Phase 1 Study of Cabotegravir Long-Acting Injectable Formulations Supports ≥4-Monthly Dose Interval

Kelong Han,[1] Ronald D'Amico,[2] Jörg Sievers,[3] Darin Brimhall,[4] Brian Spears,[5] Dale Taylor,[6] David Dorey,[7] Paul Benn,[3] Lisa Morgan,[1] Randa Hareedy,[8] Gilda Bontempo,[9] Max Lataillade,[9] William Spreen[2]

[1]GSK, Collegeville, PA, USA; [2]ViiV Healthcare, Durham, NC, USA; [3]ViiV Healthcare, Brentford, UK; [4]PPD-Thermo Fisher Scientific, Las Vegas, NV, USA; [5]PPD-Thermo Fisher Scientific, Austin, TX, USA; [6]PPD-Thermo Fisher Scientific, Orlando, FL, USA; [7]GSK, Mississauga, ON, Canada; [8]GSK, Brentford, UK; [9]ViiV Healthcare, Branford, CT, USA

KH is an employee of and holds stock in GSK.

Conference on Retroviruses and Opportunistic Infections; March 3-6, 2024; Denver, CO

Introduction

- Cabotegravir (CAB) dosed IM every 2 months is the first long-acting injectable approved for both HIV-1 prevention[1] and as a complete HIV-1 treatment regimen when dosed IM with rilpivirine monthly or every 2 months[2]
- Less frequent dosing could be of value for individuals affected by HIV-1, such as those struggling with adherence to daily oral PrEP or ART medications and those looking for additional PrEP/ART options requiring fewer clinic visits[3]
- Strategies to achieve less frequent dosing include
  - Increasing the dose by increasing the volume of the injection and/or the concentration of the formulation administered
  - Developing an ultra-long-acting formulation with a longer terminal half-life (ie, slower absorption)
- To support less frequent dosing, we evaluated the pharmacokinetics and safety of
  - The approved CAB 200 mg/mL (CAB200) formulation administered SC with recombinant human hyaluronidase PH20 (rHuPH20)
    - rHuPH20 allows for a larger SC injection volume[4,5]
  - A new ultra-long-acting CAB formulation (CAB-ULA) administered SC or IM without rHuPH20

ART, antiretroviral therapy; IM, intramuscular; PrEP, pre-exposure prophylaxis; SC, subcutaneous; ULA, ultra-long-acting.

1. Apretude [prescribing information]. ViiV Healthcare; 2023. **2.** Cabenuva [prescribing information]. ViiV Healthcare; 2023. **3.** Thoueille et al. *J Antimicrob Chemother*. 2022;77:290-302. **4.** Locke et al. *Drug Deliv*. 2019;26:98-106. **5.** Hylenex [prescribing information]. Halozyme Therapeutics Inc; 2016.

Study Design

Ongoing, open-label, single-dose, dose-escalation, phase 1 study (NCT05418868) evaluating CAB200 SC + rHuPH20 and CAB-ULA[a] SC or IM without rHuPH20

Inclusion criteria

- Aged 18-55 years
- HIV-negative
- Body weight ≥40 kg
- BMI 18-32 kg/m^2

Part A	CAB200 dose (+ rHuPH20 10,000 IU)	Route	N
A1	800 mg (4 mL)	SC[b]	10
A2	1600 mg (8 mL)	SC[b]	10
A3	3200 mg (16 mL)	SC[b]	2
Part B	Not conducted – candidate formulation not progressed		
Part C	**CAB-ULA dose**	**Route**	**N**
C1	800 mg (2 mL)	SC[b]	8
C2	800 mg (2 mL)	IM[c]	8
C3	1200 mg (3 mL)	SC[b]	8
C4	1200 mg (3 mL)	IM[c]	8
C5	1600 mg (3 mL)	IM[c]	16

Day 1 — **Week 52[d]**

Monitoring of

- PK parameters
- Adverse events, including ISRs
- Vital signs
- Clinical laboratory values

- To evaluate potential CAB-ULA dosing regimens, CAB PK profiles were simulated using an established CAB200 IM population PK model modified based on observed PK data in Part C

BMI, body mass index; CAB, cabotegravir; IM, intramuscular; ISR, injection site reaction; PK, pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; ULA, ultra-long-acting.
[a]CAB-ULA is a new formulation with higher CAB concentration than approved CAB200. [b]Abdominal. [c]Gluteus medius. [d]The study has been extended to Week 78 for C1 and C3.

Participant Demographics and Characteristics

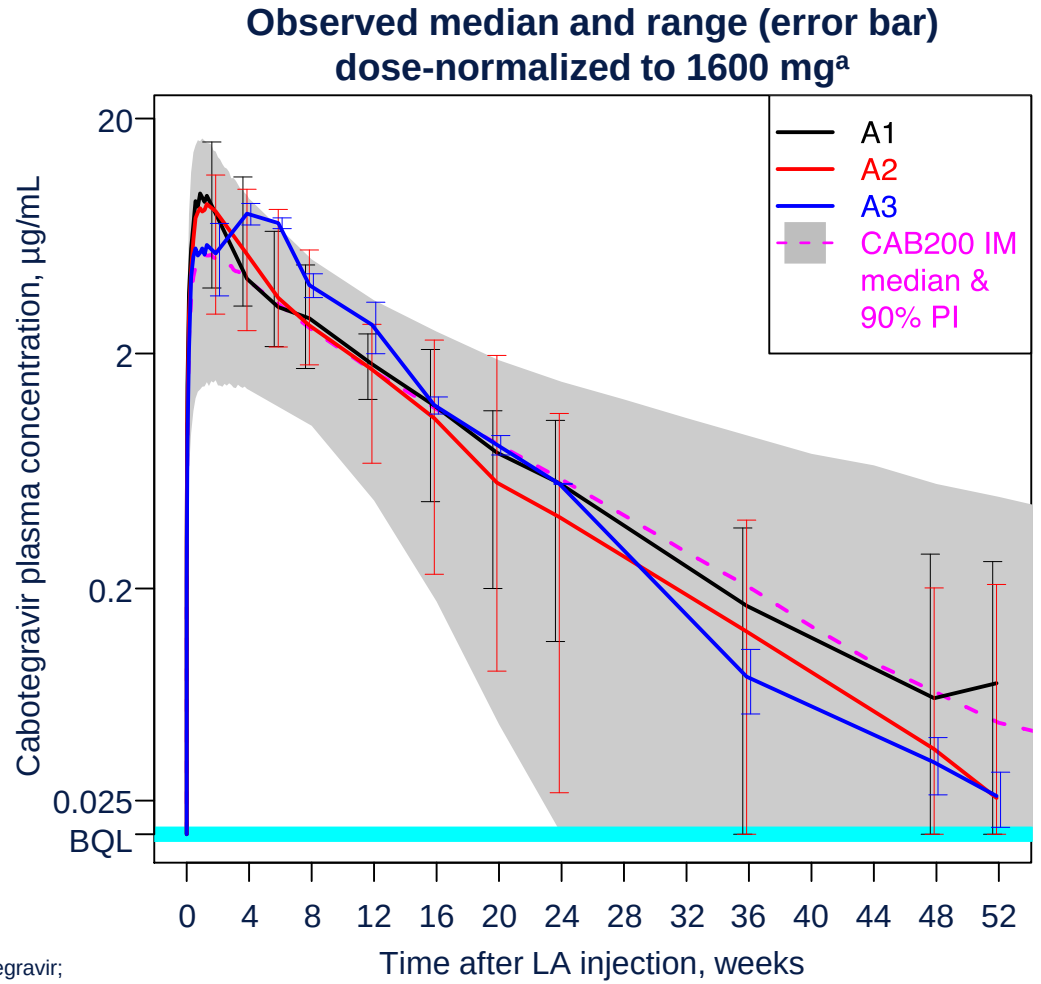
Parameter	Part A: CAB200 SC + rHuPH20 A1: 800 mg (4 mL) (N=10)	Part A: CAB200 SC + rHuPH20 A2: 1600 mg (8 mL) (N=10)	Part A: CAB200 SC + rHuPH20 A3: 3200 mg (16 mL) (N=2)	Part C: CAB-ULA SC C1: 800 mg (2 mL) (N=8)	Part C: CAB-ULA SC C3: 1200 mg (3 mL) (N=8)	Part C: CAB-ULA IM C2: 800 mg (2 mL) (N=8)	Part C: CAB-ULA IM C4: 1200 mg (3 mL) (N=8)	Part C: CAB-ULA IM C5: 1600 mg (3 mL) (N=16)
Age, median (IQR), years	29.5 (27.0-50.0)	34.5 (25.0-46.0)	32.0 (32.0-32.0)	44.0 (37.5-49.0)	37.5 (29.0-44.5)	38.0 (37.0-44.0)	43.5 (36.5-51.5)	45.0 (39.0-51.5)
Sex at birth, n (%)								
Female	6 (60)	4 (40)	0	3 (38)	3 (38)	2 (25)	4 (50)	9 (56)
Male	4 (40)	6 (60)	2 (100)	5 (63)	5 (63)	6 (75)	4 (50)	7 (44)
Race, n (%)								
Black or African heritage	4 (40)	5 (50)	2 (100)	3 (38)	1 (13)	5 (63)	2 (25)	6 (38)
White	3 (30)	4 (40)	0	5 (63)	6 (75)	3 (38)	3 (38)	8 (50)
Other races[a]	3 (30)	1 (10)	0	0	1 (13)	0	3 (38)	2 (13)
Weight, median (IQR), kg	67.0 (55.9-74.4)	65.2 (57.9-81.1)	76.2 (74.6-77.8)	79.4 (76.7-90.9)	77.6 (69.3-85.0)	92.0 (76.5-93.3)	75.5 (63.3-82.5)	77.1 (67.8-84.9)
BMI, median (IQR), kg/m^2	23.7 (21.3-27.3)	24.4 (23.2-28.4)	25.4 (24.7-26.0)	28.7 (27.0-30.1)	26.2 (23.4-27.6)	28.5 (27.3-29.8)	25.8 (23.9-28.2)	26.9 (24.2-29.7)

BMI, body mass index; CAB, cabotegravir; IM, intramuscular; IQR, interquartile range; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; ULA, ultra-long-acting.
[a]Includes Asian (n=8), Native Hawaiian or Other Pacific Islander (n=1), and multiple races (n=1).

Part A: Pharmacokinetics of CAB200 + rHuPH20

Parameter, geometric mean (%CVb)	Part A: CAB200 SC + rHuPH20		
	A1: 800 mg (4 mL) (n=10)	A2: 1600 mg (8 mL) (n=9)	A3: 3200 mg (16 mL) (n=2)
$AUC_{0-\infty}$, mg·h/mL	6.1 (27.9)	11.5 (28.7)	26.6 (8.9)
Cmax, µg/mL	4.7 (47.4)	7.7 (46.2)	16.2 (10.1)
$t_{1/2}$, days	54.6 (57.9)	47.9 (68.5)	42.3 (5.3)
tmax, hours	164 (40.0)	316 (62.6)	755 (39.4)

- $t_{1/2}$ was similar to CAB200 IM, indicating similar overall absorption rate[1,2]
- Cmax was higher than CAB200 IM, indicating faster initial absorption[2]
- Exposure increased with dose proportionally
- $AUC_{0-\infty}$ was higher than CAB200 IM, indicating potentially increased bioavailability[2]



$AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 to infinity; BQL, below quantification limit of 0.025 µg/mL; CAB, cabotegravir; Cmax, maximum observed plasma concentration; %CVb, coefficient of variation; IM, intramuscular; LA, long-acting; n, number of participants with valid PK parameters; PI, prediction interval; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; $t_{1/2}$, terminal half-life; tmax, time to Cmax.
[a]Error bars before Week 2 are not displayed for visibility. **1.** Han et al. *Br J Clin Pharmacol*. 2022;88:4607-4622. **2.** Cabenuva [prescribing information]. ViiV Healthcare; 2023.

Part A: Safety of CAB200 + rHuPH20

The overall tolerability/safety profile, along with PK considerations, led to a decision not to progress this dosing strategy:

- Non-ISR drug-related AEs were infrequent
- ISRs occurred in all participants (22/22); ISR grade increased with increasing CAB dose
  - Most common ISRs were injection site pain, erythema, swelling, and warmth
- A single drug-related SAE was reported: 1 participant who received CAB 3200 mg (16 mL) SC + rHuPH20 experienced injection site erythema with necrosis requiring wound care; the wound completely healed, and the erythema resolved by Day 105

	Part A: CAB200 SC + rHuPH20		
Parameter	**A1: 800 mg (4 mL) (N=10)**	**A2: 1600 mg (8 mL) (N=10)**	**A3: 3200 mg (16 mL) (N=2)**
Any ISR, n (%)	10 (100)	10 (100)	2 (100)
Total ISR events, n	45	48	11
Maximum grade 1, n (% of ISRs)	25 (56)	29 (60)	5 (45)
Maximum grade 2, n (% of ISRs)	20 (44)	16 (33)	1 (9)
Maximum grade ≥3, n (% of ISRs)	0	3 (6)	5 (45)[a,b]
Duration, median (IQR), days[c]	9 (7-37)	24 (7-138)	28 (15-105)

AE, adverse event; CAB, cabotegravir; IQR, interquartile range; ISR, injection site reaction; PK, pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SAE, serious AE; SC, subcutaneous.
[a]1 drug-related SAE of injection site erythema with necrosis. [b]No further participants were dosed in A3 due to the safety findings from these 2 sentinel participants. [c]Only calculated for events that have resolved (A1: 45/45 [100%]; A2: 45/48 [94%]; A3: 11/11 [100%]).

New Ultra-Long-Acting Formulation CAB-ULA

Conference on Retroviruses and Opportunistic Infections; March 3-6, 2024; Denver, CO

Part C: PK of New Ultra-Long-Acting Formulation CAB-ULA

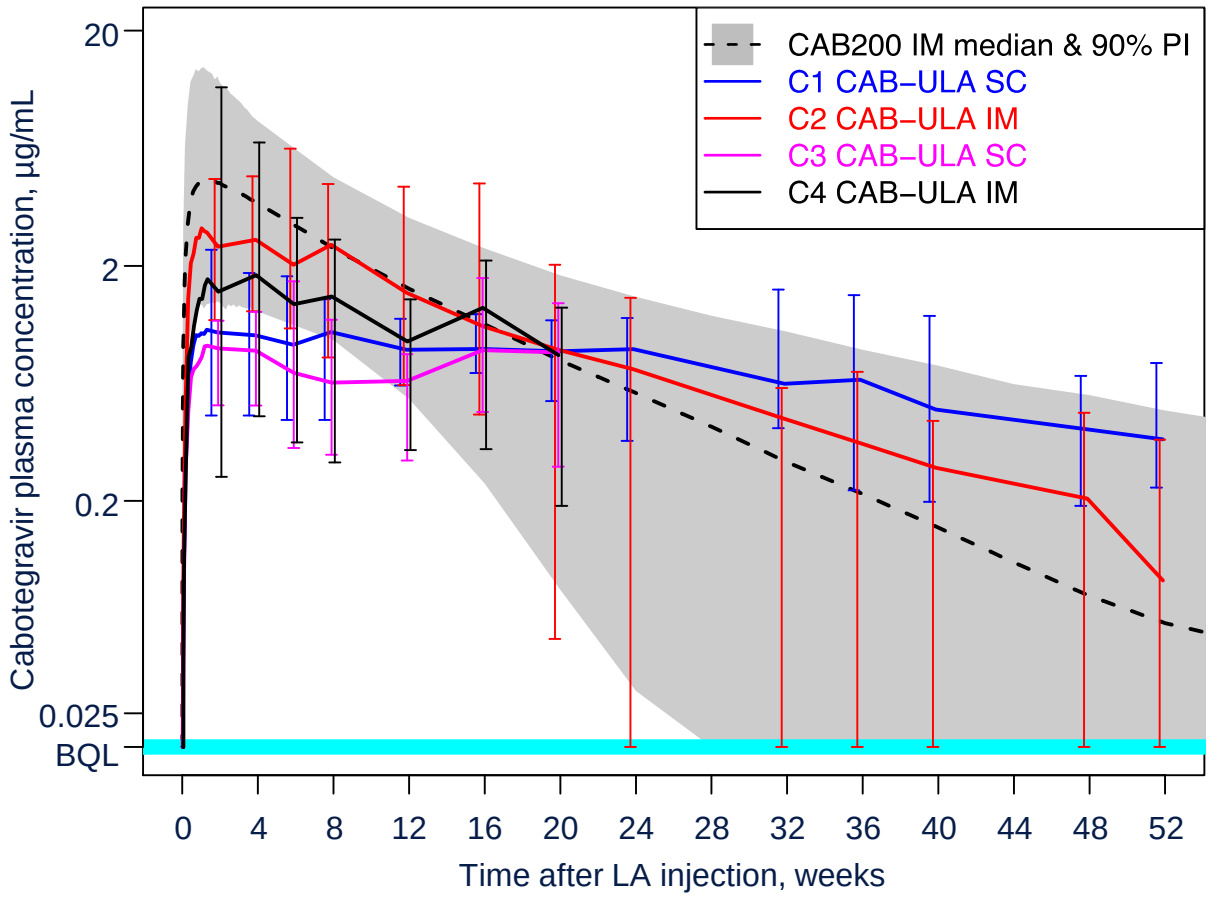
Part C: CAB-ULA

Parameter, geometric mean (%CVb)	SC		IM	
	C1 800 mg (2 mL) (n=8)	C3 1200 mg (3 mL) (n=8)	C2 800 mg (2 mL) (n=8)	C4 1200 mg (3 mL) (n=8)
Cmax, µg/mL	0.7 (35.5)	0.8 (39.0)	1.8 (53.5)	1.8 (148)
tmax, hours	570 (158)	349 (147)	298 (136)	383 (107)

CAB-ULA has slower absorption and longer $t_{1/2}$ than CAB200 IM

- PK profiles were flatter than CAB200 IM
- CAB-ULA Cmax was lower with SC than IM; both were lower than CAB200 IM[1]
- tmax was longer than CAB200 IM[1]
- **CAB-ULA $t_{1/2}$ for SC and IM was predicted to be >6x and >2x the $t_{1/2}$ of CAB200 IM, respectively[1,a]**

Observed median and range (error bar) dose-normalized to 1600 mg[b]



BQL, below quantification limit of 0.025 µg/mL; CAB, cabotegravir; Cmax, maximum observed plasma concentration; %CVb, coefficient of variation; IM, intramuscular; n, number of participants with valid PK parameters; PI, prediction interval; PK, pharmacokinetics; SC, subcutaneous; $t_{1/2}$, terminal half-life; tmax, time to Cmax; ULA, ultra-long-acting. [a]Current follow-up time is insufficient to calculate final $t_{1/2}$ value for CAB-ULA. [b]Error bars before Week 2 are not displayed for visibility. **1.** Cabenuva [prescribing information]. ViiV Healthcare; 2023.

Part C: Safety of CAB-ULA

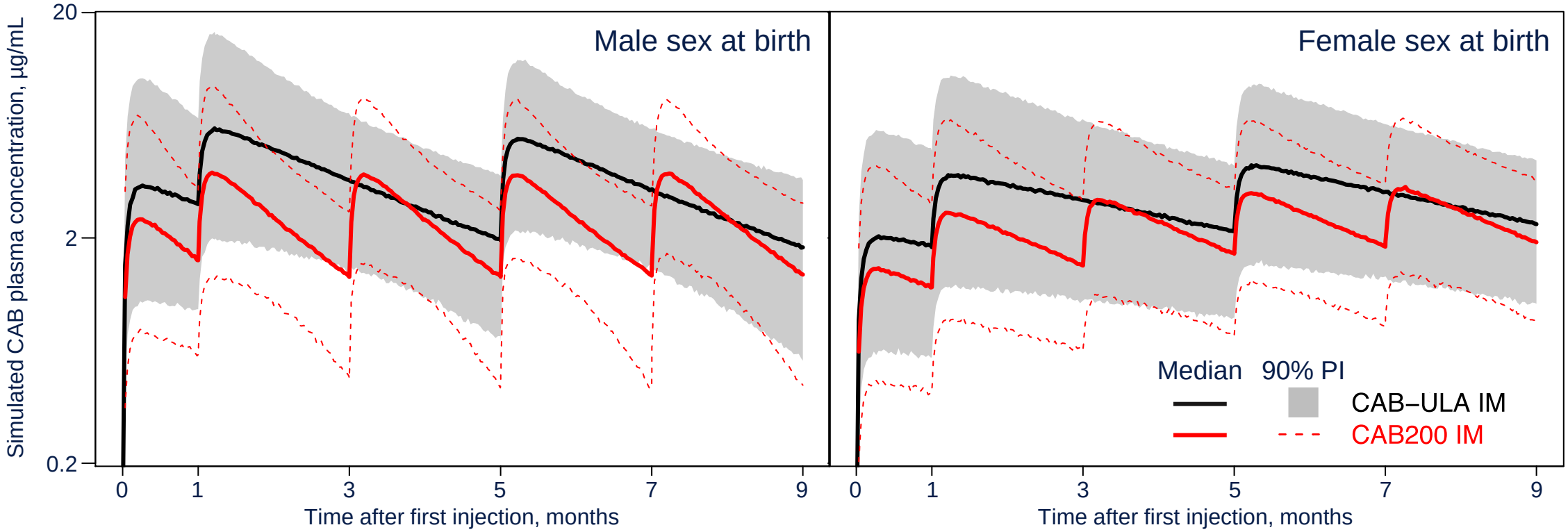
- Non-ISR drug-related AEs were infrequent
- CAB-ULA IM was better tolerated than SC
  - SC: ISRs occurred in 100% (16/16) of participants; most common SC ISRs were erythema, nodule, and pain
  - IM: ISRs occurred in 69% (22/32) of participants; most common IM ISR was pain and except for 1, all were mild (grade 1)
- CAB-ULA IM ISR profile appears comparable to established CAB200 IM ISR profile despite higher single doses of CAB-ULA

	Part C: CAB-ULA				
	SC		IM		
Parameter	C1: 800 mg (2 mL) (N=8)	C3: 1200 mg (3 mL) (N=8)	C2: 800 mg (2 mL) (N=8)	C4: 1200 mg (3 mL) (N=8)	C5: 1600 mg (3 mL) (N=16)
Any ISR, n (%)	8 (100)	8 (100)	3 (38)	8 (100)	11 (69)
Total ISR events, n	21	24	5	9	15
Maximum grade 1, n (% of ISRs)	19 (90)	22 (92)	4 (80)	9 (100)	14 (93)
Maximum grade 2, n (% of ISRs)	2 (10)	2 (8)	1 (20)	0	1 (7)
Maximum grade ≥3, n (% of ISRs)	0	0	0	0	0
Duration, median (IQR), days[a]	15 (6-41)	13 (6-21)	5 (5-8)	4 (3-5)	6 (4-8)

AE, adverse event; CAB, cabotegravir; IM, intramuscular; IQR, interquartile range; ISR, injection site reaction; SC, subcutaneous; ULA, ultra-long-acting.
[a]Only calculated for events that have resolved (C1: 15/21 [71%]; C3: 17/24 [71%]; C2: 5/5 [100%]; C4: 9/9 [100%]; C5: 12/15 [80%]).

Pharmacokinetic Simulations of CAB-ULA Q4M Dosing

- PK simulations[a] predict a CAB-ULA IM dose interval of ≥4 months achieves higher exposure than approved CAB200 IM at intervals of 2 months
- CAB-ULA IM $t_{1/2}$ was predicted to be >2x the $t_{1/2}$ of CAB200 IM



CAB, cabotegravir; IM, intramuscular; PI, prediction interval; PK, pharmacokinetics; Q4M, every 4 months; SC, subcutaneous; $t_{1/2}$, terminal half-life; ULA, ultra-long-acting. [a]1600-mg (3-mL) CAB-ULA per injection.

Conclusions

- A new CAB-ULA formulation exhibits favorable tolerability and safety, with a PK profile that supports dose intervals of ≥4 months
  - IM tolerability is encouraging at CAB-ULA doses up to 2.7x (1600 mg) the approved CAB dose
  - Additional SC evaluation is planned
- CAB-ULA has the potential for less frequent dosing and may reduce clinic visits
- CAB-ULA IM Q4M is progressing into upcoming late-stage HIV-1 PrEP and treatment studies

CAB, cabotegravir; IM, intramuscular; PK, pharmacokinetics; PrEP, pre-exposure prophylaxis; Q4M; every 4 months; SC, subcutaneous; ULA, ultra-long-acting.

Acknowledgments

- This study was funded by ViiV Healthcare

- The authors would like to acknowledge the contributions of Ciara Seal, Louise Harkness, Steve Knowles, Kjersten Offenbecker, and Christina Donatti to this work

- The authors would also like to thank the study participants; the investigators and site staff who participated in the study; and the ViiV Healthcare, GSK, and Pharmaceutical Product Development study team members

- Editorial assistance and graphic design support for this presentation were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare

Presenting author: Kelong Han; kelong.x.han@gsk.com

Disclaimer

This content was acquired following an unsolicited medical information enquiry by a healthcare professional. Always consult the product information for your country, before prescribing a ViiV medicine. ViiV does not recommend the use of our medicines outside the terms of their license. In some cases, the scientific Information requested and downloaded may relate to the use of our medicine(s) outside of their license.