Pharmacokinetics and safety of once-yearly lenacapavir: a phase 1, open-label study

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Summary

Background Long-acting antiretrovirals can address barriers to HIV pre-exposure prophylaxis (PrEP), such as stigma and adherence. In two phase 3 trials, twice-yearly subcutaneous lenacapavir was safe and highly efficacious for PrEP in diverse populations. Furthering long-acting PrEP efforts, this study assessed the pharmacokinetics and safety of two once-yearly intramuscular lenacapavir formulations.

Methods This phase 1, open-label study in participants aged 18–55 years without HIV evaluated the pharmacokinetics, safety, and tolerability of two lenacapavir free acid formulations administered by ventrogluteal intramuscular injection as a single 5000 mg dose (formulation 1 with 5% w/w ethanol, formulation 2 with 10% w/w ethanol). Pharmacokinetic samples were collected at prespecified timepoints up to 56 weeks. Lenacapavir plasma concentrations were measured with a validated liquid chromatography–tandem mass spectrometry method and summarised with non-compartmental analysis. Pharmacokinetic parameters evaluated included the area under the concentration–time curve for the once-yearly dosing interval calculated from days 1 to 365 ($AUC_{days\ 1–365}$), peak plasma concentration, time to reach peak plasma concentration, and trough concentration (C_{trough}). Plasma concentration data from phase 3 studies of twice-yearly subcutaneous lenacapavir (PURPOSE 1 and PURPOSE 2) were pooled for comparison with once-yearly intramuscular lenacapavir formulations. Safety and tolerability, including participant-reported pain scores, were assessed.

Findings 20 participants received lenacapavir formulation 1 and 20 received lenacapavir formulation 2. For estimation of pharmacokinetic parameters, sample size varied over time with at least 13 participants (formulation 1) and at least 19 participants (formulation 2) due to early discontinuations for reasons unrelated to the study drug. Following administration of intramuscular lenacapavir, concentrations increased rapidly, and median time to maximum concentration was 84·1 days (IQR 56·1–112·0) for formulation 1 and 69·9 days (55·3–105·5) for formulation 2. The highest median concentration of once-yearly intramuscular lenacapavir (247·0 ng/mL [IQR 184·0–346·0] for formulation 1, 336·0 ng/mL [233·5–474·3] for formulation 2) remained above the highest median twice-yearly subcutaneous lenacapavir concentration (67·3 ng/mL [46·8–91·4]). Median C_{trough} at the end of 52 weeks for formulation 1 was 57·0 ng/mL (IQR 49·9–72·4) and for formulation 2 was 65·6 ng/mL (41·8–87·1), exceeding the median twice-yearly subcutaneous lenacapavir C_{trough} of 23·4 ng/mL (15·7–34·3) at the end of 26 weeks. Median $AUC_{days\ 1–365}$ for formulation 1 was 1011·1 h*µg/mL (IQR 881·0–1490·2) and for formulation 2 was 1274·0 h*µg/mL (1177·3–1704·8). Adverse events were mostly grade 1 or 2. The most common was injection-site pain (16 [80%] participants given formulation 1, 15 [75%] given formulation 2), which was generally mild, resolved within 1 week, and was substantially reduced by pretreatment with ice.

Interpretation Following administration of once-yearly intramuscular lenacapavir, median plasma concentrations exceeded those associated with efficacy in phase 3 studies of twice-yearly subcutaneous lenacapavir for PrEP for at least 56 weeks. Both formulations were safe and well tolerated. These data show the potential for biomedical HIV prevention with a once-yearly dosing interval.

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Introduction

HIV-1 remains a major public health concern, with 1·3 million new infections globally in 2023.[1] Despite the availability of several HIV pre-exposure prophylaxis (PrEP) options, only 17% (3·5 million) of the 21·2 million people who would benefit from PrEP globally were receiving it in 2023.[2] Key barriers to HIV PrEP uptake and persistence include the requirement for daily adherence, stigma associated with PrEP use, concerns regarding disclosure and discrimination or other potential social harms, challenges with frequent health-care access, and the need for frequent clinic visits beyond the standard of care for PrEP.[3–5] Long-acting options could address these barriers.

Lenacapavir is a novel, first-in-class, long-acting multistage HIV-1 capsid inhibitor currently being

Research in context

Evidence before this study

There were 1·3 million new HIV infections globally in 2023. However, despite the availability of multiple pre-exposure prophylaxis (PrEP) options, only 3·5 million of the 21·2 million people who would benefit from PrEP were receiving it in 2023.

Although daily oral PrEP options are highly effective when used as directed, challenges with adherence and persistence have limited their overall effect. Longer-acting options can overcome some of the key challenges with daily oral PrEP by avoiding the requirement for adherence to daily dosing. In two phase 3 studies, twice-yearly subcutaneous lenacapavir had superior efficacy to oral PrEP at preventing HIV acquisition in gender-diverse populations. An even longer-acting PrEP option could further improve adherence and persistence, especially in settings with poor health-care access. Before the start of this study, we searched PubMed for articles published from database inception to April 10, 2020, with no language restrictions, using the search terms "HIV", "PrEP", "long-acting", AND "yearly". The search confirmed that there were no other studies of yearly administered PrEP options. This study evaluated the pharmacokinetics and safety of two once-yearly intramuscular lenacapavir formulations.

Added value of this study

In this phase 1 study of two intramuscular formulations of lenacapavir, we found pharmacokinetics to be adequate for once-yearly dosing, and intramuscular administration to be safe and well tolerated. Median plasma lenacapavir concentrations after intramuscular administration remained above median twice-yearly subcutaneous lenacapavir concentrations up to 56 weeks, indicating that similarly high efficacy can be expected.

Implications of all the available evidence

By decreasing dosing frequency and providing an additional PrEP option for people who want or need PrEP, yearly dosing of lenacapavir has the potential to further decrease current barriers to PrEP by increasing the uptake of, persistence on, and, therefore, scalability of PrEP.

developed for PrEP. Lenacapavir is characterised by high potency, low metabolic clearance, and low aqueous solubility, which facilitates drug depot-mediated, long-acting pharmacokinetics following an injection.[6,7] In-vitro, non-clinical, and clinical data suggest that upon subcutaneous injection of lenacapavir, the drug solution precipitates to form a depot at the injection site due to the low solubility of lenacapavir. The depot then dissolves over time, resulting in slow drug absorption and allowing an extended dosing interval.[8]

PURPOSE 1 and PURPOSE 2 were two phase 3, multicentre, double-blind, randomised, active-controlled trials in which twice-yearly subcutaneous lenacapavir (927 mg, administered as two 1·5 mL injections of 309 mg/mL, with oral loading doses of 600 mg on days 1 and 2) showed superiority to daily oral PrEP, as well as a background incidence with 100% efficacy in cisgender women and 99·9% efficacy in cisgender men and gender-diverse people.[9,10] In both studies, twice-yearly subcutaneous lenacapavir was well tolerated, with the most common adverse events being injection-site reactions. Additionally, twice-yearly subcutaneous lenacapavir showed better adherence than currently available daily oral PrEP options.

Twice-yearly lenacapavir has the potential to address multiple PrEP barriers because of its long duration of action and route of administration. Once-yearly intramuscular lenacapavir could build on this advantage by further decreasing the dosing frequency and need for clinic visits, reducing the potential for PrEP-related stigma, and avoiding the need for daily oral tablet adherence, thereby increasing the uptake of, persistence on, and, therefore, scalability and public health effect of PrEP in populations who would benefit most.

In this analysis, we assessed the pharmacokinetics and safety of two different once-yearly intramuscular lenacapavir formulations, with the aim of maintaining similar concentrations to twice-yearly subcutaneous lenacapavir.

Methods

Study design and participants

In this multicentre, phase 1, open-label pharmacokinetics and safety study, we assessed two lenacapavir formulations with once-yearly dosing potential in healthy participants. The study took place at two clinical research centres in the USA.

Participants were enrolled between March 9 and Sept 7, 2023. Eligible participants were individuals without HIV, without significant medical comorbidities, assigned either male or female at birth, not pregnant or lactating, and aged 18–55 years, and who had body-mass index 35·0 kg/m² or less, normal renal function (estimated creatinine clearance ≥90 mL/min by Cockcroft-Gault method), and no significant medical history. Participants had a low likelihood of HIV acquisition, as determined by the investigator at the screening evaluation. Participants tested negative for HIV with a laboratory instrumented fourth-generation HIV-1 and HIV-2 antibody and antigen test at screening, and with a point-of-care fourth-generation HIV-1 and HIV-2 antibody and antigen test at day –1. Full inclusion and exclusion criteria are listed in the appendix (pp 2–3). Data on race and ethnicity were collected by participant self-report.

See Online for appendix

This study was approved by the institutional review board at each site (Quotient Sciences [Miami, FL, USA] Pro00044040; and Pharmaron [Baltimore, MD, USA] Pro00058088) and was conducted in accordance with the guidelines of Good Clinical Practices. All participants provided written informed consent.

Procedures

Participants meeting the eligibility criteria were enrolled and received a single dose of 5000 mg lenacapavir, administered as two 5 mL intramuscular injections of either formulation 1 or formulation 2. Each formulation contained 500 mg/mL lenacapavir free acid, formulated with 5% w/w ethanol (formulation 1) or 10% w/w ethanol (formulation 2), included to reduce viscosity. Intramuscular doses were injected into the ventrogluteal site on day 1. Half of the participants who received formulation 2 were pretreated for approximately 10 min with an ice pack at the sites of injection.

Participants remained at the study centre for observation and assessment from day –1 to day 15. Intensive plasma pharmacokinetic sampling occurred relative to the morning dose of lenacapavir at the following timepoints for each cohort: day 1 at 0 (≤5 min before dose), 2, 4, 8, and 12 h after the dose; and day 2 at 24 h and 36 h after the dose. Following this period, pharmacokinetic samples were collected at prespecified visits irrespective of time (as outlined in the appendix p 4) up to day 393 (56 weeks) of follow-up.

Safety assessments included a complete physical examination at screening and before discharge, and a symptom-driven physical examination at each visit based on reported signs and symptoms. Vital signs and laboratory assessments, including HIV-1 and HIV-2 antibody and antigen testing, occurred at screening and at prespecified timepoints throughout the study. Injection sites were examined on day 1 (3 h after study drug injection), daily on day 2 up to day 15 (before discharge), and at each outpatient visit based on reported signs and symptoms. Participants completed a pain questionnaire on day 1 (following injection), day 2 (24 h after study drug injection), day 7, and day 15 (before discharge). Assessment of adverse events and concomitant medications was performed throughout the study. All adverse events and clinically significant laboratory abnormalities were graded according to the Division of AIDS (DAIDS) table for grading the severity of adult and paediatric adverse events (version 2.1; July, 2017).[11]

Outcomes

Pharmacokinetic parameters evaluated included the area under the concentration–time curve for the once-yearly dosing interval calculated from days 1 to 365 ($AUC_{days\ 1–365}$), peak plasma concentration (C_{max}), time to reach peak plasma concentration (T_{max}), and trough concentration (C_{trough}) at the end of 52 weeks (day 365). Safety outcomes included the results of the safety assessments outlined above.

Median lenacapavir concentrations of once-yearly intramuscular formulations up to 56 weeks were compared with those observed in phase 3 studies of twice-yearly subcutaneous lenacapavir for PrEP, which were established by pooling the observed concentrations from PURPOSE 1 and 2.[9,10] To ensure that trough concentrations remained similar to those observed in PURPOSE 1 and 2, the median C_{trough} at the end of 52 weeks following once-yearly intramuscular lenacapavir administration was compared with the median twice-yearly subcutaneous lenacapavir C_{trough} at the end of 26 weeks.

Bioanalysis of plasma lenacapavir concentrations

Plasma concentrations of lenacapavir were measured with a validated liquid chromatography–tandem mass spectroscopy bioanalytical method with multiple reaction monitoring and electrospray ionisation in the positive mode (Labcorp, Madison, WI, USA). Quantification was done with multiple reaction monitoring of the transitions m/z 968·4→869·3 and m/z 974·4→875·3 for lenacapavir and an isotopically labelled internal standard (lenacapavir-d6), respectively. The bioanalytical method was validated over a calibrated range of 0·5–500 ng/mL. Interassay precision, based on coefficient of variation (%CV), ranged from 2·8 to 8·5, and accuracy (% relative error) ranged from –6·5 to –4·6. All samples were analysed in the timeframe supported by frozen stability storage data.

Statistical analysis

No formal sample size calculation was performed for this study. However, a sample size of 20 participants per cohort was considered reasonable to provide a suitable assessment of the descriptive pharmacokinetics and safety. Non-compartmental analyses with Phoenix WinNonlin Professional software (version 8.2) were done

	Lenacapavir formulation 1 (N=20)	Lenacapavir formulation 2 (N=20)
Age, years	37 (29–50)	33 (29–45)
Assigned male sex at birth	13 (65%)	13 (65%)
Assigned female sex at birth	7 (35%)	7 (35%)
Race (self-reported)		
Black or African American	3 (15%)	5 (25%)
White	17 (85%)	15 (75%)
Ethnicity (self-reported)		
Hispanic or Latine	20 (100%)	16 (80%)
Not Hispanic or Latine	0	4 (20%)
Weight, kg	73·6 (68·6–86·8)	77·1 (72·5–85·6)
Body-mass index, kg/m^2	26·5 (24·1–29·4)	28·0 (24·9–30·0)

Data are n (%) or median (IQR).

Table 1: **Demographics and baseline characteristics**

	Lenacapavir formulation 1 (N=20)	Lenacapavir formulation 2 (N=20)
C_{max}, ng/mL	247·0 (184·0–346·0)	336·0 (233·5–474·3)
T_{max}, days	84·1 (56·1–112·0)	69·9 (55·3–105·5)
$AUC_{days\ 1–365}$, h*µg/mL	1011·1 (881·0–1490·2)	1274·0 (1177·3–1704·8)
$C_{trough\ (day\ 365)}$, ng/mL	57·0 (49·9–72·4)	65·6 (41·8–87·1)

Data are median (IQR). For formulation 1, n=15 (C_{max} and T_{max}) and n=13 ($AUC_{days\ 1–365}$ and C_{trough}); for formulation 2, n=19 ($AUC_{days\ 1–365}$ and C_{trough}). Relevant pharmacokinetic parameters were not estimated for participants who discontinued early (for reasons unrelated to the study drug). For formulation 1, two participants who discontinued at days 197 and 225 were included for estimation of C_{max} and T_{max} but excluded for $AUC_{days\ 1–365}$ and $C_{trough\ (day\ 365)}$ calculations. $AUC_{days\ 1–365}$=area under the concentration–time curve for the once-yearly dosing interval calculated from days 1 to 365. C_{max}=peak plasma concentration. $C_{trough\ (day\ 365)}$=trough concentration at day 365. T_{max}=time to reach peak plasma concentration.

Table 2: **Plasma pharmacokinetic parameters following once-yearly intramuscular administration of 5000 mg lenacapavir**

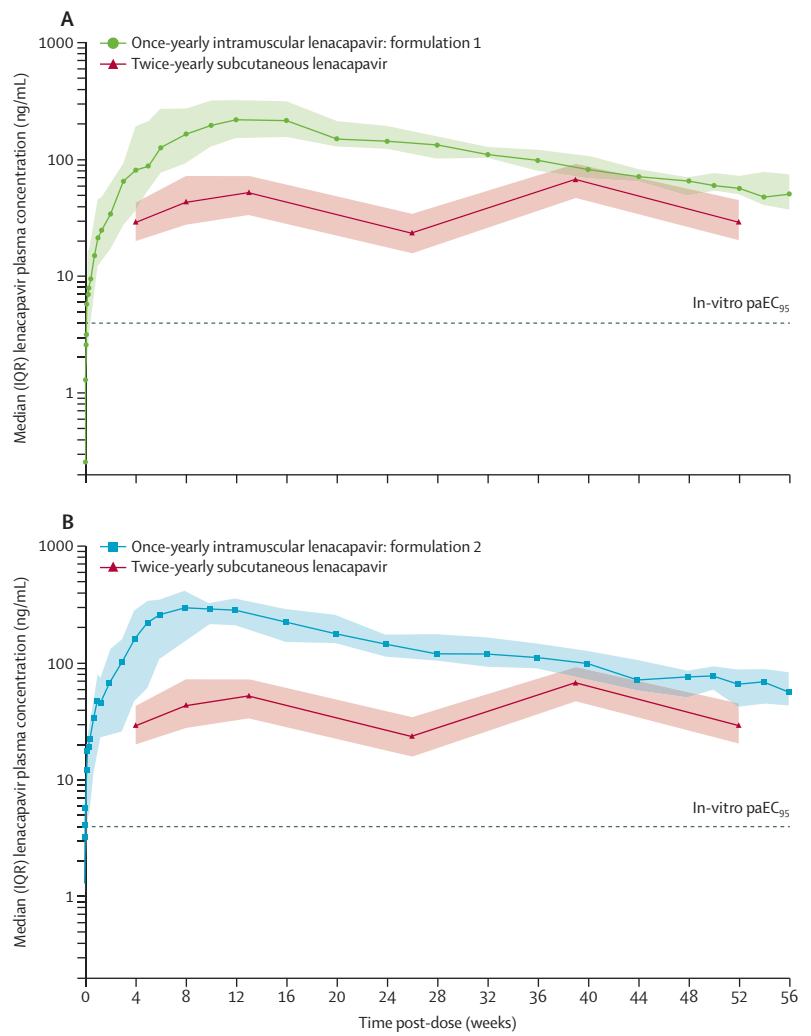

Figure 1: **Median (IQR) plasma concentration–time profiles of once-yearly intramuscular lenacapavir versus twice-yearly subcutaneous lenacapavir for formulation 1 (A) and formulation 2 (B)**
Each formulation contained 500 mg/mL lenacapavir free acid, formulated with 5% w/w ethanol (formulation 1) or 10% w/w ethanol (formulation 2). Horizontal dashed lines at 3·87 ng/mL represent in-vitro $paEC_{95}$. Red shaded region indicates observed median (IQR) plasma concentration–time profile following administration of subcutaneous lenacapavir 927 mg on day 1 and at the end of 26 weeks, with oral lenacapavir 600 mg on days 1 and 2, in PURPOSE 1 and PURPOSE 2 studies. $paEC_{95}$=protein binding-adjusted 95% effective concentration.

to estimate the pharmacokinetic parameters of lenacapavir. Lenacapavir pharmacokinetic parameters were summarised using descriptive statistics. Treatment-emergent adverse events, including injection-site reactions and laboratory abnormalities, were descriptively summarised. The safety analyses were done with SAS (version 9.4).

Role of the funding source

The funder was involved in the study design, data collection, data analysis, data interpretation, and writing of the report.

Results

20 participants received lenacapavir formulation 1 (lenacapavir 500 mg/mL with 5% w/w ethanol) and 20 participants received lenacapavir formulation 2 (lenacapavir 500 mg/mL with 10% w/w ethanol) as a single 5000 mg dose administered by intramuscular injection. Participant demographics and baseline characteristics are shown in table 1. The median age of participants was 37 years (IQR 29–50) in the formulation 1 cohort and 33 years (29–45) in the formulation 2 cohort; 13 (65%) participants in each cohort were assigned male at birth. Of those who received formulation 1, 17 (85%) participants were White and all 20 (100%) were of Hispanic or Latine ethnicity. Of those who received formulation 2, 15 (75%) were White and 16 (80%) were of Hispanic or Latine ethnicity. The median bodyweight for participants who received formulation 1 was 73·6 kg (IQR 68·6–86·8) and for those who received formulation 2 was 77·1 kg (72·5–85·6). For estimation of pharmacokinetic parameters, sample size varied over time with at least 13 participants (formulation 1) and at least 19 participants (formulation 2) due to early discontinuations for reasons unrelated to the study drug (table 2).

Table 2 shows pharmacokinetic parameters of lenacapavir following administration of both formulations. Following intramuscular administration of formulation 1 and formulation 2, plasma concentrations increased rapidly, with median T_{max} occurring approximately 12 weeks post-dose for formulation 1 and approximately 10 weeks post-dose for formulation 2 (table 2). Median lenacapavir C_{max} was 247·0 ng/mL (IQR 184·0–346·0) with formulation 1 and 336·0 ng/mL (233·5–474·3) with formulation 2 (table 2).

When evaluating the similarity of once-yearly intramuscular formulations to the twice-yearly subcutaneous formulation, median lenacapavir concentrations with once-yearly intramuscular lenacapavir remained higher than the median concentrations with twice-yearly subcutaneous lenacapavir observed in PURPOSE 1 and 2 up to at least 56 weeks (figure 1A and 1B).

The observed median lenacapavir C_{trough} for participants who received formulation 1 (n=13) was 57·0 ng/mL (IQR 49·9–72·4) at the end of 52 weeks and 50·7 ng/mL (36·6–73·7) at the end of 56 weeks, and

for those who received formulation 2 (n=19) was 65·6 ng/mL (41·8–87·1) and 55·9 ng/mL (43·2–83·3), respectively, in comparison with the median observed C_{trough} of 23·4 ng/mL (15·7–34·3) in PURPOSE 1 and 2 at week 26 (figure 2). The lenacapavir C_{trough} at the end of 52 weeks for all participants following formulation 1 and formulation 2 was similar to or higher than the lenacapavir C_{trough} for twice-yearly subcutaneous lenacapavir at the end of 26 weeks.

Table 3 shows treatment-emergent adverse events and grade 3 or higher laboratory abnormalities. On the basis of the available data, these grade 3 laboratory abnormalities are unlikely to be related to study drug (appendix p 9). The most common grade 3 laboratory abnormality observed was increased LDL (three participants received formulation 1 and one received formulation 2); all four participants had elevated LDL at baseline (grade 1 or 2). Additionally, grade 3 LDL elevations did not occur around the time of C_{max} in any of the four participants (three occurred at >31 weeks and one at approximately 2 weeks after the dose), and all returned to grade 1 or 2 by the next visit, despite continued lenacapavir exposure and without intervention. Most treatment-emergent adverse events were mild or moderate. There were no grade 4 treatment-emergent adverse events, laboratory abnormalities, or deaths. Among participants who received formulation 2, four of 20 (20%) had an adverse event of gait disturbance, which was defined as difficulty walking due to pain at the injection site, and this did not appear to interfere with daily activities per the investigator's report. None of these four participants received pretreatment with ice.

Most injection-site reactions experienced by participants were grade 1 or 2. Only one participant had a grade 3 injection-site reaction (pain; formulation 2 without ice pretreatment). Overall, injection-site pain was reported by 16 of 20 (80%) participants who received formulation 1 and 15 of 20 (75%) who received formulation 2. Injection-site bruising occurred in two (10%) participants receiving formulation 1 and one (5%) receiving formulation 2. Injection-site swelling occurred in four (20%) participants receiving formulation 1, but in none receiving formulation 2. Longer-lasting injection-site reactions, such as nodules, were not observed with either formulation. The median duration of any lenacapavir-related injection-site reaction was 4 days (IQR 2–5) following formulation 1 and 3 days (3–4) following formulation 2.

Figure 3 shows participant-reported outcomes that were collected by participant questionnaire. Most participants reported minor pain on days 1 and 2 only and none chose the options "Hurts whole lot" or "Hurts worst". Ice pretreatment (n=10) resulted in numerically lower pain ratings on days 1 and 2 for formulation 2, with the majority resolved by day 7. Additional questions were

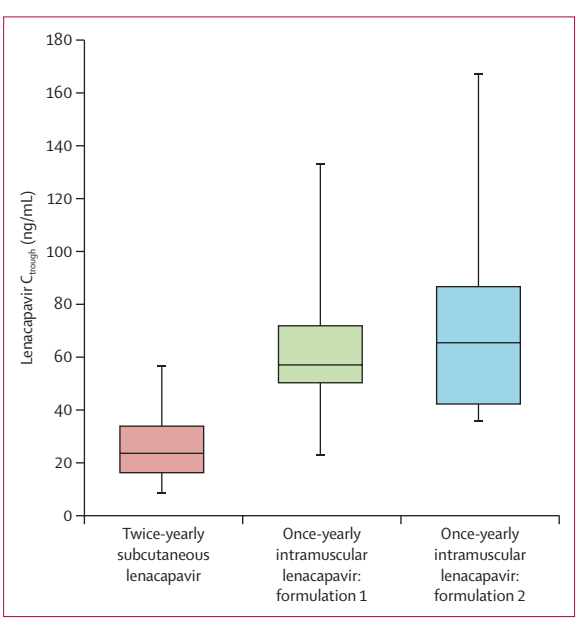

Figure 2: **Comparison of C_{trough} following once-yearly intramuscular lenacapavir 5000 mg (formulations 1 and 2) and twice-yearly subcutaneous lenacapavir from the PURPOSE 1 and PURPOSE 2 studies[9,10]**
Boxes represent the IQR, with horizontal solid lines in the middle representing the median and whiskers representing the 5th and 95th percentiles. Twice-yearly subcutaneous lenacapavir trough concentrations at the end of 26 weeks (n=423), and once-yearly intramuscular lenacapavir trough concentrations at end of 52 weeks (n=13 for formulation 1; n=19 for formulation 2). C_{trough}=trough concentration.

	Lenacapavir formulation 1 (N=20)	Lenacapavir formulation 2 (N=20)
Any TEAE	18 (90%)	16 (80%)
Adverse events occurring in ≥10% of participants in a cohort		
Diarrhoea	2 (10%)	0
Injection-site pain	16 (80%)	15 (75%)
Injection-site bruising	2 (10%)	1 (5%)
Injection-site swelling	4 (20%)	0
Gait disturbance	0	4 (20%)*
Feeling hot	0	2 (10%)
Headache	0	5 (25%)
Dizziness	0	2 (10%)
Study drug-related TEAEs	17 (85%)	16 (80%)
Any grade ≥3 TEAEs	0	2 (10%)
Study drug-related grade ≥3 TEAEs	0	1 (5%)†
Any serious TEAEs	0	1 (5%)
Study drug-related serious TEAEs	0	0
Death	0	0
Grade ≥3 laboratory abnormalities	6 (30%)‡	3 (15%)§

Data are n (%). Whether or not TEAEs were deemed related to study drug was determined by the study investigator. TEAE=treatment-emergent adverse event. *Gait disturbance defined as difficulty walking due to pain at the injection site but did not appear to limit daily activities. †One participant with lenacapavir-related grade 3 injection-site pain and syncope received formulation 2. ‡n=3 increased LDL; n=1 each of increased creatinine kinase, increased lipase, hyperkalaemia, increased triglycerides, and glycosuria. §n=2 decreased creatinine clearance; n=1 hypercholesterolaemia; n=1 increased LDL.

Table 3: **Treatment-emergent adverse events**

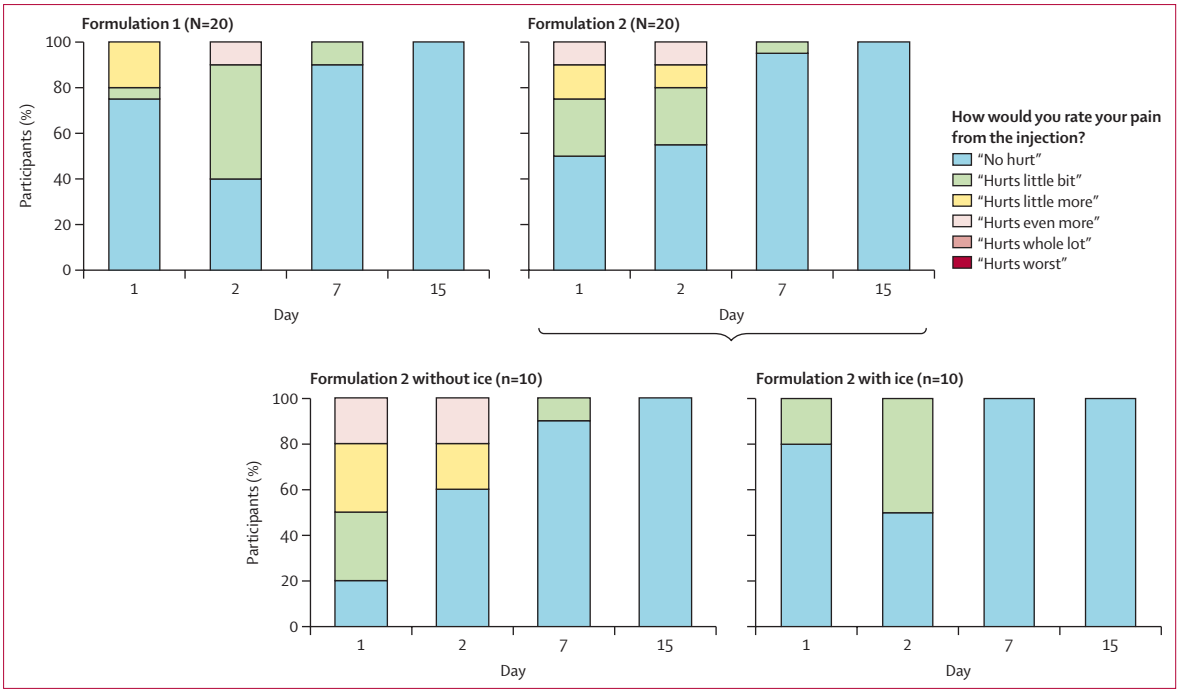

Figure 3: **Injection-site pain**

asked regarding the effect of injection-site pain on sleep. Responses to these additional questions were similar to responses about overall pain from the injection (appendix p 7).

Discussion

In this study of two lenacapavir formulations administered intramuscularly, plasma lenacapavir concentrations remained above those associated with twice-yearly subcutaneous lenacapavir efficacy for more than 1 year after administration. Injections were generally well tolerated, with injection-site pain being the most common adverse event. No clinically significant safety concerns were identified.

There is increasing recognition of the important role of longer-acting antiretrovirals for HIV prevention. Although daily oral PrEP options such as emtricitabine plus tenofovir disoproxil fumarate and emtricitabine plus tenofovir alafenamide are highly effective when used as directed, challenges with adherence and persistence have greatly reduced their overall effect. PrEP options with longer dosing intervals can overcome some of the key challenges with daily oral PrEP by removing the requirement for adherence to daily dosing. This potential was recently shown in the phase 3 studies of twice-yearly subcutaneous lenacapavir for PrEP—PURPOSE 1 and PURPOSE 2—in which lenacapavir demonstrated superior efficacy to daily oral emtricitabine plus tenofovir disoproxil fumarate in a highly diverse participant population.[9,10] Similarly, cabotegravir administered intramuscularly every 2 months was shown to be superior to daily oral emtricitabine plus tenofovir disoproxil fumarate in two phase 3 studies.[12,13] A once-yearly administered lenacapavir formulation could have substantial additional benefits by further improving adherence and persistence, thereby reducing potential periods of non-protection. Furthermore, annual administration could improve PrEP access in regions with poor PrEP services and reduce the burden on care systems that can occur with regimens that require more frequent injection administration or medication dispensation.

The median lenacapavir concentrations observed with once-yearly intramuscular lenacapavir formulations exceeded those associated with high efficacy in PURPOSE 1 and 2.[9,10] For both formulations, median C_{trough} values at the end of 52 weeks and 56 weeks after administration were higher than the median C_{trough} at the end of 26 weeks observed in PURPOSE 1 and 2. The optimal dose for once-yearly intramuscular lenacapavir to achieve similar pharmacokinetics to twice-yearly subcutaneous lenacapavir will be determined with population pharmacokinetic modelling and simulation. Considering that 5000 mg once-yearly intramuscular lenacapavir achieves a higher C_{trough} than twice-yearly subcutaneous lenacapavir, the optimal dose for future development of the once-yearly intramuscular lenacapavir is likely to be less than 5000 mg. These findings suggest that once-yearly intramuscular lenacapavir should confer similar HIV prevention efficacy as twice-yearly subcutaneous lenacapavir, thereby creating the potential to expedite the development of once-yearly lenacapavir by allowing for

the extrapolation of efficacy from twice-yearly subcutaneous lenacapavir to once-yearly intramuscular lenacapavir. Model-informed drug development approaches such as this have previously been used to extrapolate efficacy between drug formulations or routes of administration, including for antipsychotics, cancer therapeutics, and autoimmune treatments.[14–21] For example, with the monoclonal antibody ravulizumab, clinical pharmacokinetic data showing comparability to the intravenous dosing regimen with previously established efficacy and safety were used to inform the approval of the subcutaneous route of administration.[21]

We note that the highest observed median concentrations with the once-yearly formulations (247·0 ng/mL for formulation 1, 336·0 ng/mL for formulation 2) exceeded the highest observed median concentration with twice-yearly subcutaneous lenacapavir (67·3 ng/mL).[22] This observation is attributable to the higher total dose needed to achieve once-yearly pharmacokinetics and the more rapid drug absorption observed with intramuscular administration. However, systemic lenacapavir exposures up to 3·1-fold higher than those achieved with these intramuscular lenacapavir formulations have been observed and were well tolerated with no safety concerns (appendix p 6).[23,24] These data indicate that the therapeutic window of lenacapavir is wide and support further evaluation of once-yearly intramuscular lenacapavir for PrEP.

Injection tolerability is a key consideration in the development of long-acting injectables. Twice-yearly subcutaneous lenacapavir was well tolerated in phase 3 studies; palpable nodules occurring due to the subcutaneous lenacapavir drug depot were observed in some participants.[25,26] Despite the high volume of injection, intramuscular lenacapavir was well tolerated in this study. Injection-related pain was commonly reported but was of mild to moderate severity in most participants. Furthermore, pretreatment of the injection site with an ice pack seemed to substantially reduce injection pain. Superficial injection-site reactions were uncommon, with only isolated reports of bruising or swelling. Given that the optimal clinical dose for the future development of the once-yearly intramuscular formulation is likely to be lower than 5000 mg, it may be better tolerated than the doses evaluated in this phase 1 study. These findings suggest that once-yearly intramuscular lenacapavir could be a well tolerated PrEP option, and the availability of an intramuscular route of administration for lenacapavir in addition to a twice-yearly subcutaneous formulation could provide another choice for people taking PrEP and allow greater individualisation of care.

It is notable that oral lenacapavir loading doses were not given with intramuscular lenacapavir in this study, by contrast with twice-yearly subcutaneous lenacapavir, which requires oral lenacapavir to be administered on days 1 and 2 at the time of the first injection administration because of the slow initial release of lenacapavir from the subcutaneous drug depot. We observed a faster increase in initial lenacapavir plasma concentration with the once-yearly intramuscular formulations than with the twice-yearly subcutaneous lenacapavir. However, the intramuscular formulations still took a few days to reach concentrations similar to those in the PURPOSE 1 and 2 studies, and therefore oral loading may be needed.[22] The oral loading regimen for a once-yearly intramuscular lenacapavir to achieve similar pharmacokinetics to twice-yearly subcutaneous lenacapavir will be established with population pharmacokinetic modelling and simulation. Selection of the final formulation for future development and the dosing window for delayed administration of the intramuscular injection would also be informed by these population pharmacokinetic simulations.

The main limitation of this study is the small sample size, which limits the ability to detect less common adverse events and to make broadly generalisable conclusions about pharmacokinetics. Therefore, additional data from a larger number of participants and in a more diverse participant population are needed to evaluate the safety of once-yearly lenacapavir for PrEP and to adequately characterise its pharmacokinetics. Additionally, this small study did not have the necessary demographic diversity to fully evaluate the potential of once-yearly lenacapavir for PrEP. The ongoing evaluation of once-yearly lenacapavir for PrEP must be representative of groups most in need of HIV prevention, showing diversity in sex assigned at birth, gender, race, ethnicity, and body habitus. Further evaluation of long-acting lenacapavir is also necessary to understand the potential for HIV acquisition during the pharmacokinetic tail period (when drug concentrations fall below the protective threshold) and the potential clinical implications thereof. A larger study including a diverse participant population with an indication for PrEP is planned, and the population pharmacokinetic modelling is ongoing in preparation of this study.

Contributors

VJ, PP, JY, AC, and RS were involved in the study design. VJ and JL were involved in data collection. VJ, JY, JL, GS, EH, RP, CC, and RS were involved in data analysis or interpretation. All authors reviewed and critically revised the manuscript, approved the final draft, and agreed to be accountable for the manuscript's accuracy and integrity. All authors participated in the study, contributed to manuscript preparation, and provided critical comments on the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

All authors are employees and shareholders of Gilead Sciences.

Data sharing

Gilead Sciences shares anonymised individual participant data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

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