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Plain Language Summary

- This study looked at ultra-long-acting cabotegravir (CAB ULA), a new formulation of long-acting cabotegravir (CAB LA), as a potential HIV prevention option that could reduce injections from 6 per year to 3 per year
- Results from this study suggest that CAB ULA given every 4 months could provide drug levels effective for HIV prevention with a safety profile similar to CAB LA

Introduction

- Long-acting cabotegravir (CAB LA) 200 mg/mL dosed intramuscularly every 2 months (Q2M) is the first LA injectable approved for HIV-1 PrEP and is highly effective at preventing HIV-1 and generally well tolerated in clinical trials^{1,2} and real-world settings^{3,4}
- Every-4-month (Q4M) dosing represents an evolution of the current CAB LA Q2M dosing frequency that combines the convenience of fewer clinic visits with the benefits of maintaining regular sexual health screenings and ongoing care
- Assessment of pharmacokinetic (PK) data with a new ultra-long-acting (ULA) formulation of CAB, CAB ULA Q4M, and incorporation into a CAB ULA population pharmacokinetics (PopPK) model, combined with a safety profile comparable to CAB LA, supported the selection of a 1600 mg dose for registrational CAB ULA PrEP studies⁵

Methods

Phase 1 Study

- Adults aged 18-55 years without HIV-1 received a single^a intramuscular CAB ULA dose ranging from 800 to 3200 mg in this ongoing phase 1 study (NCT05418868)
- CAB PK and safety were assessed over 52 weeks
- CAB PK profiles were simulated following virtual dosing of CAB ULA (various scenarios) and were compared with profiles following CAB LA dosing every 2 months

^aDoses of 2400 mg and 3200 mg were administered as split injections.

Results

Participant Demographics

- Median participant age was 41 years; 56% were assigned male sex at birth (Table 1)

Table 1. Participant Demographics

	CAB ULA 800 mg (n=8)	CAB ULA 1200 mg (n=8)	CAB ULA 1600 mg (n=16)	CAB ULA 2400 mg (n=9)	CAB ULA 3200 mg (n=7)	Total (N=48)
Sex at birth, n (%)						
Male	6 (75)	4 (50)	7 (44)	6 (67)	4 (57)	27 (56)
Female	2 (25)	4 (50)	9 (56)	3 (33)	3 (43)	21 (44)
Age, median (IQR), years	38.0 (37.0-44.0)	43.5 (36.5-51.5)	45.0 (39.0-51.5)	35.0 (28.0-43.0)	30.0 (20.0-45.0)	40.5 (32.5-46.5)
Age group, n (%)						
18-64 years	8 (100)	8 (100)	16 (100)	9 (100)	7 (100)	48 (100)
Race, n (%)						
Black or African American	5 (63)	2 (25)	6 (38)	4 (44)	2 (29)	19 (40)
White	3 (38)	3 (38)	8 (50)	4 (44)	5 (71)	23 (46)
Asian	0	2 (25)	2 (13)	0	0	4 (8)
Other ^a	0	1 (13)	0	1 (11)	0	2 (4)
Weight, median (IQR), kg	92 (76.5-93.3)	75.5 (63.3-82.5)	77.1 (67.8-84.9)	73.1 (71.2-83.1)	64.1 (61.9-80.6)	75.7 (65.6-85.4)
BMI, median (IQR), kg/m ²	28.5 (27.3-29.8)	25.8 (23.9-28.2)	26.9 (24.2-29.7)	27.1 (25.7-28.5)	24.9 (22.8-26.4)	26.7 (24.2-29.1)

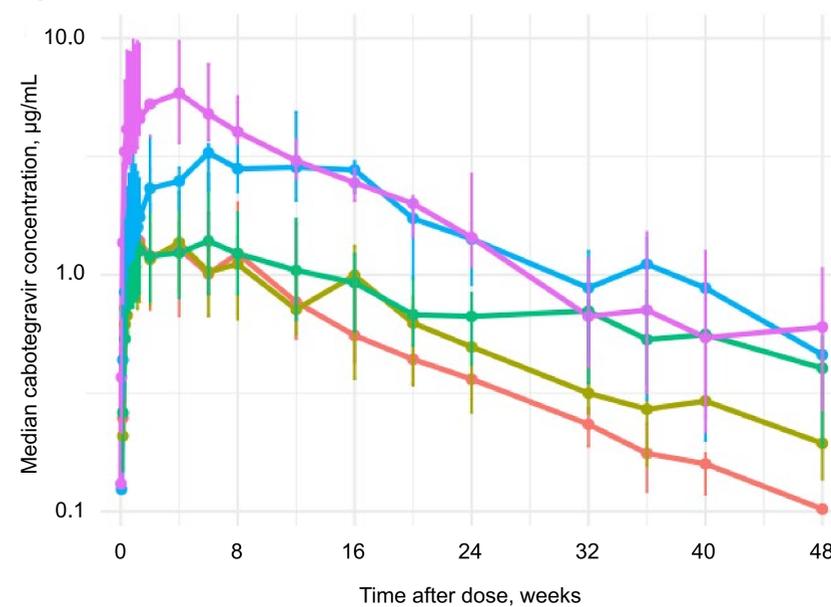
BMI, body mass index; CAB, cabotegravir; IQR, interquartile range; ULA, ultra-long-acting. ^aMixed race (n=1, 1200 mg cohort) and American Indian or Alaska Native (n=1, 2400 mg cohort).

Pharmacokinetic and modeling data, along with a safety profile consistent with CAB LA, support the continued investigation of CAB ULA 1600 mg every 4 months for HIV-1 prevention.

CAB Concentrations Over Time

- Participants (N=48) received a single injection of CAB ULA 800 mg (n=8), 1200 mg (n=8), 1600 mg (n=16), or split injections of 2400 mg (n=9) or 3200 mg (n=7; Figure 1)
- Maximum plasma concentration was typically reached within 4 weeks
- CAB ULA apparent terminal phase half-life is greater than 25 weeks
- CAB ULA is characterized by a rapid rise to concentrations associated with clinical efficacy, and an elimination consistent with the ability to achieve a longer dosing interval (Q4M)

Figure 1. Median CAB ULA Plasma Concentration Over Time



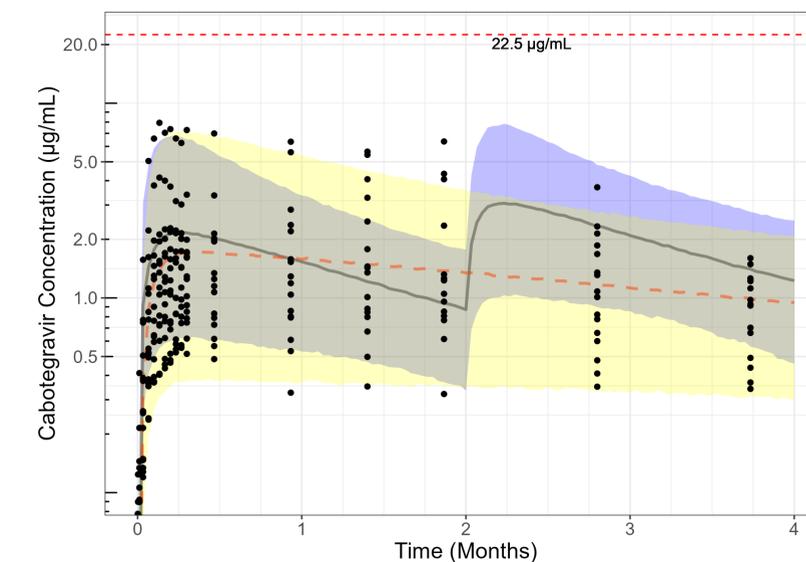
CAB ULA Dose

- 800 mg IM (1 x 2 mL)
- 1200 mg IM (1 x 3 mL)
- 1600 mg IM (1 x 3 mL)
- 2400 mg IM (1 x 2.2 mL; 1 x 2.3 mL)
- 3200 mg IM (2 x 3 mL)

PopPK Modeling of CAB ULA Doses

- The CAB ULA PopPK model was used to simulate a range of doses and ultimately support 1600 mg Q4M as a posology likely to maintain efficacious concentrations of CAB ULA for the prevention of HIV-1
- An overlay of concentration over time data from 16 participants who received CAB ULA 1600 mg in the phase 1 trial with (1) a simulated CAB ULA 1600 mg dose and (2) two doses of CAB LA 600 mg was performed (Figure 2)
- Concentrations arising from a single dose of CAB ULA 1600 mg were consistent with those predicted by the CAB ULA PopPK model

Figure 2. Observed Phase 1 Data Overlaid on Predicted Exposures After a Simulated Dose of CAB ULA 1600 mg or 2 Simulated Doses of CAB LA 600 mg



PI, prediction interval. The red dashed line indicates the CAB safety threshold of 22.5 µg/mL. The orange dashed line and yellow shading indicate the simulated median and 90% PI of CAB ULA 1600 mg. The gray line and blue shading indicate the median and 90% PI of 2 doses of CAB LA 600 mg administered 2 months apart. Black circles represent the observed concentration of CAB ULA 1600 mg from the phase 1 study.

Safety

- Overall, 85% and 81% of participants had an adverse event (AE) and drug-related AEs, respectively (Table 2)
- Injection site reactions (ISRs) were reported in 77% (37/48) of participants (Table 3)
 - Injection site pain was the most common ISR (67%, 32/48)
 - Among participants with ISRs, 86% (32/37) had ISRs of maximum grade 1 severity
 - No grade 4 ISRs were reported; 1 grade 3 ISR occurred in the 2400 mg group (injection site erythema)
- Non-ISR AEs were infrequent

Table 2. Summary of AEs

Characteristic, n (% of participants)	CAB ULA 800 mg (n=8)	CAB ULA 1200 mg (n=8)	CAB ULA 1600 mg (n=16)	CAB ULA 2400 mg (n=9)	CAB ULA 3200 mg (n=7)
Any AE	5 (63)	8 (100)	12 (75)	9 (100)	7 (100)
Maximum grade 1	3 (38)	7 (88)	10 (63)	8 (89)	5 (71)
Maximum grade 2	2 (25)	0	2 (13)	0	2 (29)
Maximum grade 3	0	1 (13)	0	1 (11)	0
Any drug-related AE	4 (50)	8 (100)	12 (75)	8 (89)	7 (100)
Maximum grade 1	3 (38)	7 (88)	11 (69)	7 (78)	5 (71)
Maximum grade 2	1 (13)	0	1 (6)	0	2 (29)
Maximum grade 3	0	1 (13)	0	1 (11)	0

AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; ULA, ultra-long-acting.

Table 3. Summary of ISRs

	CAB ULA 800 mg (n=8)	CAB ULA 1200 mg (n=8)	CAB ULA 1600 mg (n=16)	CAB ULA 2400 mg (n=9)	CAB ULA 3200 mg (n=7)
Any ISR, n (% of participants)	3 (38)	8 (100)	11 (69)	8 (89)	7 (100)
Maximum grade 1	2 (25)	8 (100)	10 (63)	7 (78)	5 (71)
Maximum grade 2	1 (13)	0	1 (6)	0	2 (29)
Maximum grade ≥3	0	0	0	1 (11)	0
Duration, median (IQR), days ^a	6.5 (5.0-8.0)	4.5 (3.5-6.5)	6.5 (4.5-31.0)	10.0 (5.0-55.0)	5.0 (4.0-8.0)

IQR, interquartile range. ^aDuration endpoints are only calculated for events with non-missing end date.

Conclusions

- Phase 1 data and PopPK modeling support a 1600 mg dose of CAB ULA Q4M as part of a viable dosing strategy for HIV-1 prevention
- CAB ULA demonstrated a safety and tolerability profile consistent with CAB LA
- This Q4M dosing strategy would decrease the number of maintenance injections from 6 per year with CAB LA to 3 per year with CAB ULA
- 2 ongoing clinical trials (NCT06741397 and NCT06786520) are evaluating this dosing strategy to support marketing authorization of CAB ULA for HIV-1 prevention

Acknowledgments: The authors would like to thank the study participants, the investigators and site staff who participated in the study, and the ViiV Healthcare, GSK, and Trialmed study team members. This study was funded by ViiV Healthcare. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by Fingerpaint Medical and funded by ViiV Healthcare.

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