

Alimatravir Oral Once Monthly in Adults With Low Likelihood of HIV Exposure: A Randomized, Double-Blind, Placebo-Controlled Study

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Background. Long-acting oral options for human immunodeficiency virus-1 (HIV-1) pre-exposure prophylaxis are needed to address challenges with adherence to once-daily regimens. Alimatravir is an oral nucleoside reverse transcriptase translocation inhibitor with pharmacokinetic properties supporting once-monthly dosing.

Methods. In this double-blind, placebo-controlled study, adults aged 18–65 years with low likelihood of HIV-1 exposure were randomly assigned 2:2:2:1 to receive 6 oral doses of alimatravir (3, 6, or 12 mg) or placebo once every 4 weeks. The primary outcome was the proportion of participants with adverse events through 8 weeks after the last dose, assessed in participants who received at least one dose of study intervention. Additional outcomes were the pharmacokinetics of alimatravir in plasma (all participants) and alimatravir-triphosphate in peripheral blood mononuclear cells (~20 participants from each alimatravir dose group).

Results. Three hundred fifty participants were included in the analyses (median age 28 years; 58% female): 301 received alimatravir 3 mg (n = 101), 6 mg (n = 101), or 12 mg (n = 99) and 49 received placebo. Adverse event rates were comparable for alimatravir 3 mg (61.4% [62/101]), 6 mg (68.3% [69/101]), 12 mg (66.7% [66/99]), and placebo (63.3% [31/49]). Study intervention was discontinued because of an adverse event in 1.0% (3/301) of participants who received alimatravir and 4.1% (2/49) who received placebo. Pharmacokinetic parameters for alimatravir and alimatravir-triphosphate were dose-proportional and support a once-monthly dosing interval.

Conclusions. The favorable safety, tolerability, and pharmacokinetics of alimatravir and alimatravir-triphosphate support continued development of alimatravir as oral monthly pre-exposure prophylaxis.

Clinical Trials Registration. [ClinicalTrials.gov](https://www.clinicaltrials.gov) Identifier NCT06045507; <https://www.clinicaltrials.gov/search>.

Keywords. HIV prevention; long-acting oral; pre-exposure prophylaxis; alimatravir; once-monthly dosing.

Human immunodeficiency virus-1 (HIV-1) remains a worldwide epidemic; in 2024, an estimated 40.8 million people globally had HIV, and approximately 1.3 million were newly infected [1]. Because HIV requires lifelong treatment and is associated with risks for multiple morbidities, the ongoing epidemic results in

a growing collective care burden. Although several prevention strategies are currently available, additional approaches to prevent HIV acquisition could help reduce global incidence.

Pre-exposure prophylaxis (PrEP) is a proven biomedical intervention for HIV prevention recommended by the World Health Organization since 2015 for individuals who are “at substantial risk” of HIV exposure [2]. Currently available PrEP options include daily oral emtricitabine (FTC) with tenofovir disoproxil fumarate or tenofovir alafenamide (TAF), bi-monthly intramuscular cabotegravir, and twice yearly subcutaneous lenacapavir. Each of these options, however, has limitations. For example, FTC/TAF is not currently approved for individuals at risk of acquiring HIV from receptive vaginal sex [3], and the effectiveness of both oral options

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depends on adherence to daily therapy [4], which can be challenging for many people who could benefit from PrEP [5–8]. The availability of injectable options may be limited by implementation and access challenges [9, 10], and some people may prefer the oral route of administration [11]. Although the dapivirine vaginal ring, designed for HIV prevention in cisgender women, has shown good efficacy that is closely correlated with consistent use, it is currently only available in some African countries [12, 13]. Expanded choices for HIV prevention, such as a monthly pill, may increase utilization, adherence, and effectiveness [14–16] and facilitate innovative delivery strategies (eg, mobile vans, home delivery, etc.).

Alimatravir (formerly known as MK-8527) is a nucleoside reverse transcriptase (RT) translocation inhibitor in development for the prevention of HIV-1. The parent drug is converted intracellularly to its active triphosphate (TP) form, alimatravir-TP, which is a specific inhibitor of HIV-1 RT with in vitro IC₅₀ of 0.21 nM [17]. Alimatravir is not anticipated to be an object or precipitant of metabolic drug interactions mediated by cytochrome P450 (CYP) modulators or by P-glycoprotein or other major transporters [17]. Although alimatravir has structural similarities with islatravir, which has been associated with exposure-dependent decreases in total lymphocyte and CD4+ T-cell counts in some clinical trials [18], doses of alimatravir studied in the clinic have not shown any impact on lymphocyte or CD4+ T-cell counts.

The antiretroviral activity of alimatravir was assessed in 2 phase 1, open-label, proof-of-concept studies in treatment-naïve adults with HIV-1 [19]. At 7 days after dosing, single oral doses of alimatravir (0.5–10 mg) achieved mean plasma HIV-1 RNA reduction of $\geq 1 \log_{10}$ copies/mL. The long intracellular half-life of alimatravir-TP (~94–291 hours across doses in phase 1 studies) [19, 20] supports once-monthly (qm) dosing, which would reduce the burden of adherence to daily regimens or clinic visits for injections. Exposure-response modeling established an efficacy threshold of 0.03 pmol/10⁶ peripheral blood mononuclear cells (PBMCs) for alimatravir-TP [19]. We conducted a phase 2 clinical study (MK-8527-007) to assess the safety, tolerability, and pharmacokinetics of alimatravir oral qm in adults with low likelihood of HIV-1 exposure.

METHODS

Study Design

MK-8527 Protocol 007 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06045507) NCT06045507) was a randomized, double-blind, placebo-controlled, phase 2a study conducted at 18 research, community, and hospital-based clinics in Israel, South Africa, and the United States. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

Individuals of any sex/gender, from 18 to 65 years of age, without HIV (negative HIV-1/HIV-2 test) and at low

likelihood of HIV exposure were eligible for the study. Individuals assigned female at birth were eligible if not pregnant, not breastfeeding and either (1) not of childbearing potential, (2) using an acceptable contraceptive method, or (3) abstinent from penile-vaginal intercourse. Sex at birth, gender identity, race, and ethnicity were self-reported by the participants. To ensure a study population with demographics similar to the target population for subsequent efficacy studies (ie, individuals at greatest likelihood of HIV-1 exposure), enrollment was planned to include $\geq 30\%$ women, $\geq 30\%$ men, $\geq 80\%$ aged 35 years or younger, and $\geq 30\%$ enrolled in Africa. Exclusion criteria included certain medical conditions, prohibited concurrent therapies, and prespecified laboratory values as described in the study protocol ([Supplementary Material](#)).

Intervention

Participants were randomly assigned 2:2:2:1 to receive alimatravir (3, 6, or 12 mg) or placebo, according to a computer-generated allocation schedule provided by the sponsor, with randomization stratified by sex assigned at birth and geographic region (Africa, non-Africa). Intervention assignments were obtained from a centralized interactive-response system and were concealed from the participants, investigators, and sponsor personnel or delegate(s) involved in administration of study intervention or clinical evaluation of participants. Alimatravir and matching placebo were provided in identical packaging (labeled only with the allocation number) to maintain blinding.

Participants received 6 oral doses of the assigned study intervention, 1 dose every 4 weeks (on day 1 and weeks 4, 8, 12, 16, and 20), witnessed by study staff. Before each dose, the likelihood of exposure to HIV was assessed, and a urine pregnancy test was performed. Participants returned for additional study visits 1 day, 4 weeks, and 8 weeks after the final dose. Protocol-specified criteria for discontinuation of study intervention included confirmed HIV-1 or HIV-2 infection, confirmed positive serum pregnancy test, and declines in total lymphocyte count (confirmed on-treatment value $< 1000 \text{ cells/mm}^3$ and $\geq 30\%$ decline from baseline) or CD4+ T-cell count (confirmed on-treatment value $< 500 \text{ cells/mm}^3$ and $\geq 30\%$ decline from baseline).

Adverse events were collected at each visit using open-ended and nonleading verbal questioning, graded for intensity according to Division of Acquired Immunodeficiency Syndrome (DAIDS) Criteria [21], and assessed for relationship to study treatment by the investigator. Adverse event terms were based on the Medical Dictionary for Regulatory Activities version 27.1. Laboratory safety tests, including total lymphocyte and CD4+ T-cell counts, and screening for HIV-1 and HIV-2 were performed at each study visit. Blood samples for measurement of alimatravir in plasma were collected from all participants on days 1 and 2, week 20 (or end of treatment), and follow-up day 1. Blood samples for measurement of alimatravir-TP in PBMCs were collected from a subset of participants

(~ 20 from each alimatrovir dose group) at each study visit and at additional visits on weeks 1, 2, and 3 and follow-up week 6.

Outcomes

The primary objective was to evaluate the safety and tolerability of alimatrovir (3, 6, and 12 mg) qm through the last follow-up visit, based on clinical review of adverse events and laboratory tests, including total lymphocyte and CD4+ T-cell counts. The primary safety endpoints were the proportion of participants with any adverse event(s) and the proportion who discontinued due to adverse events. The secondary objective was to characterize the plasma pharmacokinetics of alimatrovir qm, based on the area under the concentration-time curve (AUC_{0-last}), the maximum concentration (C_{max}), and time to maximum concentration (T_{max}). A key tertiary objective was to characterize the intracellular pharmacokinetics of alimatrovir-TP in PBMCs up to 8 weeks after the last dose, based on AUC_{0-last} , the trough concentration (ie, immediately before the next dose, C_{trough}), C_{max} , and T_{max} .

Statistical Analysis

The sample size was chosen to allow for the accumulation of ~ 150 person-years of safety data on alimatrovir. With 100 participants in the alimatrovir group and 50 in the placebo group, the study has 80% power to rule out a difference of 23 percentage points (alimatrovir minus placebo) if the underlying incidence of the adverse event is 50% (Supplementary Table 1). Safety analyses were conducted for all randomized participants who received at least one dose of study intervention ($N = 350$), with participants included in the treatment group corresponding to the intervention they received. Point estimates and 95% CIs for the difference between alimatrovir and placebo were calculated using the Miettinen–Nurminen method [22] for the incidence of adverse events overall and by category (ie, serious, drug-related, DAIDS grade 3–4, discontinuations, and deaths). For total lymphocyte and CD4+ T-cell counts, mean percent change from baseline (with 95% CI based on the t-distribution) was calculated by treatment group using the data-as-observed approach. Statistical analyses were performed using SAS® System version 9.4 (SAS Institute Inc., Cary, NC, United States). An interim safety review was performed when 50% of the planned enrollment had reached week 12 or discontinued study intervention, and the Data Monitoring Committee recommended that the study continue as planned.

Pharmacokinetic Analyses

The analysis of alimatrovir in plasma included 288 participants who received at least one dose of alimatrovir and had at least 2 pharmacokinetic measurements. Alimatrovir concentrations were determined by Pharma Medica Research Inc. using a validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method with analytical range 1–1000 ng/mL (0.00324–3.24 μ M). The analysis of alimatrovir-TP in PBMCs

included 69 participants with data available after at least one dose of alimatrovir. Alimatrovir-TP concentrations in PBMCs were determined by Syneos Health using a validated HPLC-MS/MS method with analytical range 0.2–40 ng/mL (0.000365–0.0182 nM) and were converted from nM to pmol/ 10^6 cells using the following equation: PBMC alimatrovir-TP concentration (pmol/ 10^6 cells) = (raw alimatrovir-TP concentration [nM] $\times$ dilution volume [mL]/cell count [in 10^6 cells]), with cell count determined for each PBMC sample independently. Pharmacokinetic parameters for alimatrovir and alimatrovir-TP were calculated by noncompartmental methods using Phoenix® WinNonlin® Professional (Version 8.4). C_{max} and T_{max} (and C_{trough} for alimatrovir-TP) were generated from the observed plasma or PBMC concentration-time data. AUC_{0-last} was calculated by the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down).

RESULTS

Participants

Between 08 November 2023 and 23 May 2024, 352 participants were randomized and 350 received study intervention (Figure 1). The last study visit occurred on 12 February 2025. Study intervention was completed by 93.2% of participants (328/352). The most common reasons for discontinuing study intervention were participant decision (2.0%, 7/352), adverse events (1.4%, 5/352), and loss to follow-up (1.4%, 5/352). Demographic and baseline characteristics were generally comparable across the intervention groups (Table 1). Overall, 58.3% (204/350) of participants were female, 41.4% (145/350) were Black or African American, and 16.0% (56/350) were Hispanic or Latino/a. The overall median age was 28 years (interquartile range 23–34), and 81.1% (284/350) of participants were 18 to 35 years of age.

Safety

Adverse events were reported by >60% of participants in each treatment group (Table 2). The percentage of participants with any adverse event was comparable for each alimatrovir group versus the placebo group: difference -1.9 (95% CI -17.7 , 14.9) for 3 mg, 5.1 (-10.6 , 21.6) for 6 mg, and 3.4 (-12.4 , 20.0) for 12 mg. Study intervention was discontinued because of an adverse event in 1.0% (3/301) of participants who received alimatrovir and 4.1% (2/49) who received placebo. In each alimatrovir group, the percentage of participants who discontinued due to an adverse event was comparable to the placebo group: difference -4.1 (95% CI -13.8 , -0.3) for 3 mg, -2.1 (-11.9 , 3.6) for 6 mg, and -3.1 (-12.8 , 2.1) for 12 mg. The most common adverse events were headache, reported by 12.6% (38/301) of participants on alimatrovir and 8.2% (4/49) on placebo, and upper respiratory tract infection, reported by 12.0% (36/301) and 12.2% (6/49), respectively. No HIV-1 seroconversions were observed during the study.

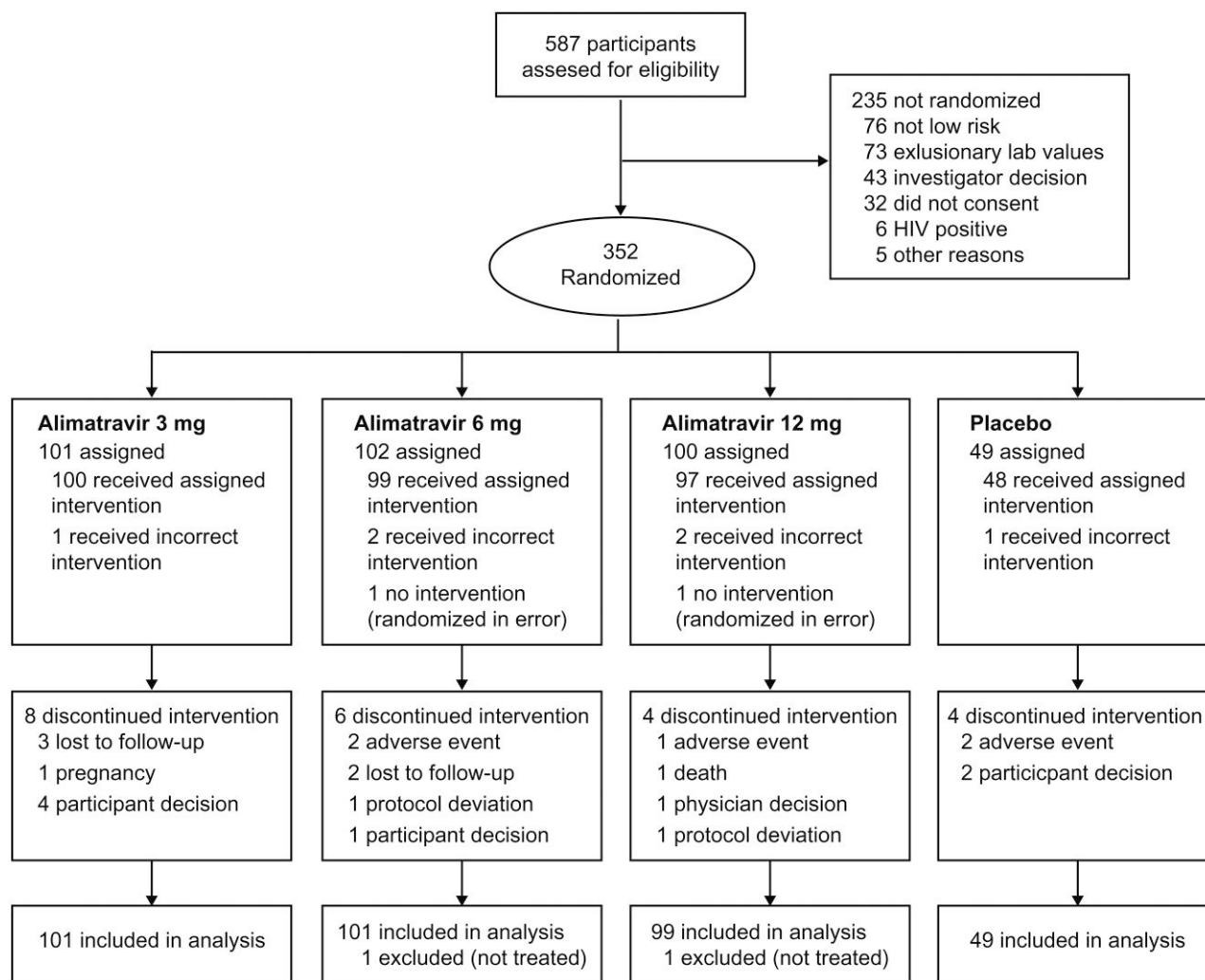


Figure 1. Flow chart of participant disposition.

The incidence of drug-related adverse events, grade 3 or 4 adverse events, and serious adverse events was comparable across the treatment groups (Table 2), with 95% CI's for the treatment difference (alimatravir minus placebo) that included zero (Supplementary Table 2). For the combined alimatravir groups, the most common drug-related adverse events were headache (3.7% [11/301] vs 2.0% [1/49] for placebo) and nausea (3.0% [9/301] vs 2.0% [1/49] for placebo). Most adverse events were categorized as grade 1 or 2 by DAIDS criteria. Grade 3 or 4 adverse events were reported by 3.7% (11/301) of the combined alimatravir groups versus 8.2% (4/49) of the placebo group (see Supplementary Table 3 for specific events) and were considered drug-related in 2 participants (0.7%) who received alimatravir and 1 (2.0%) who received placebo. Specifically, 1 participant who received alimatravir 12-mg had a drug-related grade 4 adverse event of increased lipase at follow-up week 4 (21 days after last qm dose) that resolved

within ~ 8 days with no concurrent clinical adverse events, and 1 participant who received alimatravir 3-mg had a drug-related grade 3 serious adverse event of spontaneous abortion at approximately 6 weeks gestation (1 month, 18 days after fourth qm dose); this participant had 8 previous pregnancies that resulted in 1 live birth and 7 induced abortions. In the placebo group, 1 participant had a drug-related grade 3 serious adverse event of osteoarthritis. One participant (in the alimatravir 12-mg group) died of a gunshot wound on day 131 (18 days after 5th qm dose); this event was considered not related to study intervention.

Two participants had drug-related adverse events resulting in discontinuation of alimatravir: 1 participant was in the 12-mg group and discontinued due to grade 2 hypoesthesia (numbness of cheeks) starting on day 53 (day of third qm dose) that resolved in 12 days. The 2nd participant was in the 6-mg group and discontinued due to a 36.5% decline in total

Table 1. Baseline Characteristics, All Participants as Treated

	Alimatravir Oral Once Monthly			Placebo (N = 49)
	3 mg (N = 101)	6 mg (N = 101)	12 mg (N = 99)	
Age (y)				
18–35	79 (78.2)	83 (82.2)	82 (82.8)	40 (81.6)
>35–65	22 (21.8)	18 (17.8)	17 (17.2)	9 (18.4)
Median (IQR)	27 (23, 33)	28 (24, 34)	28 (23, 34)	28 (24, 34)
Sex at birth				
Female	58 (57.4)	59 (58.4)	58 (58.6)	29 (59.2)
Male	43 (42.6)	42 (41.6)	41 (41.4)	20 (40.8)
Gender identity				
Man	39 (38.6)	35 (34.7)	39 (39.4)	20 (40.8)
Woman	51 (50.5)	51 (50.5)	45 (45.5)	23 (46.9)
Transgender man	5 (5.0)	4 (4.0)	2 (2.0)	1 (2.0)
Transgender woman	0	1 (1.0)	0	0
Genderqueer ^a	0	2 (2.0)	3 (3.0)	2 (4.1)
Other	0	0	1 (1.0)	0
Unknown	6 (5.9)	8 (7.9)	9 (9.1)	3 (6.1)
Race				
White	49 (48.5)	54 (53.5)	51 (51.5)	26 (53.1)
Black or African American	44 (43.6)	40 (39.6)	40 (40.4)	21 (42.9)
Asian	3 (3.0)	2 (2.0)	3 (3.0)	0
Other	5 (5.0)	5 (5.0)	5 (5.1)	2 (4.1)
Ethnicity				
Hispanic or Latino/a	18 (17.8)	13 (12.9)	14 (14.1)	11 (22.4)
Country				
United States	42 (41.6)	48 (47.5)	45 (45.5)	21 (42.9)
South Africa	35 (34.7)	34 (33.7)	34 (34.3)	16 (32.7)
Israel	24 (23.8)	19 (18.8)	20 (20.2)	12 (24.5)

Data shown as n (%) unless otherwise specified.

^aIncludes nonbinary and gender nonconforming.

Abbreviation: IQR, interquartile range (Q1, Q3).

lymphocyte count (to 800 cells/mm³, grade 0) and a 51.4% decline in CD4+ T-cell count (to 313 cells/mm³, grade 1), which started on day 57 (day of third qm dose) and resolved 48 days after the last dose of alimatravir. Additionally, 1 participant in the 12-mg group had a 54.1% decline in total lymphocyte count (to 610 cells/mm³, grade 1) that met the discontinuation criteria but occurred after the final dose of alimatravir; this event was considered related to study intervention and resolved 77 days after the last dose.

Adverse events of decreased lymphocyte count or CD4+ T-cell count were reported in 2.3% (7/301) and 4.0% (12/301), respectively, of the alimatravir groups, which was comparable to the 2.0% (1/49) and 4.1% (2/49), respectively, reported in the placebo group. The declines were all grade 0, 1, or 2 (Supplementary Table 4) and met the prespecified discontinuation criteria in 2 participants, as described above. The mean percent changes from baseline in total lymphocyte and CD4+ T-cell counts over time were similar across all 4 treatment groups (Figure 2A and 2B). At 4 weeks after the final dose, the mean percent change in total lymphocyte count was +2.9% (95% CI −1.5, 7.3) for alimatravir 3 mg, −0.3%

(−4.5, 3.9) for 6 mg, +4.5% (−0.2, 9.2) for 12 mg, and −0.04% (−7.0, 7.0) for placebo; mean percent change in CD4+ T-cell count was +6.1% (95% CI 0.9, 11.3), +1.6% (−3.1, 6.2), +5.7% (−0.2, 11.7), and +2.3% (−4.4, 9.0), respectively.

Pharmacokinetics

AUC_{0–last} and C_{max} for alimatravir in plasma and for alimatravir-TP in PBMCs were approximately dose proportional across the 3 dose levels (Table 3). Median T_{max} ranged from 0.55 to 0.60 hours for alimatravir in plasma and from 23.10 to 23.68 hours for alimatravir-TP in PBMCs. There was no apparent accumulation of alimatravir in plasma and minimal accumulation of alimatravir-TP in PBMCs following qm dosing (Table 3; Figure 3). Mean C_{trough} for alimatravir-TP, measured immediately before the next dose (ie, ~28 days after the previous dose), was above the efficacy threshold for HIV-1 prevention (0.03 pmol/10⁶ PBMCs) [19] after each dose of alimatravir 6 and 12 mg (Table 4) and remained above the threshold through 6 weeks after the last dose of alimatravir 12 mg (Figure 3B).

Table 2. Summary of Adverse Events, All Participants as Treated

	Alimatravir Oral Once Monthly			
	3 mg (N = 101)	6 mg (N = 101)	12 mg (N = 99)	Placebo (N = 49)
Primary adverse event (AE) endpoints, n (%) (95% CI) ^a				
One or more AEs	62 (61.4) (51.2, 70.9)	69 (68.3) (58.3, 77.2)	66 (66.7) (56.5, 75.8)	31 (63.3) (48.3, 76.6)
Discontinued due to AE	0 (0.0) (0, 3.6)	2 (2.0) (0.2, 7.0)	1 (1.0) (0.03, 5.5)	2 (4.1) (0.5, 14.0)
Secondary AE endpoints, n (%)				
Drug-related ^b AEs	15 (14.9)	16 (15.8)	20 (20.2)	9 (18.4)
Grade 3–4 AEs	5 (5.0)	2 (2.0)	4 (4.0)	4 (8.2)
Grade 3–4 drug-related ^b AEs	1 (1.0)	0 (0.0)	1 (1.0)	1 (2.0)
Serious AEs	2 (2.0)	0 (0.0)	1 (1.0)	1 (2.0)
Serious drug-related ^b AEs	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.0)
Deaths	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Discontinued due to drug-related ^b AE	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)
Most common AEs, n (%)				
Headache	9 (8.9)	18 (17.8)	11 (11.1)	4 (8.2)
Upper respiratory tract infection	16 (15.8)	10 (9.9)	10 (10.1)	6 (12.2)
Fatigue	5 (5.0)	8 (7.9)	7 (7.1)	3 (6.1)
Nausea	4 (4.0)	8 (7.9)	3 (3.0)	1 (2.0)
Most common drug-related ^b AEs, n (%)				
Headache	4 (4.0)	5 (5.0)	2 (2.0)	1 (2.0)
Nausea	3 (3.0)	4 (4.0)	2 (2.0)	1 (2.0)
Decreased CD4+ T-cell count	2 (2.0)	1 (1.0)	3 (3.0)	1 (2.0)
Decreased lymphocyte count	0 (0.0)	1 (1.0)	4 (4.0)	1 (2.0)
Fatigue	0 (0.0)	3 (3.0)	2 (2.0)	1 (2.0)

This table includes adverse events that occurred on or after day 1 through 56 days after last dose of study intervention.

^a95% CI calculated by exact Clopper–Pearson method [23].

^bDetermined by the investigator to be related to study intervention.

DISCUSSION

In this large phase 2 study of adults with low likelihood of HIV-1 exposure, 6 monthly doses of oral alimantavir (3, 6, or 12 mg) demonstrated a safety profile similar to that of placebo. The incidence of adverse events overall and discontinuations due to adverse events were comparable to placebo for each of the alimantavir dose levels. Regardless of intervention group, the majority of adverse events were DAIDS grade 1 or 2; fewer than 4% of participants had adverse events classified as grade 3 or 4. Rates of drug-related adverse events and serious adverse events were also similar for alimantavir and placebo. Although efficacy was not an objective of this study, screening for HIV seroconversion was done monthly, and no HIV-1 seroconversions were observed in any participant.

One participant receiving alimantavir had a serious adverse event of spontaneous abortion (at ~ 6 weeks gestation) that was considered potentially drug-related by the investigator. Miscarriage is the most common complication of pregnancy, and the majority (75%–80%) occurs in the first trimester. Pregnancy loss occurs in 10%–20% of clinically recognized pregnancies and ~ 30% of biochemically detected pregnancies [24–26]. Nonclinical developmental and reproductive toxicology studies have not demonstrated any teratogenicity or other

clinically relevant concerns that preclude continued dosing of alimantavir in participants who become pregnant. In accordance with guidance from the World Health Organization [27], efficacy, safety and pharmacokinetic data will be collected in participants who become pregnant during the phase 3 study of alimantavir for PrEP in women (NCT07071623). This will include pregnancy outcomes and infant safety follow-up through ~ 1 year of age, in order to provide timely information on the extent of drug exposure to women and infants during pregnancy, postpartum and lactation, as well as the efficacy, safety and tolerability of alimantavir in this population.

Because of exposure-related decreases in lymphocytes and CD4+ T cells seen with islatravir, changes in total lymphocyte and CD4+ T-cell counts were closely monitored in this study, and discontinuation was required if declines meeting pre-specified criteria were confirmed. Two of 301 participants (<1%) who received alimantavir met the protocol-specified discontinuation criteria for decline in total lymphocyte and/or CD4+ T-cell count; these declines were grade 1 by DAIDS criteria and resolved within 7 and 11 weeks, respectively, after alimantavir was stopped. No grade 3 or 4 declines in total lymphocyte or CD4+ T-cell count occurred in participants

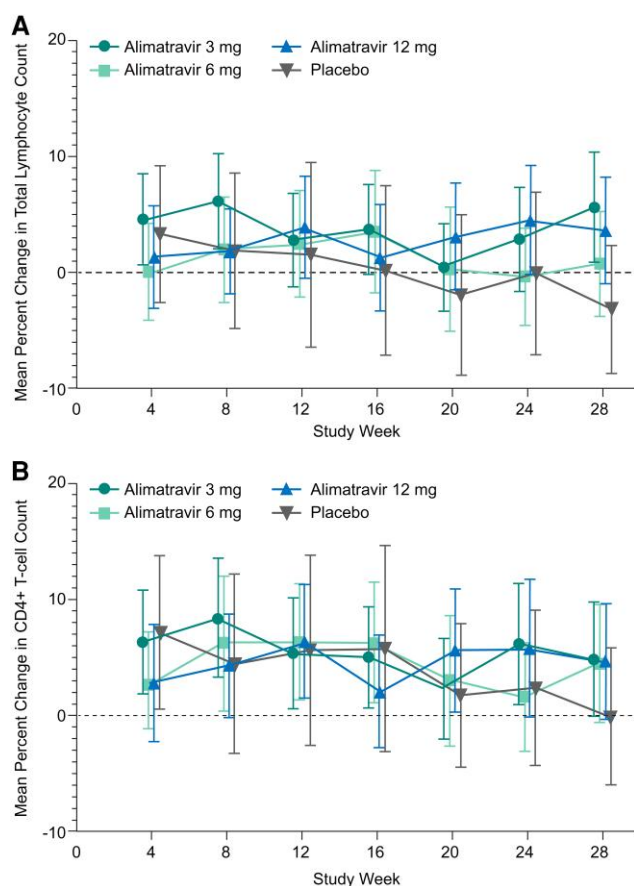


Figure 2. Mean percent change from baseline in total lymphocyte count (panel A) and CD4+ T-cell count (panel B) over time (all participants as treated). Error bars represent 95% CI.

Table 3. Pharmacokinetic Parameters After First and Last Dose of Alimatravir

Alimatravir in plasma, geometric mean (GCV%)			
First dose (day 1)	3 mg (n = 95)	6 mg (n = 96)	12 mg (n = 97)
AUC _{0–last} (h × μmol/L)	0.132 (84.8)	0.397 (36.1)	0.861 (34.1)
C _{max} (μmol/L)	0.0289 (69.0)	0.0490 (75.6)	0.113 (64.5)
T _{max} (h) ^a	0.55 (0.27–4.07)	0.60 (0.32–4.22)	0.60 (0.27–4.10)
Last dose (wk 20)	3 mg (n = 78)	6 mg (n = 92)	12 mg (n = 95)
AUC _{0–last} (h × μmol/L)	0.129 (81.5)	0.404 (37.3)	0.836 (55.0)
C _{max} (μmol/L)	0.0320 (67.5)	0.0538 (73.5)	0.108 (72.5)
T _{max} (h) ^a	0.55 (0.25–4.28)	0.56 (0.25–4.38)	0.57 (0.27–4.12)
Alimatravir-TP in peripheral blood mononuclear cells, geometric mean (GCV%)			
First dose (day 1)	3 mg (n = 21)	6 mg (n = 26)	12 mg (n = 22)
AUC _{0–last} (h × pmol/10 ⁶ cells)	52.9 (67.7)	108 (56.3)	204 (71.3)
C _{max} (pmol/10 ⁶ cells)	0.394 (89.4)	0.707 (89.7)	1.48 (79.7)
T _{max} (h) ^a	23.65 (3.53–335.40)	23.53 (3.62–25.87)	23.68 (4.00–27.22)
Last dose (wk 20)	3 mg (n = 20)	6 mg (n = 23)	12 mg (n = 19)
AUC _{0–last} (h × pmol/10 ⁶ cells)	20.7 (255.5)	128 (178.6)	287 (55.9)
C _{max} (pmol/10 ⁶ cells)	0.325 (78.7)	0.782 (72.2)	1.23 (63.9)
T _{max} (h) ^a	23.44 (3.53–27.45)	23.55 (3.67–47.07)	23.10 (3.63–26.15)

Abbreviations: GCV, geometric coefficient of variation; AUC_{0–last}, area under the concentration-time curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration; TP, triphosphate.

^aMedian (minimum–maximum).

receiving alimatravir, and the mean percent changes from baseline in total lymphocyte and CD4+ T-cell counts were comparable for alimatravir 3 mg, 6 mg, 12 mg, and placebo.

Pharmacokinetic parameters for both alimatravir and alimatravir-TP in this phase 2 study were generally consistent with results from previous phase 1 studies [19, 20] and were dose-proportional across the 3, 6, and 12 mg dose levels. Maximum concentrations of alimatravir and alimatravir-TP were achieved within 1 hour and 1 day, respectively. Exposure-response modeling using data from previous studies has established an efficacy threshold for HIV-1 prevention of 0.03 pmol/10⁶ PBMCs for alimatravir-TP [19]. In our study, the mean concentration of alimatravir-TP at the end of the dosing interval (C_{trough}) was above this efficacy threshold after each dose of alimatravir 6 and 12 mg, and remained above the threshold through 6 weeks after the last dose of alimatravir 12 mg, suggesting that alimatravir taken once monthly will be effective in preventing HIV-1 acquisition. No accumulation of alimatravir and minimal accumulation of alimatravir-TP were observed, indicating an appropriate balance between the once-monthly dosing interval and the elimination half-lives for alimatravir in plasma (~ 6–81 hours) and alimatravir-TP in PBMCs (~ 94–291 hours) [19, 20].

An important strength of this study is the enrollment of a large, diverse group of participants, representing some of the key demographics of the broader population who would be eligible for a future PrEP efficacy trial: 81% of the participants were 18–35 years of age, 58% were female, and 34% were enrolled in Africa. The number of participants enrolled and the

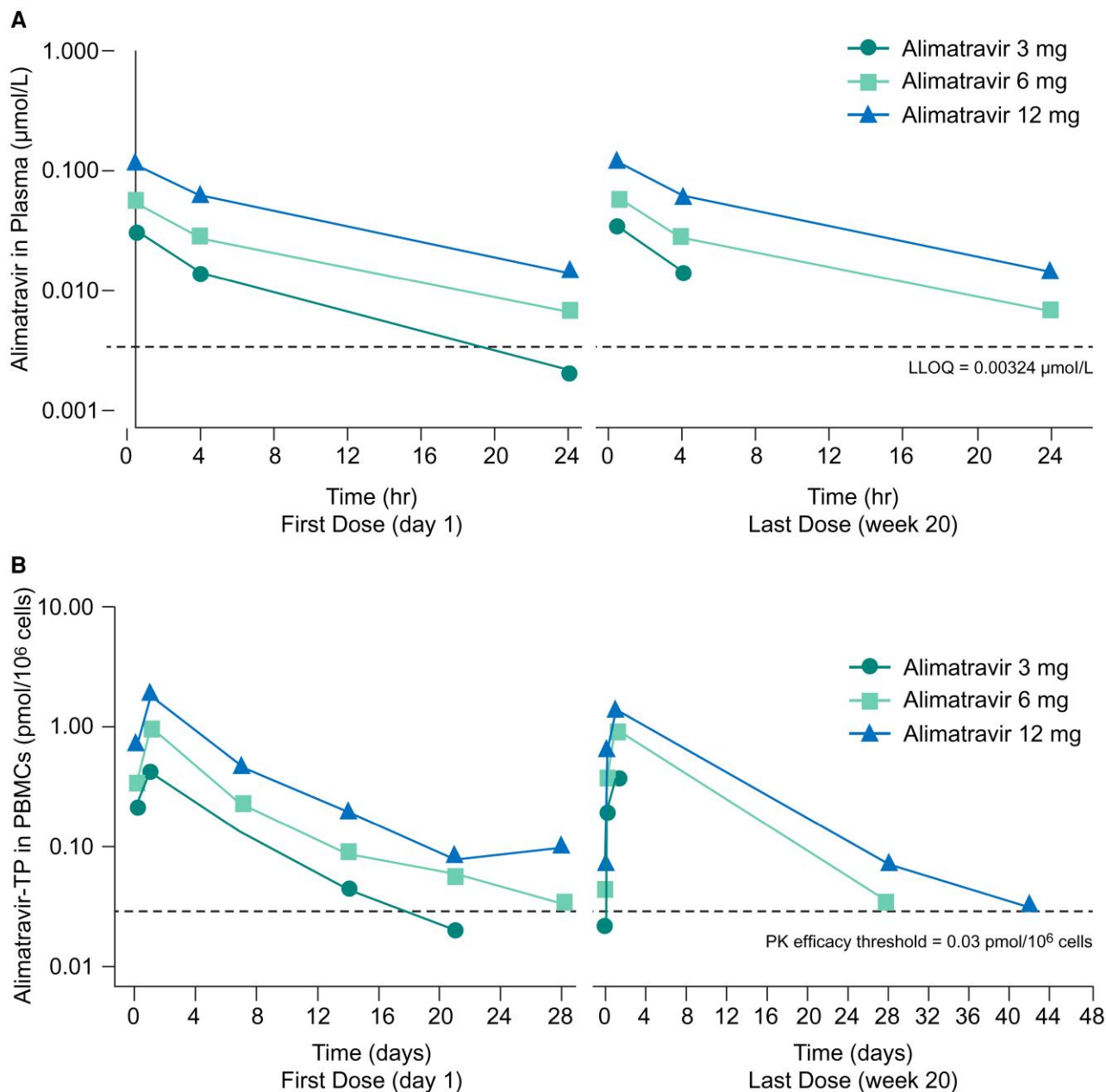


Figure 3. Mean concentration versus time profiles for alimatravir in plasma (panel A) and alimatravir-TP in PBMCs (panel B) after first and last dose (semi-log scale). Mean concentrations are not displayed if >50% of participants had levels below the limit of quantification. Abbreviations: TP, triphosphate; PBMC, peripheral blood mononuclear cells.

duration of this study yielded approximately 150 participant-years of safety and tolerability data for alimatravir. Another strength is the randomized double-blind design and inclusion of a placebo arm, which prevented bias in adverse event reporting. This study also has limitations. The efficacy of alimatravir for preventing HIV could not be tested for 2 reasons. First, in order to assess safety and tolerability, this study included a placebo arm, which required the population enrolled to be at low likelihood of exposure to HIV-1. Second, not all dose levels

used in this study were predicted to be protective against HIV-1 infection; the doses of 3, 6 and 12 mg were chosen to characterize the pharmacokinetics over a wide dose range. The sparse pharmacokinetic data from this study for both alimatravir in plasma and alimatravir-TP in PBMCs, along with intensive pharmacokinetic data from 5 phase 1 studies, were used to inform dose selection for the phase 3 studies, where the efficacy of alimatravir for HIV-1 prevention will be evaluated. Additional limitations are the small size of the placebo

Table 4. Mean C_{through} Values for Alimatravir-Triphosphate in Peripheral Blood Mononuclear Cells

Week	Alimatravir 3 mg		Alimatravir 6 mg		Alimatravir 12 mg	
	N	Mean (SD), pmol/ 10^6 cells	N	Mean (SD), pmol/ 10^6 cells	N	Mean (SD), pmol/ 10^6 cells
4	21	0.0102 (0.0239)	24	0.0348 (0.0326)	20	0.0997 (0.273)
8	19	0.0175 (0.0132)	24	0.0434 (0.0369)	16	0.0815 (0.0587)
12	21	0.0155 (0.0182)	23	0.0334 (0.0273)	17	0.0715 (0.0549)
16	19	0.0140 (0.0164)	24	0.0447 (0.0384)	19	0.0882 (0.0804)
20	16	0.0225 (0.0250)	21	0.0492 (0.0592)	18	0.0672 (0.0678)
24	18	0.0118 (0.0153)	22	0.0355 (0.0283)	17	0.0735 (0.0426)

group and the limited power to detect differences in adverse event rates. The ongoing phase 3 studies will provide further evaluation of the safety and tolerability of alimatravir.

In this randomized, double-blind, placebo-controlled study in adults with low likelihood of HIV-1 exposure, 6 consecutive monthly oral doses of alimatravir (3, 6, or 12 mg) were generally well tolerated and demonstrated a safety profile similar to placebo. The pharmacokinetics of alimatravir in plasma and alimatravir-TP in PBMCs were dose-proportional and support a monthly dosing interval. These results support the continued clinical development of alimatravir 11 mg oral monthly for PrEP and the ongoing phase 3 studies, EXPrESSIVE-10 (NCT07071623), enrolling cisgender women in eastern and southern Africa, and EXPrESSIVE-11 (NCT07044297), enrolling gender-diverse populations globally.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). **Supplementary materials** consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all **supplementary data** are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. R. M. P., R. P. M., M. N. R., and Y. K. conceived and designed the study. B. H., M. V., and B. E. implemented and coordinated the study at all sites. K. H. M., P. K., J. L., Y. C., A. P., N. P., S. K., S. Khe., A. E. S., M. R., A. G., Y. S., G. S., S. A. R., S. B., E. B.-A., and M. T. recruited the study participants and collected the data. A. G. and

C. Z. performed the statistical analyses. Y. K. performed the pharmacokinetic analyses. All authors contributed to interpretation of the results, reviewed the manuscript for important intellectual content, and approved the final version for submission.

Data sharing. The data sharing policy, including restrictions, of MSD is available at <https://trialstransparency.msdclinicaltrials.com/>. Requests for access to the clinical study data can be submitted via email to the Data Access mailbox (mailto: dataaccess@msd.com).

Protocol availability. The protocol used for this study is available as **supplementary material** (MK-8527-007 Study Protocol, with Statistical Analysis Plan).

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