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Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

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Abstract

BACKGROUND—Safe and effective long-acting injectable agents for preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection are needed to increase the options for preventing HIV infection.

METHODS—We conducted a randomized, double-blind, double-dummy, noninferiority trial to compare long-acting injectable cabotegravir (CAB-LA, an integrase strand-transfer inhibitor [INSTI]) at a dose of 600 mg, given intramuscularly every 8 weeks, with daily oral tenofovir disoproxil fumarate–emtricitabine (TDF–FTC) for the prevention of HIV infection in at-risk cisgender men who have sex with men (MSM) and in at-risk transgender women who have sex with men. Participants were randomly assigned (1:1) to receive one of the two regimens and were followed for 153 weeks. HIV testing and safety evaluations were performed. The primary end point was incident HIV infection.

RESULTS—The intention-to-treat population included 4566 participants who underwent randomization; 570 (12.5%) identified as transgender women, and the median age was 26 years (interquartile range, 22 to 32). The trial was stopped early for efficacy on review of the results of the first preplanned interim end-point analysis. Among 1698 participants from the United States, 845 (49.8%) identified as Black. Incident HIV infection occurred in 52 participants: 13 in the cabotegravir group (incidence, 0.41 per 100 person-years) and 39 in the TDF–FTC group (incidence, 1.22 per 100 person-years) (hazard ratio, 0.34; 95% confidence interval, 0.18 to 0.62). The effect was consistent across prespecified subgroups. Injection-site reactions were reported in 81.4% of the participants in the cabotegravir group and in 31.3% of those in the TDF–FTC group. In the participants in whom HIV infection was diagnosed after exposure to CAB-LA, INSTI resistance and delays in the detection of HIV infection were noted. No safety concerns were identified.

CONCLUSIONS—CAB-LA was superior to daily oral TDF–FTC in preventing HIV infection among MSM and transgender women. Strategies are needed to prevent INSTI resistance in cases of CAB-LA PrEP failure. (Funded by the National Institute of Allergy and Infectious Diseases and others; HPTN 083 ClinicalTrials.gov number, NCT02720094.)

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Despite the availability of highly effective strategies for the prevention of human immunodeficiency virus (HIV) infection, the number of new infections worldwide continues to exceed 5000 per day.[1] Daily oral tenofovir disoproxil fumarate–emtricitabine (TDF–FTC) has been reported to provide protection against HIV infection across various populations.[2–7] The efficacy of oral preexposure prophylaxis (PrEP) agents is directly correlated with adherence to prescribed dosing.[4–9] PrEP agents that do not require regular or planned oral dosing may increase acceptability and protection during periods of risk, thereby reducing the risk of HIV acquisition.

A Quick Take is available at NEJM.org

Long-acting injectable cabotegravir (CAB-LA) is an integrase strand-transfer inhibitor (INSTI) that is administered as an intramuscular injection into the gluteus muscle. CAB-LA has potent anti-HIV activity, protects nonhuman primates from a broad range of HIV exposure types, and is generally safe, without limiting toxic effects, in humans.[10–15] (See the Supplementary Appendix, available with the full text of this article at NEJM.org.)

We report the primary results of the HIV Prevention Trials Network (HPTN) 083 trial, a phase 2b–3, multicenter, randomized, double-blind, double-dummy, active-controlled trial. We compared the safety and efficacy of CAB-LA, administered intramuscularly every 8 weeks, with daily oral TDF–FTC in cisgender men who have sex with men (MSM) and in transgender women who have sex with men in the United States, Latin America, Asia, and Africa.

METHODS

TRIAL OVERSIGHT AND PARTICIPANTS

The HPTN 083 trial protocol, which is available at NEJM.org, was approved by the institutional review board, ethics committee, ministry of health, or a combination of these entities at each participating site. All the participants provided written informed consent. Full details of the trial design can be found in the trial protocol. The Division of AIDS of the National Institute of Allergy and Infectious Diseases provided regulatory sponsorship of the trial. The Division of AIDS was responsible for clinical monitoring of the trial. ViiV Healthcare and Gilead Sciences donated trial medications and matching placebos. ViiV Healthcare also provided additional funding and contributed to the design of the trial.

Eligible participants were adults (≥18 years of age) who were in general good health as determined by clinical and laboratory assessments and who had a negative HIV serologic test at enrollment, had an undetectable blood HIV RNA viral load within 14 days before trial entry, and had a creatinine clearance of 60 ml or more per minute.[16] Cisgender MSM and transgender women who have sex with men who were recruited for the trial were at high risk for HIV infection, as defined in the protocol. Key exclusion criteria were the use of illicit intravenous drugs within 90 days before enrollment, previous participation in the active treatment group of an HIV vaccine trial, coagulopathy, buttock implants or fillers, a seizure disorder, or a corrected QT interval of greater than 500 msec. Participants who had

positive results on a hepatitis B virus surface antigen test or hepatitis C virus antibody test were also excluded.

RANDOMIZATION AND TRIAL PROCEDURES

Randomization was stratified according to site and was performed with the use of permuted blocks of 8, 10, and 12; trial-group assignments occurred electronically at enrollment. Eligible participants were assigned, in a 1:1 ratio, to receive either active cabotegravir with TDF–FTC placebo (cabotegravir group) or active TDF–FTC with cabotegravir placebo (TDF–FTC group).

The trial included three phases: an oral-tablet lead-in phase, an injection phase, and a "tail phase," the time period beginning 8 weeks after the final injection and continuing for approximately 48 weeks, when plasma drug concentrations are in terminal decline. During the lead-in phase, all the participants received two oral tablets (one active and one placebo) daily for 5 weeks to verify the safety of the tablets. Active cabotegravir was given as a 30-mg tablet, and active TDF–FTC was given as a fixed-dose combination of 300 mg of TDF plus 200 mg of FTC. Participants who had at least 50% adherence to the oral tablets, as determined by pill count, and had acceptable safety laboratory results were permitted to progress to injections. During the injection phase, participants received a supply of daily oral tablets and a 3-ml intramuscular injection on inception of this phase, 4 weeks after the beginning of the phase, and every 8 weeks thereafter. CAB-LA was administered as a single 3-ml injection containing 600 mg of cabotegravir. Placebo for CAB-LA was an injectable fat emulsion (20% intralipid solution) that was visually similar to CAB-LA. Active TDF–FTC was given as described above. Masked oral tablets were dispensed at enrollment, and masked tablets were dispensed and injections administered at weeks 5, 9, and 17 and every 8 weeks thereafter through week 153, thus resulting in approximately 3 years of exposure to CAB-LA. If a planned injection visit was delayed by 8 weeks or more, a 4-week interval was used for the next two injections. Participants who discontinued injections received open-label TDF–FTC for 48 weeks to provide ongoing HIV PrEP during the tail phase.[17]

Trial visits were scheduled at weeks 2 and 4 during the oral-tablet lead-in phase. Visits during which no injections were administered and only safety was assessed were scheduled at weeks 6 and 10, and then 2 weeks after each injection. Beginning with the last scheduled visit of the injection phase (week 153), participants were provided with open-label TDF–FTC daily over 48 weeks, with four quarterly trial visits (Fig. 1A).

All the visits included an HIV rapid test (cleared by the Food and Drug Administration) and a laboratory-based HIV antigen and antibody test, assessment of adverse events, collection and storage of plasma samples, and adherence and risk-reduction counseling. (Further details are provided in the Supplementary Appendix.)[18] Routine laboratory testing was performed at all visits except the week 5 visit. Injection-site reactions were assessed at visits that occurred 1 or 2 weeks after each injection. Testing for syphilis and nucleic acid amplification testing for rectal and urethral gonorrhea and chlamydia were conducted at least every 6 months. Testing for hepatitis C virus antibodies and measurement of fasting glucose and lipid levels were performed annually. Interviewer-led and computer-assisted structured interviews were conducted approximately every second injection cycle for evaluation of

adherence, sexual behaviors, alcohol and drug use, and acceptability of the oral tablets and injections. Among participants in whom HIV infection had been confirmed at the trial site, measurement of the CD4+ T-cell count and the HIV viral load for clinical use was performed at quarterly visits for 1 year after diagnosis. Additional HIV testing was performed retrospectively at the HPTN Laboratory Center to confirm HIV status and determine the timing of HIV infection; this testing included assessment of HIV resistance for selected samples with a viral load of 500 copies or more per milliliter.[18]

PRIMARY END POINTS

The primary efficacy end point of the trial was incident HIV infection. The methods used for determination of HIV status and for end-point adjudication are described in the Supplementary Appendix; additional information is provided in a separate report.[18] An independent committee, whose members were unaware of the trial-group assignments, adjudicated HIV infections and determined the dates of first evidence of infection.[18] The primary safety end point was the occurrence of an adverse event of grade 2 or higher. The severity of all adverse events was graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1.[19]

ANALYSIS OF DRUG CONCENTRATIONS

A cohort of 390 randomly selected participants in the TDF–FTC group was assessed for measurement of the tenofovir concentration in plasma and the intraerythrocytic tenofovir–diphosphate concentration in dried blood spots.[18] Plasma cabotegravir concentrations were measured in all samples obtained from all the participants in the cabotegravir group who had HIV infection (either incident or prevalent).[18] For participants in the TDF–FTC group who had incident HIV infection, tenofovir and tenofovir diphosphate concentrations were measured in samples obtained at the first visit at which the participant was determined to be HIV positive and at selected previous visits.[17]

STATISTICAL ANALYSIS

The noninferiority margin was a hazard ratio of 1.23, which was chosen on the basis of previous placebo-controlled trials. (Details are provided in the protocol.) To achieve 90% power to detect an alternative hazard ratio of 0.75 (at a one-sided type I error rate of 0.025), we estimated that 172 incident HIV infections (events) would need to occur. Assuming an incidence of 1.75 events per 100 person-years, we enrolled approximately 4500 participants. Interim analyses were planned to be performed with the use of O'Brien–Fleming group-sequential monitoring boundaries after 43, 86, and 129 events had occurred. The primary end point was evaluated in a modified intention-to-treat analysis, which excluded participants who were found to have HIV infection at enrollment. All incident infections were included in the analysis, regardless of when the infection occurred and regardless of whether the participant received an injection. Cox regression, stratified according to geographic region, was used to estimate the hazard ratio for incident HIV infection in the cabotegravir group as compared with the TDF–FTC group; 95% confidence intervals and P values were based on the Wald statistic. The primary hazard ratio was adjusted for interim monitoring.[20] A test for proportional hazards was performed with the

use of Schoenfeld residuals, and a log-rank test, stratified according to geographic region, was performed as a sensitivity analysis.

Trial data were reviewed approximately every 6 months by an independent data and safety monitoring board. On May 14, 2020, on review of the results of the first preplanned interim end-point analysis, the data and safety monitoring board concluded that the results met the prespecified criteria for stopping the trial on the basis of efficacy (Supplementary Appendix). The analyses in this report include data collected during the blinded phase of the trial up to May 14, 2020. The trial is currently ongoing with an open-label design.

RESULTS

TRIAL PARTICIPANTS

Between December 6, 2016, and March 16, 2020, a total of 6333 participants were screened at 43 sites in the United States, Latin America, Asia, and Africa (Fig. 1B and the Supplementary Appendix). Of the 4570 participants who underwent randomization and were enrolled, 4 were ineligible, resulting in an intention-to-treat population of 4566 participants. Demographic and clinical characteristics of the two groups were similar at baseline (Table 1) and met or exceeded prespecified metrics for enrollment of certain subgroups and populations. Five participants who acquired HIV infection before enrollment (2 in the cabotegravir group and 3 in the TDF–FTC group) and 71 participants who had no follow-up HIV testing after enrollment were excluded from the primary efficacy analysis.

Participant retention was 86.5% at 1 year, with a median follow-up of 1.4 years (interquartile range [IQR], 0.8 to 1.9). Masked oral tablets and injections were permanently discontinued in 908 participants (19.9%), including 445 participants in the cabotegravir group and 463 in the TDF–FTC group (Table S1 in the Supplementary Appendix).

ADHERENCE TO ORAL TABLETS AND INJECTIONS

The median adherence during the oral-tablet lead-in phase, as determined by pill count, was 96.6% (IQR, 89.7 to 100.0) across the trial groups. During the course of the trial, in a randomly selected subgroup of 390 participants in the TDF–FTC group, 74.2% had tenofovir concentrations of greater than 40 ng per milliliter, which is consistent with the receipt of daily TDF–FTC doses in the previous week; 86.0% had concentrations above the lower limit of quantitation (0.31 ng per milliliter). Tenofovir–diphosphate concentrations (measured in dried blood spots) that were consistent with receipt of at least four TDF–FTC doses per week[21] over the previous 1 to 2 months were detected in 72.3% of the samples overall (Fig. S1); 91.5% of person-years were considered to have been “covered” by injectable CAB-LA placebo, which was defined as injections having been received with a delay of less than 2 weeks.

HIV INFECTION

Using a prespecified testing algorithm,[17] we identified HIV infection in 57 participants, including 5 (2 in the cabotegravir group and 3 in the TDF–FTC group) who had undetected HIV infection at enrollment (“baseline” infections). A total of 52 participants who acquired

HIV infection after enrollment were included in the prespecified primary efficacy analysis: 13 in the cabotegravir group (incidence, 0.41 per 100 person-years) and 39 in the TDF–FTC group (incidence, 1.22 per 100 person-years). The hazard ratio for incident HIV infection in the cabotegravir group as compared with the TDF–FTC group was 0.34 (95% confidence interval [CI], 0.18 to 0.62; P<0.001). The test for proportional hazards had modest evidence of nonproportionality (P = 0.07); a stratified log-rank test showed a significant difference between the groups (P<0.001). The direction and overall magnitude of the effect were consistent across prespecified subgroups and populations (Fig. 2) and in a per-protocol analysis (Fig. S2).

Post hoc centralized testing of stored plasma samples resulted in readjudication of the timing of the first visit at which an HIV test was positive for 2 participants in the cabotegravir group; 1 of the original 13 incident HIV infections in the cabotegravir group was readjudicated as a base line infection (case A3) (Fig. 3). No incident infections in the TDF–FTC group were readjudicated as baseline infections. An analysis that included the post hoc readjudication data provided a revised estimate of incident HIV infection in the cabotegravir group of 0.37 (95% CI, 0.19 to 0.65; hazard ratio, 0.32 [95% CI, 0.16 to 0.58]). One additional case (A4) (Fig. 3) in the cabotegravir group was also identified post hoc as a baseline infection; thus, the final number of observed infections was 58 (16 in the cabotegravir group and 42 in the TDF–FTC group). Detailed descriptions of each case, including virologic and pharmacologic assessments, are presented in a separate report.[17] The timing of the first visit at which an HIV test was positive for each of the 16 infections in the cabotegravir group is shown in Figure 3.

The 16 infections in the cabotegravir group were classified into four groups (A through D) (Fig. 3). Four infections occurred before enrollment (cases A1 through A4). Five infections occurred with no recent exposure to cabotegravir (cases B1 through B5); in 2 of these cases (B1 and B4), open-label TDF–FTC was initiated after the participant had discontinued CAB-LA. Three infections occurred before cabotegravir injection (cases C1 through C3); in 1 of these cases (C2), the participant was nonadherent to oral cabotegravir, and in the other 2 cases (C1 and C3), infection occurred during the oral-tablet lead-in phase. The remaining 4 infections occurred in participants with appropriately timed CAB-LA doses and expected plasma cabotegravir concentrations (cases D1 through D4).

DRUG RESISTANCE MUTATIONS

INSTI resistance mutations were detected in 1 of the 4 cases identified as a baseline infection (case A2) and in 4 of 9 incident cases that had a resistance test result (cases C1, C3, D3, and D4). No resistance was detected when viral escape or HIV acquisition occurred during the period of cabotegravir decay after the last injection (tail phase; cases A3, B1, B3, and B4) (Fig. 3), although varying intervals of follow-up before initiation of antiretroviral therapy (ART) do not allow direct comparison. In the TDF–FTC group, 2 of the 39 incident HIV infections occurred in cases in which the drug concentrations that were measured were consistent with good PrEP adherence (cases E16 and E34). Four incident infections and 2 baseline infections had nucleoside or nucleotide reverse-transcriptase inhibitor mutations (K65R, M184V, M184I, or a mixture of M184V and M184I with or without nonnucleoside

reverse-transcriptase inhibitor [NNRTI] mutations; cases E3, E13, E16, E25, E41, and E42) (Figs. S3 and S4).[18]

SAFETY

The primary safety population (which comprised participants who had received at least one dose of any of the oral tablets or injections) included 4562 participants (2280 in the cabotegravir group and 2282 in the TDF–FTC group). Adverse events of grade 2 or higher were reported in 92.5% of the participants overall, with no marked difference in the overall frequency between the trial groups (Table 2). Adverse events of grade 3 or higher were reported in 1494 participants (32.7%) overall; the overall frequency of these events was similar in the two trial groups. Permanent discontinuation of the oral tablets or both oral tablets and injections owing to adverse events other than injection-site reactions occurred in 172 participants (3.8%) overall, with a similar overall frequency in the two groups.

Serious adverse events were reported in 241 participants (5.3%) overall and were balanced between the two groups. Additional adverse events of interest included seizures and liver-related adverse events resulting in discontinuation of the oral tablets or both oral tablets and injections; both were uncommon, and the overall frequency of such events was similar in the two groups. A total of 11 participants died (7 in the TDF–FTC group and 4 in the cabotegravir group; hazard ratio, 0.57 [95% CI, 0.17 to 1.96]) (Table S2); 1 death in the TDF–FTC group that resulted from cardiovascular disease was considered to be related to the oral tablets or injections.

INJECTION-SITE REACTIONS

Injection-site reactions were reported in 1724 participants (81.4%) in the cabotegravir group who received at least one injection and in 652 participants (31.3%) in the TDF–FTC group who received at least one placebo injection. Injection-site reactions were mostly mild or moderate in severity and decreased in frequency over time (Fig. S5). Of the 2117 participants who received at least one active CAB-LA injection, 50 (2.4%) permanently discontinued the injections owing to an injection-related adverse event; discontinuation was strongly associated with increased severity of the injection-site reactions (Table S3). Of 10,666 injection-site reactions in the cabote gravir group, 6486 (60.8%) were pain and 2530 (23.7%) were tenderness; the events began a median of 1 day (IQR, 0 to 2) after injection and lasted a median of 3 days (IQR, 2 to 6) (Fig. S6).

SEXUALLY TRANSMITTED INFECTIONS

The overall incidence of new rectal or urethral gonorrhea was 13.49 per 100 person-years, and the incidence of new rectal or urethral chlamydia was 21.36 per 100 person-years. The incidence of new syphilis infections, which were centrally adjudicated (details provided in the Supplementary Appendix), was 16.69 per 100 person-years. The occurrence of each of these infections was similar in the two groups (Tables S4 and S5).

CHANGES IN BODY WEIGHT AND METABOLIC VARIABLES

In a post hoc analysis, a mean annualized increase in body weight of 1.23 kg per year (95% CI, 1.05 to 1.42) was noted in the cabotegravir group, as compared with an increase of 0.37

kg (95% CI, 0.18 to 0.55) in the TDF–FTC group. Differences in weight change between the groups were observed primarily in the first 40 weeks of participation and were similar in the two groups later in the trial (Fig. S12). Changes in fasting glucose and fasting lipid levels are shown in Figures S7 through S11.

DISCUSSION

In the HPTN 083 trial, we compared the safety and efficacy of CAB-LA with that of TDF–FTC for the prevention of HIV infection in MSM and transgender women who have sex with men. Although TDF–FTC is known to be effective in preventing HIV infection when adherence is high, we found that the risk of HIV infection was lower by 66% in the cabotegravir group than in the TDF–FTC group in the prespecified analysis, a result that showed the superiority of CAB-LA to TDF–FTC. This finding was similar in magnitude and direction in key populations that have lower reported rates of adherence to daily oral PrEP agents, including Black MSM in the United States, transgender women, and participants younger than 30 years of age.

Although most of the participants in the cabotegravir group reported injection-site reactions, only 2.4% chose not to receive further injections as a result. Increases in body weight associated with the use of INSTIs in the treatment of HIV infection have been reported in the literature.[22–24] We previously observed no significant difference in weight gain between HIV-uninfected participants who received CAB-LA and those who received placebo; participants in both groups gained approximately 1 kg over the course of 41 weeks. In the current trial, differences in weight change between the two groups were driven by weight loss in the TDF–FTC group in year 1; thereafter, the weight changes were similar (approximately 1 kg per year in both groups).

CAB-LA provided protection against HIV acquisition; however, 4 incident infections were observed despite on-time injections and expected cabotegravir concentrations in plasma. The risk of PrEP failure may be influenced by low plasma cabotegravir concentrations between initial injections, low cabotegravir concentrations in rectal tissue,[25] rectal inflammation related to sexually transmitted infection, or a combination of these factors.[26–30] INSTI resistance was detected in 5 participants in the cabotegravir group (1 with baseline infection and 4 with incident infection). NNRTI-based or boosted protease inhibitor–based ART should suppress viral replication in such cases, absent transmitted resistance; viral replication in some such participants may be suppressed by a regimen that includes twice-daily dolutegravir. To reduce the risk of resistance, HIV assays with increased sensitivity are being evaluated to minimize the interval between HIV infection and diagnosis; ART should be started promptly when long-acting PrEP agents have been used.

CAB-LA provided greater protection against HIV infection than TDF–FTC among MSM and transgender women who have sex with men. A similarly designed randomized, controlled trial evaluating the efficacy of CAB-LA in cisgender women in Africa was recently unblinded early after showing superiority of CAB-LA over daily oral TDF–FTC (ClinicalTrials.gov number, NCT03164564); the safety and acceptability of CAB-LA in adolescents is under evaluation (NCT04692077 and NCT04824131). Although overall

adherence to daily oral TDF–FTC was higher than anticipated in the current trial, inadequate TDF–FTC adherence among some participants appeared to drive the overall finding of HIV incidence that was three times the incidence in the cabotegravir group[18]; daily oral TDF–FTC, when used as prescribed, has been estimated to be more than 99% protective.[8]

This trial showed that CAB-LA was superior to TDF–FTC in preventing HIV acquisition among MSM and transgender women who have sex with men. The logistics involved in implementation of the use of CAB-LA for PrEP will require new consideration. CAB-LA is an effective strategy for the prevention of HIV infection that will expand PrEP options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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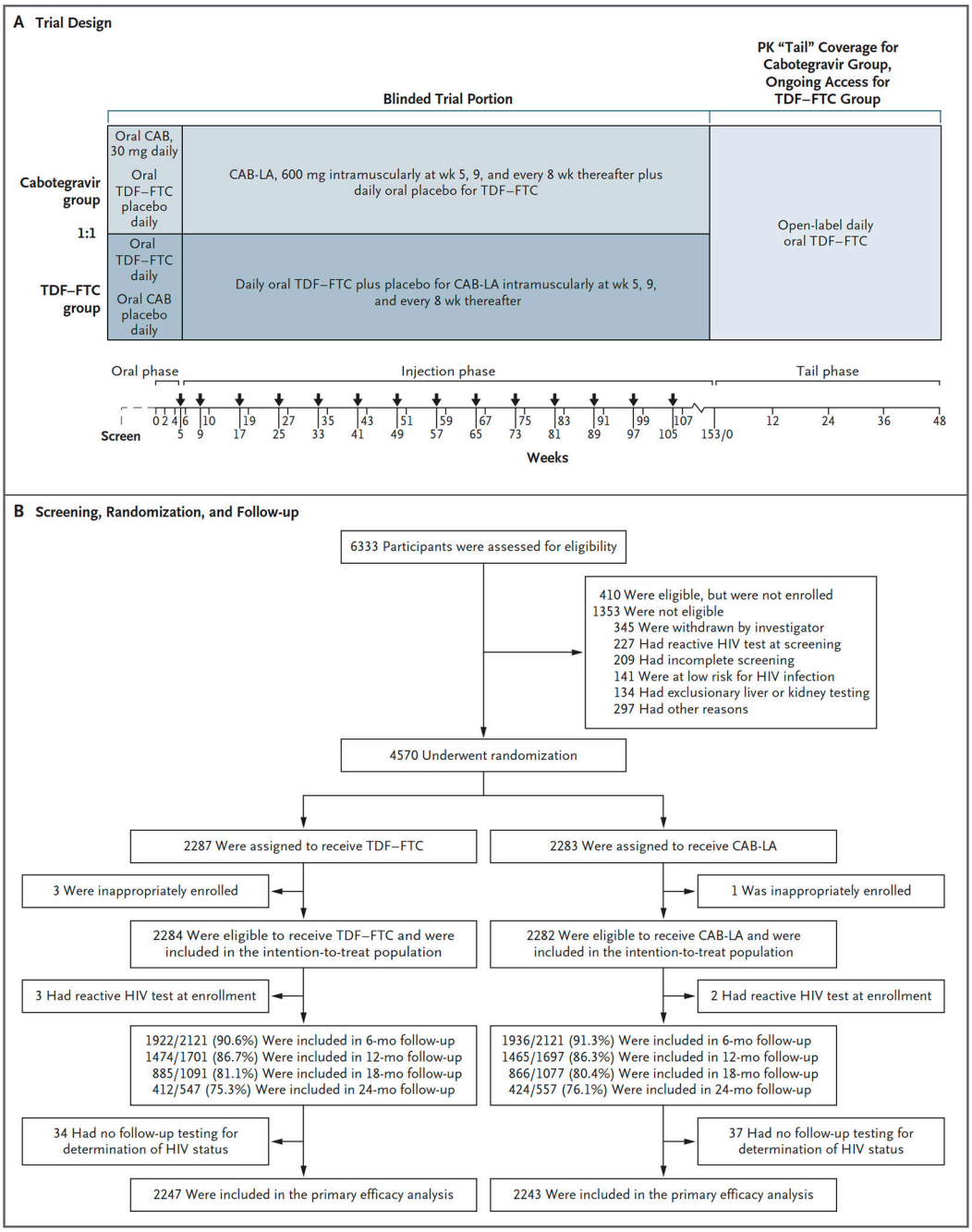

Figure 1. Trial Design, Screening, Randomization, and Follow-up.

CAB denotes cabotegravir, CAB-LA long-acting injectable CAB, HIV human immunodeficiency virus, PK pharmacokinetic, and TDF–FTC tenofovir disoproxil fumarate–emtricitabine.

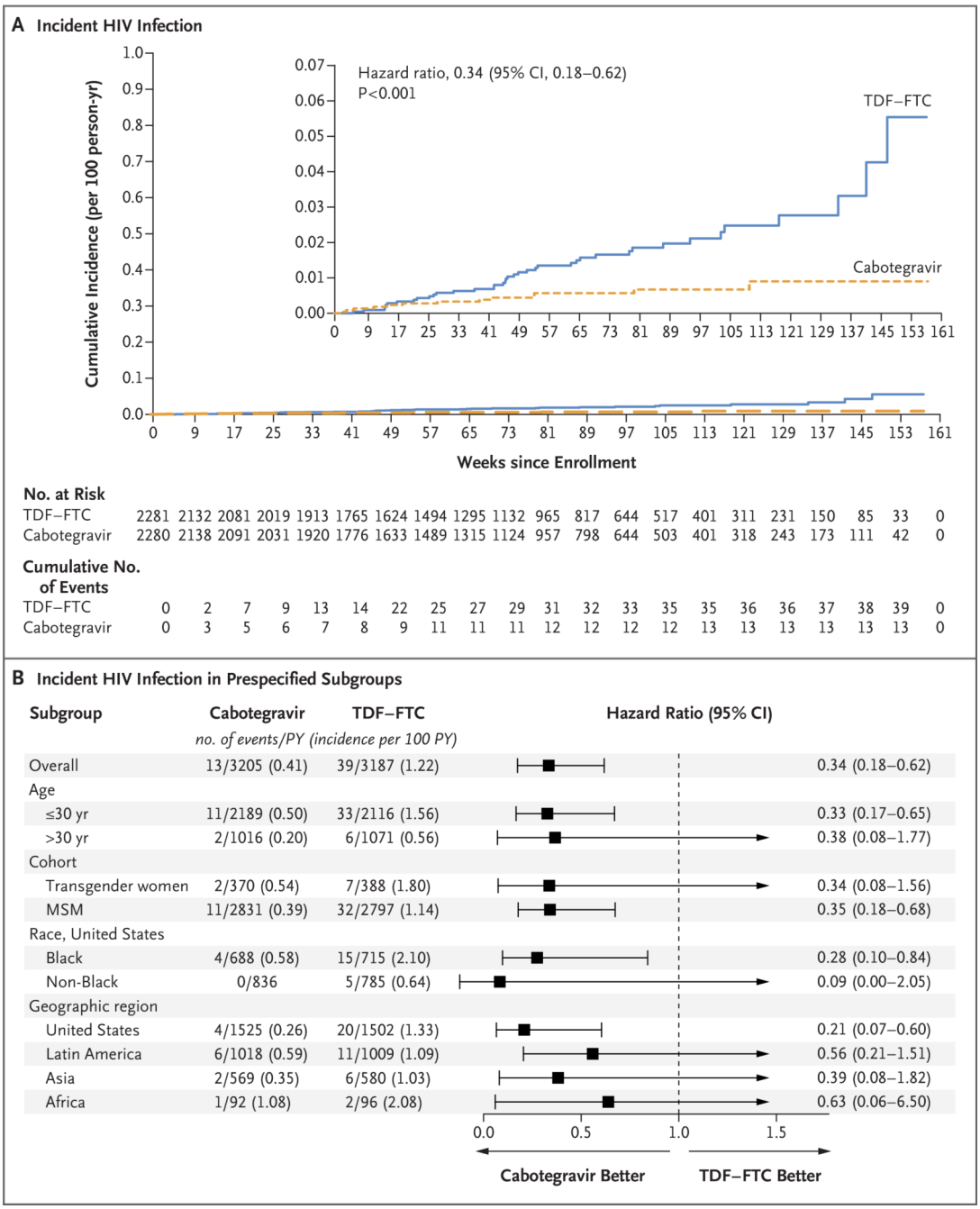

Figure 2. Incident HIV infection.

Panel A shows Kaplan–Meier estimates of incident HIV infection. The inset shows the same data on an enlarged y axis. Panel B shows hazard ratios for incident HIV infection in the prespecified subgroups. Race was reported by the participant. MSM denotes men who have sex with men, and PY person-years.

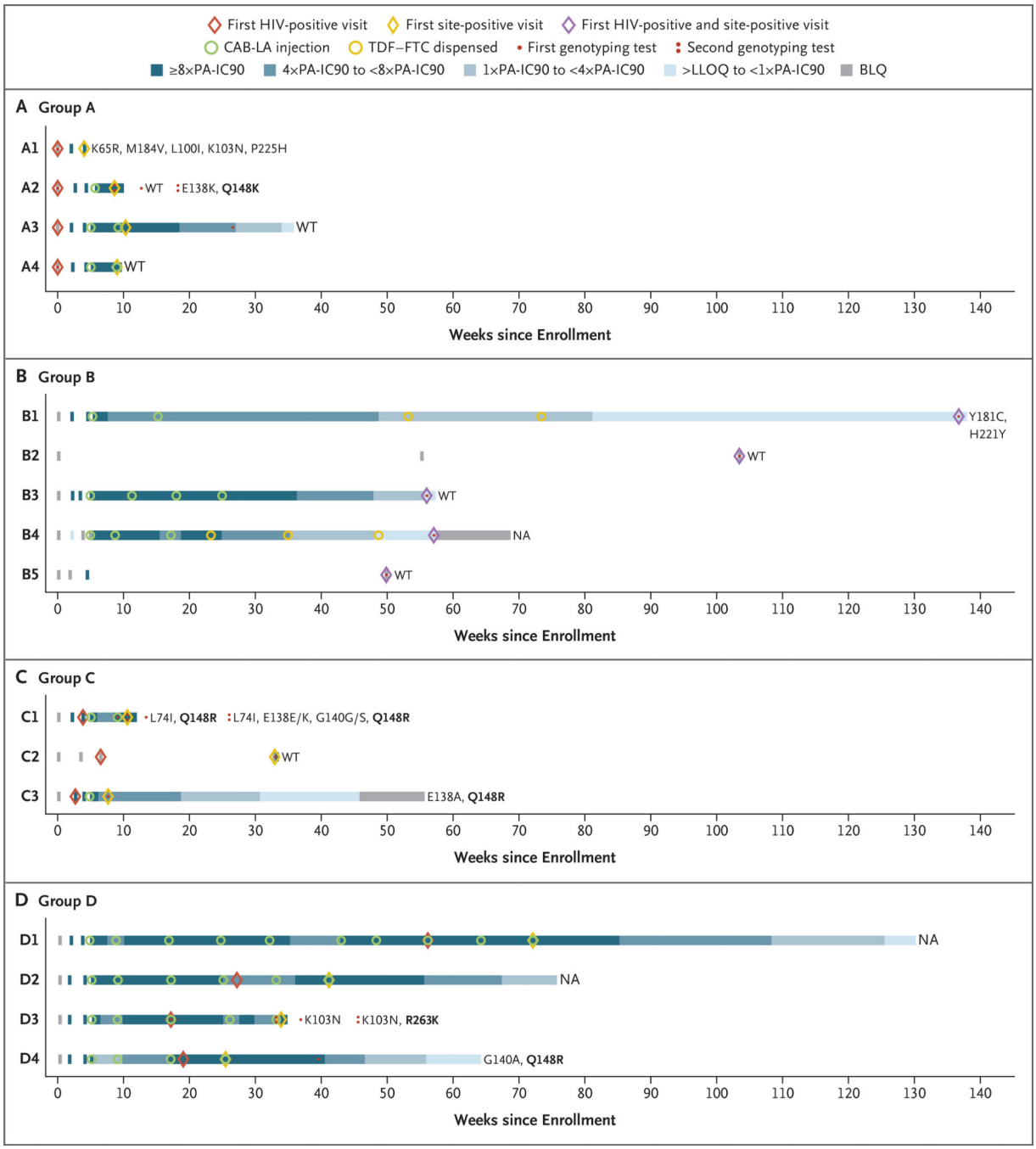

Figure 3. Pharmacologic and Virologic Data for HIV Infections in the Cabotegravir Group.

Panels A through D show the timing of key events for the 16 infections that occurred in the cabotegravir group. These infections were classified into four groups: group A (Panel A) includes infections that occurred before enrollment; group B (Panel B) includes infections that occurred with no recent exposure to cabotegravir; group C (Panel C) includes infections that occurred before cabotegravir injection; and group D (Panel D) includes infections that occurred in participants with appropriately timed CAB-LA doses and expected plasma cabotegravir concentrations. The “first HIV-positive visit” refers to the first visit at which

the participant was determined to be HIV positive. The “first site-positive visit” refers to the first visit at which evidence of HIV infection was identified at the trial site. HIV genotyping results are shown to the right of each horizontal bar. Major resistance mutations are shown for nucleoside or nucleotide reverse-transcriptase inhibitors (K65R and M184V) and nonnucleoside reverse-transcriptase inhibitors (L100I, K103N, Y181C, H221Y, and P225H). All integrase strand-transfer inhibitor (INSTI) resistance mutations are shown (L74I, E138K or E138E/K, E138A, G140A, G140G/S, Q148R or Q148K, and R263K); major INSTI mutations are shown in bold text. Genotyping results are shown for the first visit at which the viral load was 500 copies or more per milliliter and for follow-up visits at which such a viral load occurred, denoted as one dot or two dots, respectively. The number of days between the first HIV-positive visit and the visit with additional mutations was 60 days for case A2, 10 days for case C1, and 112 days for case D3. NA indicates that the genotyping result was not available (either no visit occurred at which viremia was found to be sufficient for performance of the genotyping assay or the assay failed to produce a genotyping result). BLQ denotes below the limit of quantification, LLOQ lower limit of quantification, PA-IC90 protein-adjusted 90% cabotegravir inhib itory concentration, and WT wild type.

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Table 1.

Demographic and Clinical Characteristics of the Participants at Baseline.[*]

Characteristic	Overall (N = 4566)	Cabotegravir Group (N = 2282)	TDF-FTC Group (N = 2284)
Cohort — no. (%)			
MSM	3992 (87.4)	2013 (88.2)	1979 (86.6)
Transgender women who have sex with men	570 (12.5)	266 (11.7)	304 (13.3)
Participant preferred not to answer	4 (0.1)	3 (0.1)	1 (<0.1)
Age category — no. (%)			
18–29yr	3080 (67.5)	1572 (68.9)	1508 (66.0)
30–39yr	1048 (23.0)	498 (21.8)	550 (24.1)
40–49 yr	315 (6.9)	145 (6.4)	170 (7.4)
50–59yr	110 (2.4)	60 (2.6)	50 (2.2)
≥60 yr	13 (0.3)	7 (0.3)	6 (0.3)
Median age (IQR) — yr	26 (22–32)	26 (22–32)	26 (22–32)
Latinx or Hispanic ethnic group, according to geographic region — no./total no. (%)[†]			
United States			
Yes	303/1698 (17.8)	149/849 (17.6)	154/849 (18.1)
No	1394/1698 (82.1)	700/849 (82.4)	694/849 (81.7)
Data missing	1/1698 (<0.1)	0	1/849 (0.1)
Latin America			
Yes	1806/1964 (92.0)	894/980 (91.2)	912/984 (92.7)
No	158/1964 (8.0)	86/980 (8.8)	72/984 (7.3)
SexPro score, according to geographic region — no./total no. (%)[‡]			
United States			
≤16	1447/1698 (85.2)	729/849 (85.9)	718/849 (84.6)
>16	251/1698 (14.8)	120/849 (14.1)	131/849 (15.4)
Latin America			
≤16	1675/1964 (85.3)	825/980 (84.2)	850/984 (86.4)
>16	289/1964 (14.7)	155/980 (15.8)	134/984 (13.6)
Geographic region — no. (%)			
United States	1698 (37.2)	849 (37.2)	849 (37.2)

Characteristic	Overall (N = 4566)	Cabotegravir Group (N = 2282)	TDF-FTC Group (N = 2284)
Latin America			
Argentina	337 (7.4)	169 (7.4)	168 (7.4)
Brazil	796 (17.4)	395 (17.3)	401 (17.6)
Peru	831 (18.2)	416 (18.2)	415 (18.2)
Asia			
Thailand	553 (12.1)	275 (12.1)	278 (12.2)
Vietnam	199 (4.4)	100 (4.4)	99 (4.3)
Africa	152 (3.3)	78 (3.4)	74 (3.2)
Race, according to geographic region — no./total no. (%)†			
United States			
Black	845/1698 (49.8)	411/849 (48.4)	434/849 (51.1)
Non-Black	851/1698 (50.1)	437/849 (51.5)	414/849 (48.8)
Data missing	2/1698 (0.1)	1/849 (0.1)	1/849 (0.1)
Latin America			
Black or mixed	392/1964 (20.0)	198/980 (20.2)	194/984 (19.7)
Indigenous	862/1964 (43.9)	435/980 (44.4)	427/984 (43.4)
Asian	8/1964 (0.4)	6/980 (0.6)	2/984 (0.2)
White	659/1964 (33.6)	319/980 (32.6)	340/984 (34.6)
Other	43/1964 (2.2)	22/980 (2.2)	21/984 (2.1)
Asia			
Asian	749/752 (99.6)	374/375 (99.7)	375/377 (99.5)
Other	3/752 (0.4)	1/375 (0.3)	2/377 (0.5)
Africa			
Black	119/152 (78.3)	62/78 (79.5)	57/74 (77.0)
Other	5/152 (3.3)	2/78 (2.6)	3/74 (4.1)
Mixed	28/152 (18.4)	14/78 (17.9)	14/74 (18.9)
Marital status — no. (%)			
Married, civil union, or legal partnership	177 (3.9)	79 (3.5)	98 (4.3)
Living with primary or main partner	292 (6.4)	138 (6)	154 (6.7)
Have primary or main partner, not living together	335 (7.3)	171 (7.5)	164 (7.2)
Single, divorced, or widowed	3751 (82.2)	1888 (82.7)	1863 (81.6)

Characteristic	Overall (N = 4566)	Cabotegravir Group (N = 2282)	TDF-FTC Group (N = 2284)
Other	11 (0.2)	6 (0.3)	5 (0.2)
Educational level — no. (%)			
No schooling	8 (0.2)	2 (0.1)	6 (0.3)
Primary school	70 (1.5)	28 (1.2)	42 (1.8)
Secondary school	1012 (22.2)	490 (21.5)	522 (22.9)
Technical training	375 (8.2)	187 (8.2)	188 (8.2)
College or university or higher	3101 (67.9)	1575 (69.0)	1526 (66.8)

[*] Percentages may not sum to 100 because of rounding. IQR denotes interquartile range, MSM men who have sex with men, and TDF–FTC tenofovir disoproxil fumarate–emtricitabine.

[†] Race and ethnic group were reported by the participant.

[‡] SexPro is a Web-based tool that provides a sexual health promotion score. It is validated to predict the 6-month risk of HIV acquisition on the basis of sexual behaviors, sexual networks, substance use, history of sexually transmitted infections, race or ethnic group (United States only), and age. Additional background on the SexPro tool is provided in the protocol. Scores range from 1 to 20, with higher scores indicating a lower risk of acquiring HIV infection.

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Table 2.

Adverse Events.*

Event	Overall (N = 4562)	Cabotegravir Group (N = 2280)	TDF-FTC Group (N = 2282)
		number of participants (percent)	
Any adverse event of grade 2 or higher	4222 (92.5)	2106 (92.4)	2116 (92.7)
Most common adverse events of grade 2 or higher†			
Decreased creatinine clearance	3257 (71.4)	1588 (69.6)	1669 (73.1)
Increased creatine kinase	953 (20.9)	484 (21.2)	469 (20.6)
Nasopharyngitis‡	844 (18.5)	447 (19.6)	397 (17.4)
Increased serum creatinine	810 (17.8)	382 (16.8)	428 (18.8)
Upper respiratory infection‡	516 (11.3)	257 (11.3)	259 (11.3)
Musculoskeletal discomfort‡	513 (11.2)	254 (11.1)	259 (11.3)
Increased lipase	509 (11.2)	249 (10.9)	260 (11.4)
Headache‡	458 (10.0)	237 (10.4)	221 (9.7)
Increased aspartate aminotransferase	384 (8.4)	188 (8.2)	196 (8.6)
Increased alanine aminotransferase	351 (7.7)	159 (7.0)	192 (8.4)
Increased blood glucose	322 (7.1)	199 (8.7)	123 (5.4)
Increased amylase	317 (6.9)	148 (6.5)	169 (7.4)
Diarrhea‡	313 (6.9)	152 (6.7)	161 (7.1)
Rash‡	260 (5.7)	116 (5.1)	144 (6.3)
Hypoglycemia‡	246 (5.4)	120 (5.3)	126 (5.5)
Pyrexia	185 (4.1)	122 (5.4)	63 (2.8)
Any adverse event of grade 3 or higher	1494 (32.7)	727 (31.9)	767 (33.6)
Most common adverse events of grade 3 or higher§			
Increased creatine kinase	633 (13.9)	324 (14.2)	309 (13.5)
Decreased creatinine clearance	349 (7.7)	159 (7.0)	190 (8.3)
Increased serum creatinine	156 (3.4)	80 (3.5)	76 (3.3)
Increased lipase	152 (3.3)	76 (3.3)	76 (3.3)
Increased aspartate aminotransferase	122 (2.7)	53 (2.3)	69 (3.0)
Increased alanine aminotransferase	55 (1.2)	23 (1.0)	32 (1.4)

Event	Overall (N = 4562)	Cabotegravir Group (N = 2280)	TDF-FTC Group (N = 2282)
		number of participants (percent)	
Serious adverse event	241 (5.3)	120 (5.3)	121 (5.3)
Adverse events of special interest			
Seizure	7 (0.2)	2 (0.1)	5 (0.2)
Liver-related adverse event resulting in discontinuation of oral tablets or both oral tablets and injections	95 (2.1)	47 (2.1)	48 (2.1)

[*] Included are only adverse events that were assigned *Medical Dictionary for Regulatory Activities,* version 23.1 (MedDRA) terms by clinical staff. Injection-site reactions and sexually transmitted infections are not included. Inappropriately enrolled participants and participants who did not receive any oral trial drug are excluded. In cases in which a participant had multiple events with the same MedDRA term, only one event is counted.

[†] Only adverse events that were reported in at least 5% of the participants in either trial group are shown.

[‡] This adverse event category combines multiple MedDRA terms that were too similar to report individually.

[§] Only adverse events that were reported in at least 1% of the participants in either trial group are shown.

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