic data[b]
593,008	428	✓
630,132	19	✓
633,199	445	✓
675,028	131	✓
690,490	112	No virologic data[b]
707,457	226	✓
750,721	335	✓
764,540	520	✓
877,058	276	✓
953,600	544	No virologic data[b]

987,059	245	✓
2,317,510	27	✓

AE, adverse event; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine). [a]Participant had HIV-1 RNA 80 copies/mL at Week 96. [b]Participants discontinued before Week 96 for reason other than efficacy or AEs with HIV-1 RNA <50 copies/mL at last on-study assessment. [c]Participant discontinued shortly after baseline for not meeting entry criteria (screening HIV-1 RNA >500,000 copies/mL).

SUPPLEMENTAL DIGITAL CONTENT 8

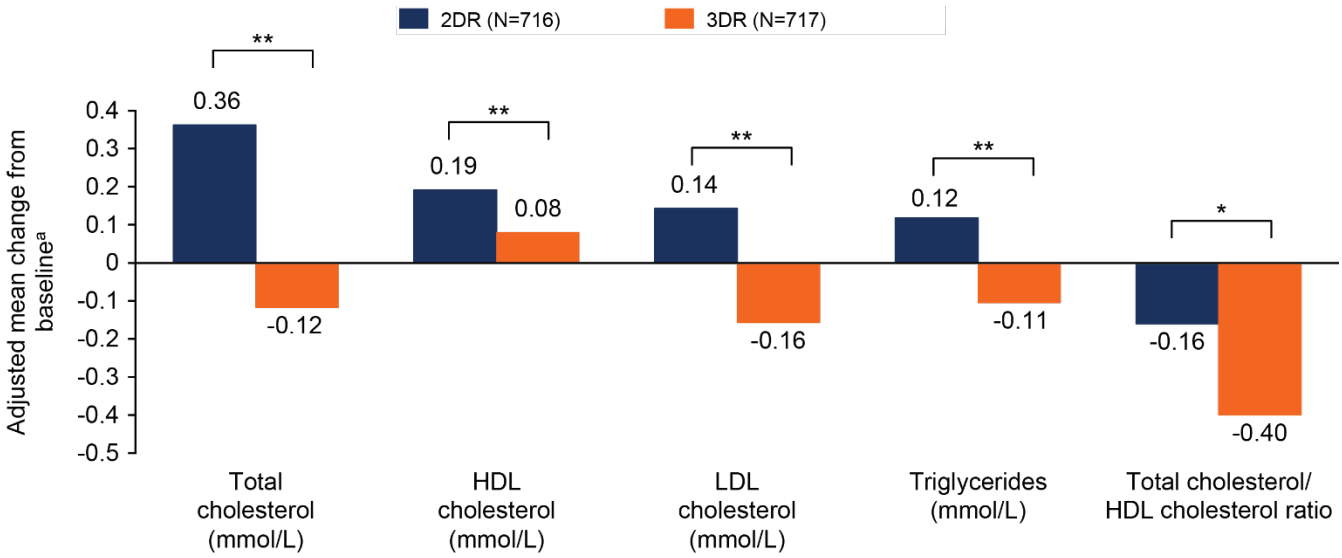
Post hoc analysis of the proportion of participants with BMI shift at Week 96 with **(A)** normal or **(B)** overweight BMI at baseline in the pooled safety population from GEMINI-1 and GEMINI-2.



BMI, body mass index; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine).

SUPPLEMENTAL DIGITAL CONTENT 9

Mean change from baseline in serum or plasma lipids at Week 96.



2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]The 96-week analysis used mixed-effect model repeat measurement. Mean change from baseline adjusted for study, treatment, visit, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age, baseline value, treatment-by-visit interaction, and baseline value-by-visit interaction. No assumptions were made about the correlations between participant readings of biomarkers (the correlation matrix for within-participant errors was unstructured). *P<0.05. **P<0.001.

SUPPLEMENTAL DIGITAL CONTENT 10

Baseline and Week 96 Scores on EQ-5D-5L Health State Utility Scale and VAS

	2DR		3DR		Adjusted mean change (95% CI)	*P* value
	Baseline, mean (SD)	Week 96, mean (SD)	Baseline, mean (SD)	Week 96, mean (SD)		
EQ-5D-5L	0.950 (0.076)	0.960 (0.083)	0.940 (0.105)	0.957 (0.088)	−0.0008 (−0.0088, 0.0072)	0.843
VAS	86.5 (12.1)	90.3 (10.4)	85.1 (13.4)	89.3 (11.2)	0.5 (−0.5, 1.5)	0.361

2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); EQ-5D-5L, EuroQol–5 Dimensions–5 Levels; SD, standard deviation; VAS, visual analog scale.

SUPPLEMENTAL DIGITAL CONTENT 11

GEMINI-1 and GEMINI-2 Investigators

Argentina: Cahn, Cassetti, David, Figueras, Figueroa, Losso, Lopardo, Lupo, Porteiro, Sánchez

Australia: Bloch, Cooper, Finlayson, Kelleher, Koh, Lewis, McMahon, Moore, Roth, Shields

Belgium: De Wit, Florence, Goffard, Demeester, Lacor, Vandercam, Vandekerckhove

Canada: Angel, Baril, Conway, de Pokomandy, Szabo, Walmsley

France: Bouchaud, Chidiac, Delobel, Girard, Goujard, Katlama, Molina, Pialoux, Philibert

Germany: Bogner, Esser, Krznaric, Lehmann, Rockstroh, Spinner, Stellbrink, Stephan, Stoehr

Italy: Antinori**,** Barchi, Caramello, Castelli, Cattelan, D'Arminio Montforte, Di Biargo, Di Perri, Gori, Gulminetti, Lazzarin, Maggiolo, Menzaghi, Migliorino, Mussini, Penco, Puoti, Quirino, Rizzardini, Sighinolfi, Viale

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Netherlands: Den Hollander, Rijnders

Peru: Hidalgo, Hercilla, Illescas

Poland: Olczak

Portugal: Correia Pacheco, Mansinho, Saraiva da Cunha, Sarmento e Castro, Serrão, Teófilo

Romania: Arbune, Jianu, Oprea, Preotescu, Prisacariu

Republic of Korea: Lee, Kim S-W, Kim S-I, Kim WJ

Russia: Belonosova, Borodkina, Chernova, Gankina, Kizhlo, Kulagin, Kurina, Nagimova, Pokrovsky, Riamova, Voronin, Yakovlev

South Africa: Kaplan

Spain: Antela Lopez, Arribas Lopez, Casado Osorio, Castabo Carracedo, De Los Santos Gil, Estrada Perez, Falco Ferrer, Force, Galinda Puerto, Garcia Deltoro, Gatell, Goenaga Sanchez, Gonzalez Cordon, Knobel, Lopez Bernaldo de Quiros, Losa Garcia, Masia, Montero-Alsonso,

Ocampo Hermida, Pasquau Liapo, Portilla Sogorb, Pulido, Rivero Roman, Santos Fernandez, Torres Perea, Troya, Viciana

Switzerland: Calmy, Hauser, Fehr

Taiwan: Cheng, Huang, Hung, Ko, Lin, Lu, Tseng, Wang, Wong, Wu, Yang

USA: Arduino, Benson, Berhe, Bredeek, Brinson, Campbell, Crofoot, Cunningham, DeJesus, Dretler, Eron, Fichtenbaum, Flamm, Goldstein, Gupta, Hagins, Hoffman-Terry, Jayaweera, Kinder, Klein, McDonald, Mills, Nahass, Ortiz, Osiyemi, Overton, Parks, Prelutsky, Ramgopal, Schrader, Sha, Simon, Sims, Skiest, Slim, Tashima, Thedinger

United Kingdom: Clarke, Gazzard, Fox, Johnson, Kegg, Khoo, Mazhude, Orkin, Schembri, Ustianowski