TITLE PAGE

Protocol Title: A Phase 1, Two-part, Double-blind, Active-control, Randomized Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Repeat-Dose Cabotegravir (CAB 400 mg/mL formulation) Long-Acting Injection Following Subcutaneous or Intramuscular Administration in Healthy Adult Participants

Protocol Number: 212482/Amendment 06

Compound Number or Name: GSK1265744/CAB 400 mg/mL formulation

Study Phase: Phase 1

Short Title: CAB 400 mg/mL formulation Pharmacokinetic, Safety and Tolerability study

ViiV Healthcare group of companies

Sponsor Name and Legal Registered Address (excluding US):

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 1 919 438 2100

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

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SPONSOR SIGNATORY

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Max Lataillade, DO, MPH
VP and Head, Global Research Strategy
ViiV Healthcare

Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 6	*28-OCT-2021*	*TMF-13988926*
Amendment 5	*07-SEP-2021*	*TMF-12473296*
Amendment 4	*17-Feb-2021*	*TMF-11724805*
Amendment 3	*29-Oct-2020*	*2019N416043_03*
Amendment 2	*26-Jun-2020*	*2019N416043_02*
Amendment 1	*22-Apr-2020*	*2019N416043_01*
Original Protocol	*14-Feb-2020*	*2019N416043_00*

Amendment 6: 28-OCT-2021

Overall Rationale for the Amendment:

The primary reason for this amendment is to include a further cohort in Part 1 (Cohort 4h) which will evaluate the pharmacokinetics, safety and tolerability of a single subcutaneous abdominal injection of CAB 400 mg/mL formulation or CAB 200 mg/mL formulation administered with recombinant human hyaluronidase PH20; relevant sections throughout the protocol were updated accordingly.

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis, Rationale	Description of Cohort 4h added	For completeness
1.1 Synopsis, Objectives and Endpoints 3. Objectives and Endpoints, Primary	Update to PK and safety objectives and endpoints	To reflect inclusion of Cohort 4h with this amendment
1.1 Synopsis, Overall Design	New paragraph describing Cohort 4h added	To describe the design of Cohort 4h
1.1 Synopsis, Overall Design 1.3.1. Screening Period and Oral Lead-in Phase: All Cohorts 1.3.4. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow- up: Part 1 Cohort 4h (CAB 400 mg/mL or CAB 200 mg/mL with rHuPH20)	Randomization of Cohort 4h participants will occur on Day 1 of the injection phase	To describe the design of Cohort 4h
1.1 Synopsis, Number of Participants	Overall participant numbers updated	20 more participants are to be enrolled and randomised in the study (Cohort 4h)
1.1 Synopsis, Intervention Groups and Duration	Information on injection in Cohort 4h added	To specify injections, doses and route of administration in Cohort 4h and to include information on length of clinic stay following injection in this cohort

Section # and Name	Description of Change	Brief Rationale
6.2.1. Dosage and Administration		
1.1 Synopsis, Intervention Groups and Duration 1.3.4. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow- up: Part 1 Cohort 4h (CAB 400 mg/mL or CAB 200 mg/mL with rHuPH20) 2.3. Benefit/Risk Assessment 11.8. Appendix 8: Permissible Procedures during the COVID-19 Pandemic	Participants in Cohort 4h will stay in the clinic for 4-7 days after the injection and may be discharged between Day 5 and Day 8; where SARS-CoV-2 is circulating in the community, a SARS-CoV-2 test is required upon discharge from the clinic between Day 5 and Day 8.	To introduce flexibility regarding the in-clinic stay
1.2. Schema	Schema for Cohort 4h added	To describe the design of Cohort 4h
1.3.4. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow-up: Part 1 Cohort 4h (CAB 400 mg/mL or CAB 200 mg/mL with rHuPH20)	Cohort 4h schedule of activities added	To describe the type and timing of assessments in Cohort 4h
2.2. Background	Brief description of rHuPH20and its use added	To provide information on rHuPH20
2.3. Benefit/Risk Assessment 2.3.1. Risk Assessment, Injection Site Reactions (ISRs)	Sentinel dosing strategy in Cohort 4h outlined	CAB has not been administered with rHuPH20 in humans before
2.3.1. Risk Assessment 2.3.3. Overall Benefit: Risk Conclusion	Potential risks and mitigation strategies for rHuPH20 included; the potential risks identified with rHuPH20 are well understood	To reflect inclusion of Cohort 4h with this amendment
2.3.1.1. Other Clinically Relevant Information	Reference made to rHuPH20 investigator's brochure where relevant	To reflect the use of rHuPH20 in Cohort 4h
4.1. Overall Design 4.1.1. Part 1 4.1.5. Washout Period and Injection Phases	Information on Cohort 4h added	To describe the design of Cohort 4h
4.2.2. Long Acting Injectable Dose	Data on the impact of rHuPH20 on the pharmacokinetics of CAB 200 mg/mL in rats added	To provide non-clinical data on CAB and rHuPH20 co-administration
4.2.3. rHuPH20	Section on what dose of rHuPH20 to use with CAB 200 mg/mL and CAB 400 mg/mL formulations included	To reflect the use of rHuPH20 in Cohort 4h
5.2. Exclusion Criteria	Exclusion criterion added: A known hypersensitivity to hyaluronidases	To reflect the use of rHuPH20 in Cohort 4h
6.1.1.2. Cabotegravir Injectable Suspension (CAB 400 or CAB 200)	Information on rHuPH20 added to table of study interventions	To reflect the use of rHuPH20 in Cohort 4h

Section # and Name	Description of Change	Brief Rationale
6.1.3. Recombinant human hyaluronidase PH20 (rHuPH20)	New section on rHuPH20 included	To describe the use of rHuPH20 in Cohort 4h
8.9. Immunogenicity Assessments 11.2. Appendix 2: Clinical Laboratory Tests, Table 5	New section/information added	To reflect the use of rHuPH20 in Cohort 4h, i.e. collect plasma sample for storage of potential immunogenicity analyses if there are safety events suggestive of immune-mediated reactions to rHuPH20
10.2. Sample Size Determination	Information on Cohort 4h sample size added	To provide rationale for Cohort 4h sample size
10.4.2. Primary Endpoints	Update to PK primary analyses	To reflect inclusion of Cohort 4h with this amendment
10.5. Planned Analyses	An additional preliminary analysis of data from Cohort 4h has been added Information on formal and interim analyses has been updated	To reflect inclusion of Cohort 4h with this amendment To allow for a conference presentation of interim results
Throughout	Minor editorial and document formatting revisions	Minor and therefore have not been summarized

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase I, Two-part, Double-blind, Active-control, Randomized Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Repeat-Dose Cabotegravir (CAB 400 mg/mL formulation) Long-Acting Injection Following Subcutaneous or Intramuscular Administration in Healthy Adult Participants

Short Title: CAB 400 mg/mL Pharmacokinetic, Safety and Tolerability study

Rationale:

Long acting injectable versions of antiretrovirals are being developed to enable therapy with infrequent dosing schedule. A two-drug regimen of cabotegravir (CAB) 200 mg/mL formulation long-acting (LA) plus rilpivirine LA offers many potential advantages over daily oral regimens including infrequent dosing that decreases the daily reminder to patients of their HIV status, better tolerability, less likely to develop viral resistance due to intermittent compliance. GSK1265744/CAB 400 mg/mL formulation LA is a more concentrated formulation and may allow the administration of a higher dose of CAB potentially affording a longer interval between injections or administration at different sites (SC or IM lateral thigh) such that self-administration would be possible. This may increase the convenience of long-acting regimens including CAB LA and may result in better adherence to therapy and positively impact treatment outcomes and acceptability.

This GSK1265744 CAB 400 mg/mL formulation study is a Phase I, active control, randomized study to investigate the safety, tolerability and pharmacokinetics of repeat dose administration of long acting CAB 400 mg/mL formulation intramuscular (IM, *gluteus medius* and *vastus lateralis*) and subcutaneous (SC, abdominal) injections in healthy adult participants. Participants will be randomized on Day 1 of the oral lead-in (OLI) phase (Part 1 Cohorts 1-4b) or Day 1 of the injection phase (Part 1 Cohort 4h and Part 2). All participants undergo initial repeat dose administration of GSK1265744 30 mg tablets p.o. q24 h for 28 days to establish the short-term safety and tolerability prior to LA administration. Repeat long acting parenteral (LAP) dosing will be performed via IM (*gluteus medius* or *vastus lateralis*) or subcutaneous routes. All injections will be healthcare provider (HCP) administered. The study will assess the relative bioavailability of the CAB 400 mg/mL formulation administered by IM (*vastus lateralis*) and SC routes compared to the CAB 400 mg/mL administered IM (*gluteus medius*) and also compared with historical data of CAB 200 mg/mL formulation administered IM (*gluteus medius*) by comparing the trough concentrations ($C\tau$) and plasma exposures area under the concentration – time curve for each injected dose from time zero to last quantifiable time point (AUC0-t) and to use this data to bridge to future Phase 2b studies in an HIV patient population. As part of protocol amendment 6, Cohort 4h has been added which will evaluate the pharmacokinetics, safety and tolerability of cabotegravir 200 mg/mL and 400 mg/mL formulations with recombinant human hyaluronidase PH20 (rHuPH20). When other drugs are injected with hyaluronidase, dispersion of the co-injected drugs is enhanced.

Objectives and Endpoints:

Objectives	Endpoints
Primary	Primary
To describe the pharmacokinetic (PK) profiles of CAB 400 mg/mL formulation following multiple injections administered intramuscularly (*gluteus medius* or *vastus lateralis*) or subcutaneously (abdominal) in healthy adult participants	Summary measures to include: • Maximum observed plasma concentration (Cmax) [Injection 1 and 2] • Time of maximum observed plasma concentration (tmax) [Injection 1 and 2] • Area under the concentration – time curve for each injected dose from time zero to last quantifiable time point or 4 weeks following injection whichever is earlier (AUC0-t) • Trough concentrations (Cτ) at 4 weeks following first injection (or earlier if the second injection occurs at <4-week interval) and 4 weeks following the second injection • Apparent terminal phase half-life (t½) and absorption rate constant (KALA) [Injection 2]
To assess the relative bioavailability of a CAB 400 mg/mL formulation administered via different routes (i.e., IM (*vastus lateralis*), IM (*gluteus medius*) or SC routes)	• Pair-wise comparisons of geometric mean ratios of plasma trough concentrations (Cτ), Cmax, and AUC0-t [injection phase] for Cohorts 1, 2, 3, 4, 4b, and 4h
To compare exposures after CAB 400 mg/mL formulation administered via different routes with historical data of CAB 200 mg/mL formulation administered IM (*gluteus medius*)	• Geometric mean ratios of plasma trough concentrations (Cτ) for Cohorts 1, 2, 3, 4, 4b, 4h, 5, and 6 (if conducted) compared to historical CAB 200 mg/mL data
Safety	Safety
To assess safety and tolerability of CAB 400 mg/mL formulations following repeated intramuscular injections in the *gluteus medius*, *vastus lateralis* (lateral thigh) or subcutaneously	Safety and tolerability parameters including adverse events, clinical laboratory tests, and vital sign assessments

Objectives	Endpoints
(abdomen) of healthy adult participants To assess safety and tolerability of CAB 200 mg/mL with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants To assess safety and tolerability of CAB 400 mg/mL with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants	
Secondary	Secondary
To assess the tolerability of CAB 400 mg/mL formulation following repeated intramuscular injections in the *gluteus medius*, *vastus lateralis* (lateral thigh) or subcutaneously (abdomen) of healthy participants To assess the tolerability of CAB 200 mg/mL formulation with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants To assess the tolerability of CAB 400 mg/mL formulation with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants	Tolerability parameters (adverse events) and liver biochemistry abnormalities

Objectives	Endpoints
PK	PK
Secondary	Secondary
To describe the PK profiles of CAB 200 mg/mL and CAB 400 mg/mL formulations with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants	Summary measures to include: • Maximum observed plasma concentration (Cmax) • Time of maximum observed plasma concentration (tmax) • Area under the concentration – time curve from time zero to last quantifiable time point or 4 weeks following the injection whichever is earlier (AUC0-t) • Trough concentrations (Cτ) through the Follow-up Phase • Apparent terminal phase half-life (t½) and absorption rate constant (KALA)
To describe the pharmacokinetic (PK) profiles of oral CAB 30 mg following daily administration in healthy adult participants	• Cmax • tmax • AUC(0-t) • C24 • Day 29 Cτ

Overall Design:

212482 is a Phase I, double-blind (sponsor-unblind), active control, randomized, study to investigate the safety, tolerability and pharmacokinetics of repeat dose four weekly (Q4W) and twelve weekly (Q12W) administration of long-acting CAB 400 mg/mL or CAB 200 mg/mL formulations either administered intramuscularly (IM, *gluteus medius* or *vastus lateralis*) or via subcutaneous (SC, abdominal) injections in healthy adult participants. The study will assess the relative bioavailability of the CAB 400 mg/mL formulation administered by IM (*vastus lateralis*) and SC routes compared to the CAB 400 mg/mL administered IM (*gluteus medius*) and also compared with historical data of CAB 200 mg/mL formulation administered IM (*gluteus medius*) by comparing the trough concentrations (Cτ) and plasma exposures (AUC0-t) and to use this data to bridge to future Phase 2b studies in an HIV patient population. .

In Part 1 of the study, participants will be enrolled sequentially into Cohorts 1, 2 and 3 (n=20 each). Participants will be recruited to Cohort 1 first, then Cohort 2 and followed by Cohort 3. Participants will be randomized (9:1 Active vs Active Control [AC]) according to a pre-generated randomization schedule to receive two Q4W injections of CAB 400 mg/mL 4 weeks apart (600 and 400 mg respectively) IM (n=18, *gluteus medius,* Cohort 1), SC (n=18, abdominal*,* Cohort 2) and IM (n=18, lateral thigh/*vastus lateralis*, Cohort 3) or two Q4W injections of CAB 200 mg/mL 4-weeks apart as active

controls (n=2 in each cohort). Cohorts 1-3 in Part 1 will each have a total of 20 participants (18 active and 2 active control) with a view to a minimum of 15 participants having evaluable data following both injections. All injections will be administered by an HCP. In Cohorts 1 and 3 the active control of CAB 200 mg/mL will be matched for dose e.g. 600 mg and 400 mg. In Cohort 2, subcutaneous dosing of active control (CAB 200 mg/mL) will be matched to the volume of CAB 400 mg/mL formulation administered.

The requirement for an optional Cohort 4 and determination of the dose and dosing schedule will be determined based on a review of the safety and tolerability data and any available PK data from Cohorts 1-3. This determination will be undertaken by the Study Team safety & PK Review (STR) and will be based on the comparison to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program. Cohort 4, if required, will assess the PK, safety and tolerability of alternative doses and/or dosing via SC and/or IM routes among 20 participants (18 active and 2 active control).

At the 22 December 2020 STR meeting, it was agreed to conduct Cohort 4 evaluating two Q4W injections of CAB 400 mg/mL 4 weeks apart (n=18, first injection 400 mg IM *gluteus medius* and second injection 200 mg SC) or two Q4W injections of CAB 200 mg/mL 4 weeks apart as active controls (n=2, first injection 400 mg IM *gluteus medius* and second injection 100 mg SC).

Cohort 4b, has been added to the study as part of protocol amendment 5. Cohort 4b will assess the PK, safety and tolerability of alternative doses via the SC route among 24 participants. All participants will receive two injections of 300 mg of CAB 400 mg/mL 4 weeks apart. CCI [redacted] Participants (n=24) will be randomized according to a pre-generated randomization schedule to one of two sequences (i.e. 12 per sequence) of two treatments to be administered along with injection 1 and injection 2, respectively: CCI [redacted]

Cohort 4h has been added to the study as part of protocol amendment 6. In Cohort 4h, the PK, safety and tolerability will be evaluated among 20 participants receiving cabotegravir 200 mg/mL and 400 mg/mL formulations with recombinant human hyaluronidase PH20 (rHuPH20). Ten participants will receive one subcutaneous injection of 400 mg of CAB 400 mg/mL with 5000 U of rHuPH20, and another 10 participants will receive one subcutaneous injection of 400 mg of CAB 200 mg/mL with 5000 U of rHuPH20 based on 1:1 randomization. rHuPH20 and CAB formulations will be administered sequentially. To conservatively assess safety in Cohort 4h, the first two participants enrolled in each group will serve as sentinel participants. These sentinel participants will be followed clinically for 10 days after dose administration to monitor the emergence of adverse events. Assuming that there are no significant safety concerns upon 10-day review of safety data (e.g. vital signs, ECGs, and adverse events) for these sentinel participants, the remaining participants will be treated with either CAB 400 mg/mL formulation (n=8) or CAB 200 mg/mL formulation (n=8) according to randomization schedules.

The study will consist of a screening period, a 28-day oral lead-in (OLI) phase at a CAB dose of 30 mg tablets once a day with sparse PK sampling through day 29, a 7-14 days washout period starting on Day 29 (which may be extended if deemed necessary by the investigator and sponsor), and injection phase and a follow-up phase of 52 weeks post last injection. A window of ±3 days either side of the scheduled date for the second injection is permitted. Randomization of participants will occur on Day 1 prior to oral CAB dosing (Part 1 Cohorts 1-4b) or on Day 1 of the injection phase (Part 1 Cohort 4h and Part 2).

Part 2 will commence once data (trough concentrations (Cτ) and Plasma AUC_{0-t} up to and including Week 8 following injection 1 (i.e. Week 4 following Injection 2 [Injection 2 Day 28/Week 4 follow-up]) from all participants in Cohort 1, and any safety and tolerability data available at this time from Cohorts 1-3) are reviewed and compared to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program. The first injection in Part 2 Cohort 5 will be administered once safety and tolerability data observed within the first ten days after the first injection for at least 50% of Cohort 4 participants (n=10) have been reviewed by the STR. If pausing criteria due to ISRs are met in Cohort 4, Cohort 5 will be paused until further discussion. The determination of the dose and dosing schedule will be governed by the STR with the aim of selecting a safe dose predicted to achieve approximately 95% of dosed participants having trough concentrations higher than the Phase 3 benchmark.

In Part 2 of the study, Cohort 5, Q12W IM, participants will receive two IM gluteal injections 12 weeks apart, Q12W IM administered by an HCP into the *gluteus medius*. A total of 22 participants will be recruited to Cohort 5 and, following the OLI phase and washout period, will be randomized on Day 1 of the injection phase to receive a dose up to 1200 mg of CAB 400 mg/mL formulation (n=20) or to receive CAB 200 mg/mL (n=2) with a view to a minimum of 16 participants having evaluable data following both injections. In Cohort 5, intramuscular dosing of active control (CAB 200 mg/mL) will be matched to the volume of CAB 400 mg/mL formulation administered via the *gluteus medius*. To conservatively assess safety in Cohort 5, the first four subjects enrolled will serve as sentinel participants with three receiving CAB 400 mg/mL formulation (dose up to 1200 mg based upon data from Part 1) and one receiving active control (based on 3:1 randomization). These sentinel participants will be followed clinically for 10 days after dose administration to monitor the emergence of adverse events. Assuming that there are no significant safety concerns upon 10-day review of safety data (e.g. vital signs, ECGs, and adverse events) for the sentinel participants, the remaining participants will be treated with either CAB 400 mg/mL formulation (n=17) or AC (n=1) according to randomization schedules. Dose administration for the remaining participants (n=18) will be staggered:

- A further 7 participants will be randomized and have their first injection.
- Following a review of safety data from the initial 7 participants (10 days post first injection), the remaining 11 participants will receive the first injection.
- These remaining participants may start the OLI phase prior to the 10-day reviews of safety data but they may only be randomized and proceed to the injection phase following the relevant safety review and if there are no significant safety concerns.

The requirement for an optional further cohort (Cohort 6) will be based upon a review of the available safety, tolerability and PK data from Cohorts 1-4 and safety, tolerability and PK data (12 weeks after injection 1) from Cohort 5 and comparison to historical PK data of the CAB 200 mg/mL formulation. This determination will be undertaken by the STR. Cohort 6, if required, will assess the PK, safety and tolerability of alternative doses and/or dosing schedule among 22 participants (20 active and 2 active control). Sentinel dosing and randomization will also occur as in Cohort 5. Intramuscular dosing of active control (CAB 200 mg/mL) will be matched to the volume of CAB 400 mg/mL formulation administered via the *gluteus medius*.

Injection 2 is to occur 4 weeks after injection 1 (±3 days) for Part 1 and 12 weeks after injection 1 (±3 days) for Part 2.

In circumstances where recruitment to or dosing of a cohort is paused, participants may be recruited or re-randomized (only prior to the injection phase) to subsequent cohorts if deemed appropriate by the investigator and sponsor.

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participant's ability to attend clinic visits. Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to allow flexibility to allow conduct of the study.

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Participants will be followed up for 52 weeks following the last injection or until plasma concentrations of cabotegravir are below the level of quantification if this occurs prior to Week 52.

Disclosure Statement: This is an interventional, double-blind, randomized, Phase I, PK, safety, tolerability and relative bioavailability study.

Number of Participants:

Overall, approximately up to 168 participants will be included depending on the number of cohorts required in Parts 1 and 2.

In Part 1,

- 80 participants will be randomly assigned study intervention (CAB 400 mg/mL or AC CAB 200 mg/mL; Cohorts 1-4),
- 24 participants in Cohort 4b will receive study intervention with CAB 400 mg/mL, and
- approximately 20 participants in Cohort 4h will be randomly assigned study intervention (CAB 400 mg/mL or CAB 200 mg/mL) with rHuPH20

such that approximately 93 evaluable participants receiving CAB (15 in each of cohorts 1-4 and Cohort 4h, 18 in Cohort 4b) complete the study. Participants will be equally enrolled into one of the six cohorts. In Part 2, 22-44 participants will be randomly assigned within Cohorts 5 and 6 (if conducted) to study intervention (CAB 400 mg/mL or AC CAB 200 mg/mL) such that approximately 16 evaluable participants receiving CAB from each cohort complete the study.

We aim to recruit approximately 20% of women in each of the cohorts 1-6.

Intervention Groups and Duration:

Dosage and Administration

Oral Lead-In	
OLI Days 1 to 28	Take 1 tablet CAB 30 mg once daily. *Should be taken with or without a meal once daily at approximately the same time each day.*
7-14 Day Washout Period (from Day 29)	
Part 1	
First Injection (Loading Dose)	
Cohort 1	Receive CAB 600 mg given as 1 x 1.5 mL CAB 400 mg/mL formulation or 600 mg as 1 x 3 mL CAB 200 mg/mL IM gluteal injection
Cohort 2	Receive CAB 600 mg given as 1 x 1.5 mL CAB 400 mg/mL formulation or 300 mg as 1 x 1.5 mL CAB 200 mg/mL subcutaneous abdominal injection
Cohort 3	Receive CAB 600 mg given as 1 x 1.5 mL CAB 400 mg/mL formulation or 600 mg as 1 x 3 mL CAB 200 mg/mL IM lateral thigh injection The STR agreed[1]: Receive CAB 400 mg given as 1 x 1 mL of CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM lateral thigh injection
Cohort 4	Optional cohort. Receive CAB 400 mg/mL formulation (to a maximum of 1200 mg/3 mL if given IM or 600 mg/1.5 mL if given SC) or matched volume of CAB 200 mg/mL formulation if SC, and matched dose if IM. Dose determination by STR The STR agreed[2]: Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM gluteal injection

[1] At their meeting on 22 December 2020, the STR agreed to reduce the dose of the first injection for remaining Cohort 3 participants based on interim PK data from Cohorts 1 and 2.

[2] At their meeting on 22 December 2020, the STR agreed to conduct Cohort 4.

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Cohort 4b	Receive CAB 300 mg given as 1 x 0.75 mL CAB 400 mg/mL formulation subcutaneous abdominal injection[3]
Cohort 4h	Receive 5000 U of rHuPH20 followed by CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 1 x 2 mL CAB 200 mg/mL given as subcutaneously abdominal injection (sequential administration).[4]
Second Injection (Week 4 ± 3 days)	
Cohort 1	Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM gluteal injection
Cohort 2	Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 200 mg as 1 x 1 mL CAB 200 mg/mL subcutaneous abdominal injection The VSLC agreed[5]: Receive CAB 200 mg given as 0.5 mL CAB 400 mg/mL formulation or 100 mg as 1 x 0.5 mL CAB 200 mg/mL subcutaneous abdominal injection
Cohort 3	Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM lateral thigh injection
Cohort 4	Optional cohort. Receive CAB 400 mg/mL formulation (to a maximum of 1200 mg/3mL if IM or 600 mg/1.5mL if SC) or matched volume of CAB 200 mg/mL formulation if SC, and matched dose if IM. Dose determination by STR The STR agreed[6]: Receive CAB 200 mg given as 1 x 0.5 mL CAB 400 mg/mL formulation or 100 mg as 1 x 0.5 mL CAB 200 mg/mL subcutaneous abdominal injection
Cohort 4b	Receive CAB 300 mg given as 1 x 0.75 mL CAB 400 mg/mL formulation subcutaneous abdominal injection[3]

[3] CCI [redacted]

[4] rHuPH20 and CAB will be injected via a single butterfly needle. Due to a dead volume of 0.331 mL in the butterfly tube, a larger volume of CAB 200 mg/mL or CAB 400 mg/mL formulation will be required. Therefore, 1.4 mL of CAB 400 mg/mL and 2.4 mL of CAB 200 mg/mL will be used for injection and the exact doses of CAB 400 mg/mL and CAB 200 mg/mL administered will be 427.6 mg (1.069 mL) and 413.8 mg (2.069 mL), respectively.

[5] At the VSLC meeting on 13 November 2020, it was agreed to modify the conduct of Cohort 2 based upon interim PK and safety data.

[6] At their meeting on 22 December 2020, the STR agreed to conduct Cohort 4.

Part 2	
First Injection	
Cohort 5	Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose 1400 mg/3.5 mL IM). Dose determination by STR. The STR agreed[7]: Receive CAB 800 mg given as 1 x 2 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM gluteal injection
Cohort 6	Optional Cohort. Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of <2000 mg/5 mL IM). Dose determination by STR.
Second Injection (Week 12 ± 3 days)	
Cohort 5	Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of 1400 mg/3.5 mL IM). Dose determination by STR. The STR agreed[8]: Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of 1200 mg/3 mL IM)
Cohort 6	Optional Cohort. Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of <2000 mg/5 mL IM). Dose determination by STR.

Participants will remain in the clinic for 24 hours (Part 1 Cohorts 1, 2 and 3) or 7 days (Part 1 Cohorts 4 and 4b; Part 2 Cohorts 5 and 6) after each injection or for 4-7 days after

[7] At their meeting on 4 February 2021, the STR agreed to conduct Cohort 5 evaluating two Q12W injections of CAB 400 mg/mL 12 weeks apart (n=20, first injection 800 mg, 2 mL IM *gluteus medius* and second injection informed by safety and PK data 4 weeks after injection 1) or two Q12W injections of CAB 200 mg/mL 12 weeks apart as active controls (n=2, first injection 400 mg, 2 mL IM *gluteus medius* and second injection matched on volume to CAB 400 mg/mL IM *gluteus medius*).

[8] At their meeting on 4 February 2021, the STR agreed to conduct Cohort 5 evaluating two Q12W injections of CAB 400 mg/mL 12 weeks apart (n=20, first injection 800 mg, 2 mL IM *gluteus medius* and second injection informed by safety and PK data 4 weeks after injection 1) or two Q12W injections of CAB 200 mg/mL 12 weeks apart as active controls (n=2, first injection 400 mg, 2 mL IM *gluteus medius* and second injection matched on volume to CAB 400 mg/mL IM *gluteus medius*). The dose of the second injection will be guided by safety and PK data when ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments.

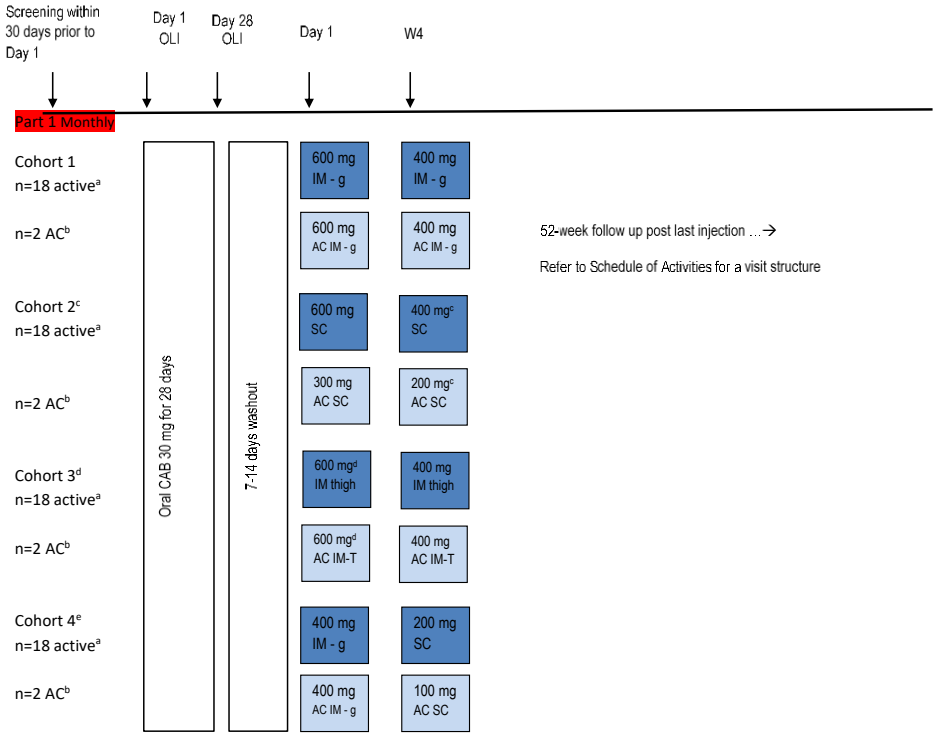
the injection (Cohort 4h) until the completion of the scheduled procedures and will return to the clinic for follow-up assessments as per the schedule of assessments.

Participants will undergo assessments in the follow-up phase from Week 4 after their last injection in Part 1 and from Week 12 after their last injection in Part 2, for 52 weeks post last injection or until CAB levels are below the level of quantification if this occurs prior to Week 52.

Data Monitoring or other Safety Committee: Yes. The review of study results will occur via a Study Team safety & PK Review (STR) similar to a Dose Escalation Committee.

1.2. Schema

Part 1 (Cohorts 1-4):



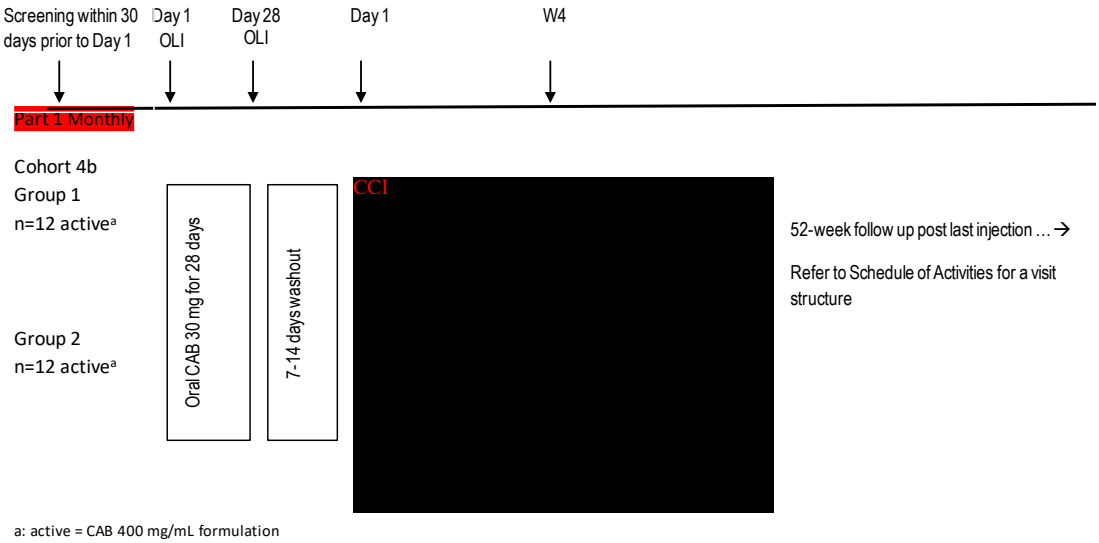
a: active = CAB 400 mg/mL formulation
b: AC = Active control CAB 200 mg/mL formulation
c: At the VSLC meeting on 13 November 2020, it was agreed to modify the conduct of Cohort 2 based upon interim data: participants will receive a second subcutaneous abdominal injection of CAB 200 mg given as 0.5 mL CAB 400 mg/mL formulation or 100 mg as 1 x 0.5 mL CAB 200 mg/mL.
d: At their meeting on 22 December 2020, the STR agreed to reduce the dose of the first IM lateral thigh injection for remaining Cohort 3 participants based on interim PK data from Cohorts 1 and 2, i.e. CAB 400 mg given as 1 x 1 mL of CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL.
e: At their meeting on 22 December 2020, the STR agreed to conduct optional Cohort 4.

The need for an optional cohort (Cohort 4) will be based upon a review of the safety and tolerability data and any available PK data from Cohorts 1-3. This determination will be undertaken by the STR and will be based on the comparison to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program. Cohort 4, if required, will assess the PK, safety and tolerability of alternative doses and/or dosing via SC and/or IM routes among 20 participants (18 active and 2 active controls).

At a 22 December 2020 STR meeting, it was agreed

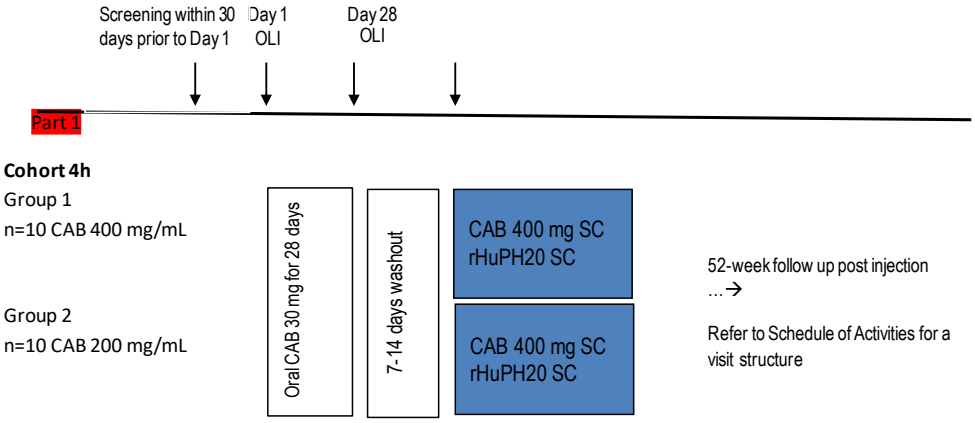
- to conduct Cohort 4 evaluating two Q4W injections of CAB 400 mg/mL 4 weeks apart (n=18, first injection 400 mg IM *gluteus medius* and second injection 200 mg SC) or two Q4W injections of CAB 200 mg/mL 4 weeks apart as active controls (n=2, first injection 400 mg IM *gluteus medius* and second injection 100 mg SC), and
- to reduce the dose of the first injection for the remaining Cohort 3 participants based on interim PK data from Cohorts 1 and 2. Participants yet to receive Injection 1# in Cohort 3 will receive CAB 400 mg given as 1 x 1 mL of CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM lateral thigh injection

Part 1 (Cohort 4b):



Cohort 4b will assess the PK, safety and tolerability of long-acting CAB 400 mg/mL formulation administered subcutaneously (abdominal) CCI [redacted]

Part 1 (Cohort 4h):



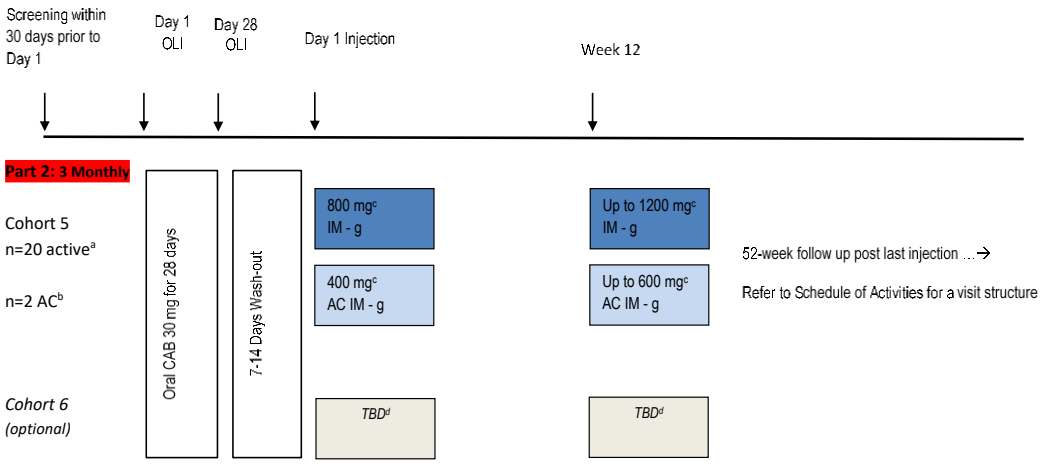
Cohort 4h will assess the PK, safety and tolerability of long-acting CAB 400 mg/mL and CAB 200 mg/mL formulations administered subcutaneously (abdominal) following recombinant human hyaluronidase PH20 (rHuPH20) administration.

Part 2:

Part 2 will commence once data (trough concentrations [Cτ] and Plasma AUC0-t up to and including Week 8 following Injection 1 from all participants in Cohort 1, and any safety and tolerability data available at this time from Cohort 1-3) are reviewed and compared to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3

program. The determination of the dose and dosing schedule will be governed by the STR with the aim of selecting a safe dose predicted to achieve approximately 95% of dosed participants having trough concentrations higher than the Phase 3 benchmark. The dose of the second injection in Cohort 5 will be guided by safety and PK data when ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments.

The requirement for an optional further cohort (Cohort 6) will be based upon a review of the available safety, tolerability, and PK data from Cohorts 1-4 and safety, tolerability and PK data (12 weeks after injection 1) from Cohort 5 and comparison to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program. This determination will be undertaken by the STR. Cohort 6, if required, will assess the PK, safety and tolerability of alternative doses and/or dosing schedule among 22 participants (20 active and 2 active control). Sentinel dosing will also occur for this cohort.



a: active = CAB 400 mg/mL formulation

b: AC = Active control CAB 200 mg/mL formulation

c: Cohort 5 will commence following preliminary analysis once data (Trough concentrations (Cτ) and Plasma AUC (0-τ) data up to and including week 8 data following injection one from all active subjects in Cohort 1, and safety and tolerability from each cohort 1-3) are reviewed and compared to historical data of the CAB 200 mg/mL formulation). The determination of the dose and dosing schedule will be governed by the STR. Further, the first injection in Cohort 5 will not be administered until data on ISRs observed within the first ten days after the first injection for at least 50% of Cohort 4 participants (n=10) have been reviewed by the STR. If pausing criteria due to ISRs are met in Cohort 4, Cohort 5 will be placed on hold until further discussion. The dose of the first injections has been agreed by the STR; the dose of the second injection will be guided by safety and PK data when ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments.

d: The requirement for an optional Cohort 6 will be based upon a review of the safety, tolerability and PK data from Cohorts 1-4 and safety, tolerability and PK data (12 weeks after injection 1 in cohort 5) from cohort 5 and comparison to historical data of the CAB 200 mg/mL formulation. This determination will be undertaken by the STR.

1.3. Schedule of Activities (SoA)

The timing and number of planned study assessments as outlined in the SoA below, including safety and pharmacokinetic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) and to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF. Appendix 8 summarizes permissible procedures during the COVID-19 pandemic (Section 11.8).

1.3.1. Screening Period and Oral Lead-in Phase: All Cohorts

Study Period	**Screening[1]**		**Oral Lead-in[8]**			**Day 29**	**Early withdrawal[10]**	**Washout Period**
			Dosing Days 1-28					
Visit Window	**Within 30 days of oral lead-in**	**Within 5 days of admission to the clinic**	**Day 1**	**Day 2**	**Day 14**	**Within 24 hours of the Day 28 last dose**	**EW**	**7 – 14 days[11]**
Informed Consent	X							
Demographics	X							
Medical / Medication / Drug / Alcohol History	X							
Inclusion/Exclusion Criteria[2]	X		X					
Height, Weight, BMI	X						X	
Physical Exam	X						X	
Vital Signs[3]	X		X	X	X	X	X	
Triplicate 12-Lead ECG[3]	X		X			X	X	
Drug / Alcohol Screen[4]	X		X					
Pregnancy Test[3,4]	X		X		X	X	X	
Testing for SARS-CoV-2	X	X[5]						
Hepatitis B, Hepatitis C Screening	X							
HIV Test	X							
Haematology with differential; Clinical Chemistry Tests; Urinalysis[3,4]	X		X	X	X	X	X	
Coagulation Tests	X					X	X	
Admit to clinic			X[4,5]					

Study Period	**Screening[1]**		**Oral Lead-in[8]**			**Day 29**	**Early withdrawal[10]**	**Washout Period**
			Dosing Days 1-28					
Visit Window	**Within 30 days of oral lead-in**	**Within 5 days of admission to the clinic**	**Day 1**	**Day 2**	**Day 14**	**Within 24 hours of the Day 28 last dose**	**EW**	**7 – 14 days[11]**
Dispense Oral lead-in IP[6]			X					
Administer oral CAB[6]			X	X	X			
Provide dosing diary card			X					
Discharge from clinic				X				
Drug accountability/ pill count/review drug diary				X	X	X	X	
Blood plasma PK sampling[7]			X	X	X	X	X	
AE Assessment[8]			X	X	X	X	X	
Concomitant Medication Review	X		X	X	X	X	X	
Genetic sample[9]			X					

1. Screening may occur over more than one visit but within 30 days of the first dose in the oral lead in phase.
2. Eligibility criteria must be carefully assessed at the Screening visit and confirmed at the Day 1 Oral lead-in phase visit.
3. Prior to administering the first oral dose of CAB, study personnel must verify the following pre-dose assessments to be within normal limits prior to administration: vital signs, triplicate 12-lead ECG, pregnancy test (negative; females of reproductive potential [FRP] only). The results of the Drug/Alcohol screen, haematology with differential, clinical chemistry tests and urinalysis on Day 1 are not required prior to administering the first oral dose of CAB but samples should be drawn/collected prior to CAB administration.
4. Participants may be admitted to the clinic before Day 1 of the Oral Lead-in Phase. They may have some assessments, such as drug/alcohol screen, pregnancy test and haematology/chemistry/urinalysis, done on the day before Day 1.
5. The second test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be performed within 5 days of admission (ideally within 24 hours), and negative results for both tests are required prior to dosing. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. **Where SARS-CoV-2 is circulating in the community**, participants are admitted for the second test for SARS-CoV-2; prior to the second test result being known, they should follow strict infection control procedures (personal protective equipment (PPE)/social distancing) and should be isolated within an area of the unit to avoid exposure to COVID-19 negative participants. Once the second test result is a confirmed negative, they can be released into the unit and follow infection control practices as per unit guidance. **Where SARS-CoV-2 is NOT circulating in the community**, the second test for SARS-CoV-2 may be performed within 5 days of admission to the clinic, and if participants are not admitted, they will be advised to avoid exposure to COVID-19 and self-quarantine until entrance to the unit while awaiting final testing clearance. Sponsor approval is required for site(s) to adopt SARS-CoV-2 testing within 5 days of admission to the clinic if study participants do not remain and isolate within the unit until test results are known.
6. Randomization in Part 1 Cohorts 1-4b to occur on Day 1 prior to oral dosing; randomization in Part 1 Cohort 4h and in Part 2 to occur on Day 1 of the injection phase (prior to the first injection). Oral CAB dosing Days 1 to 28. Day 1, Day 2, and Day 14 doses should be administered in the clinic. The tablet should be taken at approximately the same time each day.

7. PK sampling – On Day 1 (1 h, 2 h, 3 h, 4 h, and 6 h, and in addition for Cohort 5 and Cohort 6 [if conducted] at 8 h, and 12 h) and Day 2 PK between 20 h and 28 h post first oral dose. Day 14 is a pre-dose PK sample. Day 29 assessments should occur between 20 h and 28 h of the last dose on Day 28. A total of 8 PK samples (10 PK samples for Cohorts 5 and 6) will be collected during oral lead-in phase. Please refer to Section 8.5 for permitted PK window for OLI phase.
8. AE assessment will include a brief, symptom-directed physical exam as needed.
9. Genetic sample Day 1 collect the sample at the earliest convenient time after the first dose in the oral lead in phase.
10. If a participant is withdrawn prior to receiving the CAB LA injection, a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB.
11. The washout period may be extended if deemed necessary by the investigator and sponsor.

1.3.2. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow- up: Part 1 Cohorts 1-4

		Injection Phase															Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 /EW[1]**
Procedures		Pre-dose[2]	1 h	2 h	8 h	24 h																		
Permitted window for PK collection		Within 1 h prior to dosing	±15 min	±30 min	±1 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±1 day	±1 day	±1 day		±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Interim Medical /Medication/ Drug / Alcohol History		X																						
Pregnancy Test[3,8]		X											X				X	X	X			X	X	X
Triplicate 12-Lead ECG		X		X																				
Testing for SARS-CoV-2	X[3]										X[3]													

		Injection Phase															Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 /EW[1]**
Procedures		Pre-dose[2]	1 h	2 h	8 h	24 h																		
HIV Test[3,9]		X															X							X
Haematology; Clinical Chemistry; Urinalysis[3]		X									X		X				X	X	X			X	X	X
Coagulation Tests[3]		X																						X
Brief Physical Exam		X				X					X						X	X	X			X	X	X
Weight																	X				X			X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			X	X	X
Admit to clinic		X[3]																						
Administer CAB 400 mg/mL or CAB 200 mg/mL LA[4]		X																						

		Injection Phase															Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 /EW[1]**
Procedures		Pre-dose[2]	1 h	2 h	8 h	24 h																		
CCI																								
Provide diary card regarding injection site reactions		X																						
Discharge from the clinic											X													
Injection site reaction assessment[10]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
AE Assessment[6]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Concomitant Medication Review			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Blood plasma PK Sampling[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

1. Participants will have PK monitoring up to and including Week 52 post last injection. Participants with undetectable CAB concentrations before this timepoint will be deemed to have completed follow up and return to the clinic for a last study visit at which activities specified for the Week 52/EW visit will be performed. Participants who withdraw from the study before week 52 post last injection will be asked to return to the site for a withdrawal visit.
2. On Day 1, study personnel must verify the following pre-dose assessments to be within normal limits prior to injection: triplicate 12-lead ECG, brief physical exam, vital signs, pregnancy test (negative; FRP only), AE assessment, and concomitant medication assessment. If a clinical abnormality, clinically significant AE, or prohibited medication that precludes injection is observed/recorded, the medical monitor must be contacted for further instruction.
3. Participants may be admitted to the clinic before Injection 1 Day 1 and Injection 2 Day 1. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. **Where SARS-CoV-2 is circulating in the community**, participants should have one SARS-CoV-2 test approximately 1 week prior to admission to the clinic. A second test would be done upon admission; prior to the test result being known, participants should follow strict infection control procedures (PPE/social distancing) and should be isolated within an area of the unit to avoid exposure to COVID-19 negative participants until the test result is known. Once the test result is a confirmed negative, they can be released into the unit and follow infection control practices as per unit guidance. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. A further test will be done on Day 8 upon discharge from the clinic. **Where SARS-CoV-2 is NOT circulating in the community**, SARS-CoV-2 testing prior to dosing may be performed within 5 days of admission to the clinic, and if participants are not admitted, they will be advised to avoid exposure to COVID-19 and self-quarantine until entrance to the unit while awaiting final testing clearance. Sponsor approval is required for site(s) to adopt SARS-CoV-2 testing within 5 days of admission to the clinic if study participants do not remain and isolate within the unit until test results are known. A further test is NOT required on Day 8 upon discharge from the clinic. Participants may have some assessments, such as HIV test, drug/alcohol screen, pregnancy test, haematology/chemistry/urinalysis and coagulation tests, done on the day before Injection 1 Day 1 and Injection 2 Day 1.
4. CAB 400 mg/mL - injection 1 loading dose of 600 mg and injection 2 400 mg; Cohort 1 Q4WM IM – via *gluteus medius*, Cohort 2 Q4W SC and Cohort 3 Q4W IM – lateral thigh/*vastus lateralis*. Cohort 4 dose and dosing schedule determination by STR based upon data from cohorts 1-3 and historical CAB 200 mg/mL data. Active controls will be administered CAB 200 mg/mL formulation matched on dose or volume to the CAB 400 mg/mL participants in Cohorts 1 and 3 and Cohort 2, respectively.
5. CCI [redacted]
6. AE assessment will include a brief, symptom-directed physical exam as needed.
7. A total of 36 PK samples will be collected through the injection phase and Follow-up.
8. Urine or plasma pregnancy testing to be performed pre-injection where relevant
9. HIV antibody test (either a laboratory or point of care test).
10. See Section 8.2.6.

1.3.3. CAB 400 mg/mL LA Injection Phase and Follow- up: Part 1 Cohort 4b

			Injection Phase																Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day -1**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 4**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day -1**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 4**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures			Pre-dose[2]	1 h	2 h	8 h	24 h																			
Permitted window for PK collection			Within 1 h prior to dosing	±15 min	±30 min	±1 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±1 day	±1 day	±1 day		±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Interim Medical /Medication/ Drug / Alcohol History			X																							
Pregnancy Test[3,8]			X												X				X	X	X			X	X	X
Triplicate 12-Lead ECG			X		X																					
Testing for SARS-CoV-2	X[3]												X[3]													

			Injection Phase																Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day -1**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 4**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day -1**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 4**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures			Pre-dose[2]	1 h	2 h	8 h	24 h																			
HIV Test[3,9]			X																X							X
Haematology; Clinical Chemistry; Urinalysis[3]			X										X		X				X	X	X			X	X	X
Coagulation Tests[3]			X																							X
Brief Physical Exam			X				X						X						X	X	X			X	X	X
Weight																			X				X			X
Vital Signs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			X	X	X
Admit to clinic			X[3]																							
Administer CAB 400 mg/mL[4]			X																							
CCI																										

			Injection Phase																Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day -1**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 4**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day -1**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 4**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures			Pre-dose[2]	1 h	2 h	8 h	24 h																			
CCI [redacted] CCI																										
Provide diary card regarding injection site reactions			X																							
Discharge from the clinic													X													
Injection site reaction assessment[10]				X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
AE Assessment[6]				X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Concomitant Medication Review				X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

			Injection Phase																Follow-up Phase							
Injection 1	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day -1**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 4**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	***Inj 1 Day 28 – proceed to Inj 2 Day 1***	**Follow-up post last injection**							
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day -1**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 4**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	***Inj 2 Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures			Pre-dose[2]	1 h	2 h	8 h	24 h																			
Blood plasma PK Sampling[7]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

1. Participants will have PK monitoring up to and including Week 52 post last injection. Participants with undetectable CAB concentrations before this timepoint will be deemed to have completed follow up and return to the clinic for a last study visit at which activities specified for the Week 52/EW visit will be performed. Participants who withdraw from the study before week 52 post last injection will be asked to return to the site for a withdrawal visit.
2. On Day 1, study personnel must verify the following pre-dose assessments to be within normal limits prior to injection: triplicate 12-lead ECG, brief physical exam, vital signs, pregnancy test (negative; FRP only), AE assessment, and concomitant medication assessment. If a clinical abnormality, clinically significant AE, or prohibited medication that precludes injection is observed/recorded, the medical monitor must be contacted for further instruction.
3. Participants may be admitted to the clinic before Injection 1 Day 1 and Injection 2 Day 1. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. **Where SARS-CoV-2 is circulating in the community**, participants should have one SARS-CoV-2 test approximately 1 week prior to admission to the clinic. A second test would be done upon admission; prior to the test result being known, participants should follow strict infection control procedures (PPE/social distancing) and should be isolated within an area of the unit to avoid exposure to COVID-19 negative participants until the test result is known. Once the test result is a confirmed negative, they can be released into the unit and follow infection control practices as per unit guidance. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. A further test will be done on Day 8 upon discharge from the clinic. **Where SARS-CoV-2 is NOT circulating in the community**, SARS-CoV-2 testing prior to dosing may be performed within 5 days of admission to the clinic, and if participants are not admitted, they will be advised to avoid exposure to COVID-19 and self-quarantine until entrance to the unit while awaiting final testing clearance. Sponsor approval is required for site(s) to adopt SARS-CoV-2 testing within 5 days of admission to the clinic if study participants do not remain and isolate within the unit until test results are known. A further test is NOT required on Day 8 upon discharge from the clinic. Participants may have some assessments, such as HIV test, drug/alcohol screen, pregnancy test, haematology/chemistry/urinalysis and coagulation tests, done on the day before Injection 1 Day 1 and Injection 2 Day 1.
4. CAB 400 mg/mL - injection 1 loading dose of 300 mg and injection 2 300 mg Q4W SC.

5. CCI [redacted]
6. AE assessment will include a brief, symptom-directed physical exam as needed.
7. A total of 38 PK samples will be collected through the injection phase and Follow-up.
8. Urine or plasma pregnancy testing to be performed pre-injection where relevant
9. HIV antibody test (either a laboratory or point of care test).
10. See Section 8.2.6.
11. See Section 6.1.2. CCI [redacted]
12. Participants will be asked to describe any preference for Injection 1 or 2 and provide reasons for their preference (if any). The CCI [redacted] will be completed 4 weeks after Injection 2.

1.3.4. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow- up: Part 1 Cohort 4h (CAB 400 mg/mL or CAB 200 mg/mL with rHuPH20)

		Injection Phase																	Follow-up Phase							
Injection	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj Day 1**						**Inj Day 2**	**Inj Day 3**	**Inj Day 4**	**Inj Day 5**	**Inj Day 6**	**Inj Day 7**	**Inj Day 8**	**Inj Day 10**	**Inj Day 14**	**Inj Day 17**	**Inj Day 22**	***Inj Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures		Pre-dose[2]	1 h	2 h	4 h	8 h	12 h	24 h																			
Permitted window for PK collection		Within 1 h prior to dosing	±15 min	±30 min	±1 h	±1 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±1 day	±1 day	±1 day		±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Interim Medical /Medication/ Drug / Alcohol History		X																									
Pregnancy Test[3,8]		X														X				X	X	X			X	X	X
12-Lead ECG		X		X				X	X	X	X	X	X	X	X												
Testing for SARS-CoV-2	X[3]													X[3]													
HIV Test[3,9]		X																		X							X
Haematology; Clinical Chemistry; Urinalysis[3]		X							X[13]		X[13]			X		X				X	X	X			X	X	X
Coagulation Tests[3]		X																									X

		Injection Phase																	Follow-up Phase							
Injection	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj Day 1**						**Inj Day 2**	**Inj Day 3**	**Inj Day 4**	**Inj Day 5**	**Inj Day 6**	**Inj Day 7**	**Inj Day 8**	**Inj Day 10**	**Inj Day 14**	**Inj Day 17**	**Inj Day 22**	***Inj Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures		Pre-dose[2]	1 h	2 h	4 h	8 h	12 h	24 h																			
Brief Physical Exam		X						X						X						X	X	X			X	X	X
Weight																				X				X			X
Vital Signs		X	X	X		X		X	X		X	X	X	X	X	X	X	X		X	X	X			X	X	X
Admit to clinic		X[3]																									
Administer rHuPH20 followed by CAB 400 mg/mL or CAB 200 mg/mL[4]		X																									
CCI																											
Provide diary card regarding injection site reactions		X																									
Discharge from the clinic														X[12]													
Injection site reaction assessment[10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment[6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		Injection Phase																	Follow-up Phase							
Injection	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj Day 1**						**Inj Day 2**	**Inj Day 3**	**Inj Day 4**	**Inj Day 5**	**Inj Day 6**	**Inj Day 7**	**Inj Day 8**	**Inj Day 10**	**Inj Day 14**	**Inj Day 17**	**Inj Day 22**	***Inj Day 28 – proceed to follow-up***	**Week 4/ Day 28**	**Week 8**	**Week 12**	**Week 20**	**Week 28**	**Week 36**	**Week 44**	**Week 52 / EW[1]**
Procedures		Pre-dose[2]	1 h	2 h	4 h	8 h	12 h	24 h																			
Concomitant Medication Review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Blood plasma PK Sampling[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Blood plasma sampling (rHuPH20 immunogenicity)[11]		X														X				X							

1. Participants will have PK monitoring up to and including Week 52 post last injection. Participants with undetectable CAB concentrations before this timepoint will be deemed to have completed follow up and return to the clinic for a last study visit at which activities specified for the Week 52/EW visit will be performed. Participants who withdraw from the study before week 52 post last injection will be asked to return to the site for a withdrawal visit.
2. On Day 1, study personnel must verify the following pre-dose assessments to be within normal limits prior to injection: ECG, brief physical exam, vital signs, pregnancy test (negative; FRP only), AE assessment, and concomitant medication assessment. If a clinical abnormality, clinically significant AE, or prohibited medication that precludes injection is observed/recorded, the medical monitor must be contacted for further instruction.
3. Participants may be admitted to the clinic before Injection Day 1. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. **Where SARS-CoV-2 is circulating in the community**, participants should have one SARS-CoV-2 test approximately 1 week prior to admission to the clinic. A second test would be done upon admission; prior to the test result being known, participants should follow strict infection control procedures (PPE/social distancing) and should be isolated within an area of the unit to avoid exposure to COVID-19 negative participants until the test result is known. Once the test result is a confirmed negative, they can be released into the unit and follow infection control practices as per unit guidance. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. A further test will be done upon discharge from the clinic (between Day 5 and Day 8 – see footnote 12). **Where SARS-CoV-2 is NOT circulating in the community**, SARS-CoV-2 testing prior to dosing may be performed within 5 days of admission to the clinic, and if participants are not admitted, they will be advised to avoid exposure to COVID-19 and self-quarantine until entrance to the unit while awaiting final testing clearance. Sponsor approval is required for site(s) to adopt SARS-CoV-2 testing within 5 days of admission to the clinic if study participants do not remain and isolate within the unit until test results are known. A further test is NOT required upon discharge from the clinic. Participants may have some assessments, such as HIV test, drug/alcohol screen, pregnancy test, haematology/chemistry/urinalysis and coagulation tests, done on the day before Injection Day 1.

4. Randomization to occur on Day 1 prior to the injection. CAB 400 mg/mL and CAB 200 mg/mL - injection dose of 400 mg SC. Participants receive 5000 U of rHuPH20 followed by CAB 200 mg/mL or 400 mg/mL formulation via a subcutaneous injection via a single butterfly needle. Due to a dead volume of 0.331 mL in the butterfly tube, a larger volume of CAB 200 mg/mL or 400 mg/mL formulation will be required. Therefore, 1.4 mL of CAB 400 mg/mL and 2.4 mL of CAB 200 mg/mL for injection will be used, and the exact doses of CAB 400 mg/mL and CAB 200 mg/mL administered will be 427.6 mg (1.069 mL) and 413.8 mg (2.069 mL), respectively.
5. CCI [redacted]
6. AE assessment will include a brief, symptom-directed physical exam as needed.
7. A total of 25 PK samples will be collected through the injection phase and Follow-up.
8. Urine or plasma pregnancy testing to be performed pre-injection where relevant
9. HIV antibody test (either a laboratory or point of care test).
10. See Section 8.2.6.
11. Plasma samples (K3-EDTA) for optional rHuPH20 immunogenicity analysis at pre-dose, Day 14 and Day 28. Analysis will be event-driven, (e.g. only if there are safety observations suggestive of an immune-mediated event).
12. Participants may be discharged from the clinic between Injection Day 5 and Injection Day 8. If participants are discharged prior to Injection Day 8, they would return to the clinic for assessments on the days specified in the SoA. **Where SARS-CoV-2 is circulating in the community,** participants should have a SARS-CoV-2 test on the day they are being discharged from the clinic.
13. No urinalysis needs to be performed on Days 3 and 5.

1.3.5. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow- up: Part 2 Cohorts 5 and 6

		Injection Phase																		Follow-up Phase			
Injection 1[10]	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	**Inj 1 Week 4**	**Inj 1 Week 6**	**Inj 1 Week 8**	**Inj 1 Week 10**	***Inj 1 Week 12 – proceed to Injection 2 Day 1***	**Follow-up post last injection**			
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	**Inj 2 Week 4**	**Inj 2 Week 6**	**Inj 2 Week 8**	**Inj 2 Week 10**	***Inj 2 Week 12 – proceed to follow-up***	**Week 12**	**Week 24**	**Week 40**	**Week 52/EW[1]**
		Pre-dose[2]	1 h	2 h	8 h	24 h																	
Permitted window for PK collection		Within 1 h prior to dosing	±15 min	±30 min	±1 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±2 h	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day		±3 days	±3 days	±3 days	±3 days
Interim Medical / Medication/ Drug / Alcohol History		X																					
Pregnancy Test[3,8]		X											X				X				X	X	X	X
Triplicate 12-Lead ECG		X		X		X	X	X	X	X	X	X												

		Injection Phase																		Follow-up Phase			
Injection 1[10]	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	**Inj 1 Week 4**	**Inj 1 Week 6**	**Inj 1 Week 8**	**Inj 1 Week 10**	***Inj 1 Week 12 – proceed to Injection 2 Day 1***	**Follow-up post last injection**			
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	**Inj 2 Week 4**	**Inj 2 Week 6**	**Inj 2 Week 8**	**Inj 2 Week 10**	***Inj 2 Week 12 – proceed to follow-up***	**Week 12**	**Week 24**	**Week 40**	**Week 52/EW[1]**
		Pre-dose[2]	1 h	2 h	8 h	24 h																	
Testing for SARS-CoV-2	X[3]										X[3]												
HIV Test[3,9]		X																			X			X
Haematology; Clinical Chemistry; Urinalysis[3]		X				X[11]	X[11]	X[11]		X		X	X		X	X		X			X	X	X	X
Coagulation Tests[3]		X													X									X
Brief Physical Exam		X				X			X			X			X		X				X		X	X
Weight		X																			X	X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Admit to clinic		X[3]																						

		Injection Phase																		Follow-up Phase			
Injection 1[10]	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	**Inj 1 Week 4**	**Inj 1 Week 6**	**Inj 1 Week 8**	**Inj 1 Week 10**	***Inj 1 Week 12 – proceed to Injection 2 Day 1***	**Follow-up post last injection**			
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	**Inj 2 Week 4**	**Inj 2 Week 6**	**Inj 2 Week 8**	**Inj 2 Week 10**	***Inj 2 Week 12 – proceed to follow-up***	**Week 12**	**Week 24**	**Week 40**	**Week 52/EW[1]**
		Pre-dose[2]	1 h	2 h	8 h	24 h																	
Administer CAB 400 mg/mL or CAB 200 mg/mL LA[4]		X																					
CCI																							
Provide diary card regarding injection site reactions		X																					
Discharge from the clinic											X[10]												
Injection site reaction assessment[12]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

		Injection Phase																		Follow-up Phase			
Injection 1[10]	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 1 Day 1**				**Inj 1 Day 2**	**Inj 1 Day 3**	**Inj 1 Day 5**	**Inj 1 Day 6**	**Inj 1 Day 7**	**Inj 1 Day 8**	**Inj 1 Day 10**	**Inj 1 Day 14**	**Inj 1 Day 17**	**Inj 1 Day 22**	**Inj 1 Week 4**	**Inj 1 Week 6**	**Inj 1 Week 8**	**Inj 1 Week 10**	***Inj 1 Week 12 – proceed to Injection 2 Day 1***	**Follow-up post last injection**			
Injection 2	**Within 7 and/or 5 days of admission to the clinic[3]**	**Inj 2 Day 1**				**Inj 2 Day 2**	**Inj 2 Day 3**	**Inj 2 Day 5**	**Inj 2 Day 6**	**Inj 2 Day 7**	**Inj 2 Day 8**	**Inj 2 Day 10**	**Inj 2 Day 14**	**Inj 2 Day 17**	**Inj 2 Day 22**	**Inj 2 Week 4**	**Inj 2 Week 6**	**Inj 2 Week 8**	**Inj 2 Week 10**	***Inj 2 Week 12 – proceed to follow-up***	**Week 12**	**Week 24**	**Week 40**	**Week 52/EW[1]**
		Pre-dose[2]	1 h	2 h	8 h	24 h																		
AE Assessment[6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Blood plasma PK Sampling[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

1. Participants will have PK monitoring up to and including Week 52 post last injection. Participants with undetectable CAB concentrations before this timepoint will be deemed to have completed follow up and return to the clinic for a last study visit at which activities specified for the Week 52/EW visit will be performed. Participants who withdraw from the study before Week 52 post last injection will be asked to return to the site for a withdrawal visit.
2. On Day 1, study personnel must verify the following pre-dose assessments to be within normal limits prior to injection: triplicate 12-lead ECG, brief physical exam, vital signs, pregnancy test (negative; FRP only), AE assessment, and concomitant medication assessment. If a clinical abnormality, clinically significant AE, or prohibited medication that precludes injection is observed/recorded, the medical monitor must be contacted for further instruction.
3. Participants may be admitted to the clinic before Injection 1 Day 1 and Injection 2 Day 1. Any new Phase I unit participating in this study will adhere to the following SARS-CoV-2 testing procedures. **Where SARS-CoV-2 is circulating in the community**, participants should have one SARS-CoV-2 test approximately 1 week prior to admission to the clinic. A second test would be done upon admission; prior to the test result being known, participants should follow strict infection control procedures (PPE/social distancing) and should be isolated within an area of the unit to avoid exposure to COVID-19 negative participants until the test result is known. Once the test result is a confirmed negative, they can be

released into the unit and follow infection control practices as per unit guidance. A further test will be done on Day 8 upon discharge from the clinic. **Where SARS-CoV-2 is NOT circulating in the community**, SARS-CoV-2 testing prior to dosing may be performed within 5 days of admission to the clinic, and if participants are not admitted, they will be advised to avoid exposure to COVID-19 and self-quarantine until entrance to the unit while awaiting final testing clearance. Sponsor approval is required for site(s) to adopt SARS-CoV-2 testing within 5 days of admission to the clinic if study participants do not remain and isolate within the unit until test results are known. A further test is NOT required on Day 8 upon discharge from the clinic. Participants may have some assessments, such as HIV test, drug/alcohol screen, pregnancy test, haematology/chemistry/urinalysis and coagulation tests, done on the day before Injection 1 Day 1 and Injection 2 Day 1.

4. Randomization in Part 2 to occur on Day 1 prior to the first injection. CAB 400 mg/mL – (dose determination by SRT following cohort 1) injection via *gluteus medius* on Day 1 and Week 12 (± 3 days for second injection). Active control participants will receive CAB 200 mg/mL matched on volume to CAB 400 mg/mL participants.
5. CCI [redacted]
6. AE assessment will include a brief, symptom-directed physical exam as needed.
7. A total of 40 PK samples will be collected through the injection phase and Follow-up.
8. Urine or plasma pregnancy testing to be performed pre-injection where relevant.
9. HIV antibody test (either a laboratory or point of care test).
10. The first four participants enrolled in Cohort 5 and Cohort 6 (if conducted) will serve as sentinel participants with three receiving CAB 400 mg/mL formulation and one receiving active control (based on 3:1 randomization). These sentinel participants will be followed clinically for 10 days after Injection 1 (including a stay in the clinic until Day 8) to monitor the emergence of adverse events and other assessments specified for Days 1 to 10. If there are no significant safety concerns upon 10-day review of safety data for the sentinel participants, the remaining participants will subsequently be treated with either CAB 400 mg/mL formulation (n=17) or AC (n=1). Dose administration for these remaining participants (n=18) will be staggered: a further 7 participants will have their first injection and following a review of safety data from the initial 7 participants 10 days post first injection, the remaining 11 participants will receive their first injection. All participants will remain in the clinic for 7 days following each injection.
11. No urinalysis needs to be performed on these Days 2, 3 and 5.
12. See Section 8.2.6.

2. INTRODUCTION

2.1. Study Rationale

Long acting injectable versions of antiretrovirals are being developed to enable therapy with infrequent dosing schedule. These therapeutic options hold great promise for future treatment and represent an emerging paradigm for the treatment of HIV infection. CAB is a potent integrase inhibitor that possesses attributes that allow formulation and delivery as a long-acting parenteral product.

A two-drug regimen of CAB (200 mg/mL formulation) LA plus RPV LA offers many potential advantages over daily oral regimens including infrequent dosing that decreases the daily reminder to patients of their HIV status, better tolerability, less likely to develop viral resistance due to intermittent compliance. Results from several on-going Phase 2 and 3 studies have demonstrated the efficacy of a two-drug regimen of CAB + RPV LA as maintenance therapy.

GSK1265744 CAB (400 mg/mL formulation) LA, a more concentrated formulation, may allow the administration of a higher dose of CAB potentially affording a longer interval between injections or administration at different sites (SC or IM lateral thigh) such that self-administration would be possible. This may increase the convenience of long acting regimens including CAB LA and may result in better adherence to therapy and positively impact treatment outcomes and acceptability.

This is a double-blind (sponsor-unblind), randomized, active control, Phase 1 study to assess the safety, tolerability and pharmacokinetic profile of GSK1265744 CAB 400 mg/mL formulation in healthy adult participants. The study will evaluate the relative bioavailability of GSK1265744 CAB 400 mg/mL formulation administered IM (*vastus lateralis*) and SC with CAB 400 mg/mL administered IM (*gluteus medius*) and with the historical data from the CAB 200 mg/mL formulation. Comparisons of the trough concentrations (Cτ) and plasma exposures (AUC0-t) will be made and these data will be used to bridge to future Phase 2b studies in an HIV patient population.

2.2. Background

It is estimated that approximately 38 million people are currently living with HIV/Acquired Immunodeficiency Syndrome (AIDS) and that the worldwide epidemic continues to grow at a rate of 1.8 million new infections and cause 0.9 million deaths per year [UNAIDS, 2019]. The current paradigm in the treatment of HIV involves life-long therapy with multiple antiretrovirals. This dependency on medical therapy requires a need for continuous improvement on the durability, tolerability and convenience of all antiretroviral classes.

As of 18 October 2020, 40 CAB clinical studies (32 ViiV Healthcare-sponsored) have been initiated; 25 Phase I/IIa studies (including several proof-of-concept studies, this Phase I study with the CAB 400 mg/mL formulation (212482) and a thigh PK study (208832), 2 prophylactic studies in HIV negative PrEP participants), 4 Phase IIb studies in HIV-infected participants (1 in adolescents) and 1 Phase IIb in HIV negative PrEP

adolescent participants, 4 Phase III studies (including 2 studies in HIV-negative PrEP participants and 2 studies in HIV-infected participants), 4 Phase IIIb studies in HIV-infected participants, and 1 study is a compassionate use programme (treating physician as sponsor). An estimated 7143 people (including HIV-positive participants and HIV-negative PrEP participants, healthy volunteers including participants from the ongoing thigh PK study and this study, 212482) have received CAB to date in ViiV Healthcare sponsored and supported studies (included blinded studies), of whom 6279 have received the LA formulation [CAB IB 2021 ViiV Healthcare Document Number RPS-CLIN-004375].

The primary efficacy analysis of 201585 (ATLAS) and 201584 (FLAIR) demonstrated that once-monthly CAB + RPV was non-inferior to continuing oral combination antiretroviral therapy (CAR) in maintaining virologic suppression in HIV-1 infected subjects at Week 48 (median Cτ of 2.99 μg/mL from FLAIR and ATLAS studies combined), with few subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot Algorithm in either group for the ITT-E and PP populations. The combination of CAB + RPV LA was generally well tolerated. No relationships between CAB concentrations and QTc changes, ALT changes from baseline or changes in bilirubin were observed in the studies 210585 (ATLAS) and 201584 (FLAIR). Currently NDAs are under review by regulators for monthly administration of CAB + RPV LA IM [ATLAS, 2019 and FLAIR, 2019].

In the Phase 2 and Phase 3 studies of CAB LA + RPV LA has been healthcare provider (HCP) administered intramuscular injections into the *gluteus medius* muscle. GSK1265744 CAB (400 mg/mL formulation) LA; a more concentrated formulation, may allow the administration of a higher dose of CAB potentially affording a longer interval between injections or administration at different sites (SC or IM lateral thigh) such that self-administration would be possible. This may increase the convenience of long acting regimens including CAB LA and may result in better adherence to therapy and positively impact treatment outcomes and acceptability. HCPs will administer the injections via these alternate sites during this study. In future studies self-administration of CAB 400 mg/mL will be evaluated.

Recombinant human hyaluronidase (rHuPH20) is a highly purified, soluble form of the naturally occurring human hyaluronidase enzyme. When other drugs are injected with hyaluronidase, dispersion of the co-injected drugs is enhanced. By depolymerizing hyaluronan, hyaluronidase temporarily facilitates dispersion by reducing the viscosity of interstices. The permeability barrier in these tissues is restored to pre-injection levels within 24 to 48 hours after injection of hyaluronidase. rHuPH20 is the active ingredient of

- the commercial product *Hylenex*®, hereafter referred to as HYLENEX recombinant (hyaluronidase human injection), which obtained regulatory agency approval for marketed use in the United States in December 2005, and
- ENHANZE™ Drug Product (EDP), which is suitable for early-stage clinical studies, allows preparation of drug + rHuPH20 formulation on-site at clinical pharmacies and is used in this study.

As of 15 November 2020, 1,592 subjects were exposed to HYLENEX and other rHuPH20 drug products in 30 clinical studies conducted under Investigational New Drug (IND) 66,888 or in post-marketing Phase 4 studies [rHuPH20 IB, 2021]. In addition to these studies, a large clinical safety database exists for rHuPH20 as a tissue permeability enhancer co-administered with several approved products in the US and/or European Union [rHuPH20 IB, 2021].

In this study, the relative bioavailability will be assessed by comparing the week 4 and 8 trough concentrations after IM (*vastus lateralis*) or SC administration of CAB 400 mg/mL formulation with trough concentration after IM (*gluteus medius*) administration of CAB 400 mg/mL and also with the phase 3 (CAB 200 mg/mL) trough concentration benchmark. CCI [redacted] Cohort 4h will assess PK, safety and tolerability among participants receiving CAB with rHuPH20.

2.3. Benefit/Risk Assessment

This section outlines the risk assessment and mitigation strategy for this protocol.

More detailed information about the known and expected risks and expected adverse events of GSK1265744 CAB (200 mg/mL and 400 mg/mL formulations) LA may be found in the Investigator's Brochure [CAB IB 2021 ViiV Healthcare Document Number RPS-CLIN-004375].

The main safety concern for this study with GSK1265744 CAB (400 mg/mL formulation) LA relate to injection site reactions as this is a new formulation and there are limited data regarding administration of CAB 200 mg/mL via alternative injection sites other than via the *gluteus medius*. Compared to the current CAB 200 mg/mL formulation, the CAB 400 mg/mL formulation includes a different wetting agent; Poloxamer 338. Poloxamer 338 is a component of the rilpivirine LA formulation. The concentration of P338 within the CAB 400 mg/mL formulation will be similar to the RPV formulation used in Phase 2b and 3 studies and will be less than the concentration used in the GLP toxicity and safety studies of RPV (50 mg/mL) [RPV IB, 2020]. The CAB 400 mg/mL formulation containing Poloxamer 338, was tested in a GLP rat study to assess potential systemic toxicity of the new formulation including the novel excipient Poloxamer 338 and was found to be generally well tolerated [CAB IB 2021 ViiV Healthcare Document Number RPS-CLIN-004375].

The CAB 400 mg/mL formulation will be administered by HCPs in a clinic setting and participants will remain in clinic

- for 24 hours (Cohorts 1, 2 and 3), or
- until Day 8 (as per protocol amendments 4 and 5; Cohorts 4, 4b, 5 and 6 [if conducted]) following each injection, or
- until between Day 5 and Day 8 following the injection in Cohort 4h.

Since CAB has not been administered with rHuPH20 in humans before and to assess safety in Cohort 4h, the first two participants enrolled in each group will serve as sentinel

participants. These sentinel participants will be followed clinically for 10 days after dose administration to monitor the emergence of adverse events. Assuming that there are no significant safety concerns upon 10-day review of safety data (e.g. vital signs, ECGs, and adverse events) for these sentinel participants, the remaining participants will be treated with either CAB 400 mg/mL formulation with rHuPH20 (n=8) or CAB 200 mg/mL formulation with rHuPH20 (n=8) according to randomization schedules.

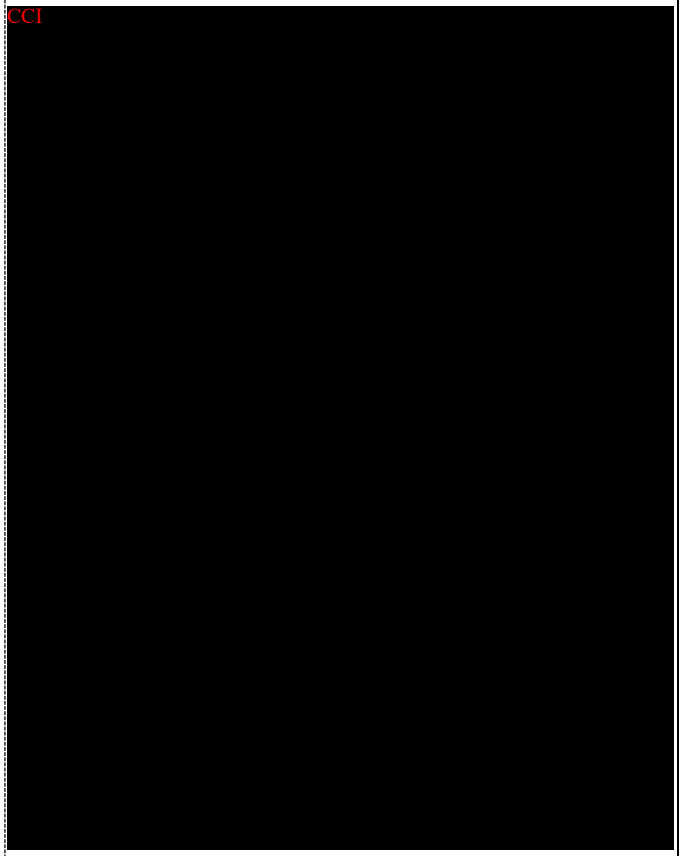
To minimize the risk of higher doses/volumes of CAB, a sentinel dosing strategy will be utilized in Cohorts 5 and 6. Sentinel participants will be followed clinically for 10 days after dose administration and if there are no significant safety concerns upon a 10-day review of safety data, the remaining participants will be dosed with either CAB 400 mg/mL or CAB 200 mg/mL. Dose administration for these remaining participants (n=18) will be staggered:

- A further 7 participants will have their first injection.
- Following a review of safety data from these 7 participants (10 days post first injection), the remaining 11 participants will receive their first injection.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product (IP) CAB [GSK 1265744]	
Drug Induced Liver Injury (DILI)	A small proportion of participants in the CAB program to date (total exposure approximately 1909 people; 3640 person years to 31 December 2018) have developed transaminitis (elevated liver transaminases characterised by predominant alanine aminotransferase (ALT) elevation). In most participants, transient transaminitis was explained by viral hepatitis infection. In a small number of participants, there was not an alternative explanation, suggesting a mild form of drug induced liver injury (DILI) without hepatic dysfunction, which resolved upon withdrawal of treatment with CAB. All six participants with suspected DILI identified in HIV treatment/ drug-drug interaction (DDI) studies, were received oral CAB, as of 13 January 2019.	*Exclusion criteria (Section 5.2) will prohibit participants with i) an elevated ALT >1.5x ULN or ii) a bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35 or iii) a current or chronic history of liver disease, or known hepatic or biliary abnormalities from participation in the study* *A 4-week oral lead-in Phase is being implemented in this study, where all participants will receive oral CAB prior to the administration of IM CAB to assess individual safety and tolerability* *Liver transaminases (ALT and AST) will be monitored throughout this study (refer to SoA) and the liver chemistry stopping criteria will be adopted (Section 7.1.1).* *Sentinel dosing in Cohorts 5 & 6 and staggered dosing is included in Cohorts 5 & 6* *Additional liver biochemistry monitoring is included during the injection phase.* *If any of the stopping criteria related to liver biochemistry are met in Cohorts 5 or 6 further dosing will be paused pending VSLC review (see Section 7.1).*
Effects in late stage pregnancy seen in non-clinical studies	In animal reproduction studies, CAB when administered to rats at > 30 times the systemic exposure at the maximum recommended oral human dose (MRHD) of 30 mg during organogenesis through delivery, had adverse effects on labor and delivery that may be related to a delay in the onset of parturition, resulting in increased fetal mortality (stillbirths) and neonatal deaths immediately after birth. The clinical significance of these finding in humans is unknown.	*As a routine precaution, pregnant women are excluded from participation in this study and females of reproductive potential (FRP) are required to adopt highly reliable means of contraception during participation and throughout the long term follow up phase of this study following exposure to CAB LA.* *FRP are also required to undergo regular pregnancy testing throughout study conduct to enable early discontinuation of CAB LA if pregnancy is identified.*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product (IP) CAB [GSK 1265744]	
Potential effects in women exposed to dolutegravir during conception and early pregnancy	Preliminary findings from an unscheduled analysis of a birth outcomes surveillance study conducted in Botswana and presented in May 2018 showed a higher than expected number of neural tube defects (NTDs) among newborns whose mothers were exposed to dolutegravir (DTG)-based ART at conception. The final pre-scheduled results from the Tsepamo study show that the estimated prevalence of NTDs with DTG exposure at conception has decreased in magnitude from 0.94% to 0.19%; 7 cases of NTDs were reported in 3,591 deliveries (0.19%) to mothers taking DTG-containing regimens at the time of conception compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-DTG-containing regimens at the time of conception. In the same study, no increased risk of NTDs was reported in women who started DTG during pregnancy: 2 out of 4,448 deliveries (0.04%) to mothers who started DTG during pregnancy had an NTD, compared with five out of 6,748 deliveries (0.07%) to mothers who started non-DTG-containing regimens during pregnancy. A causal relationship of these events to the use of DTG has not been established. The incidence of NTDs in the general population ranges from 0.5-1 case per 1,000 live births. As NTDs occur within the first 4 weeks of fetal development (at which time the neural tubes are sealed) this potential risk would concern women exposed to DTG at the time of conception and in early pregnancy. The clinical relevance of either of these findings in relation to CAB use is unknown	*As a routine precaution, pregnant women are excluded from participation in clinical trials of CAB at this time and females of reproductive potential (FRP) are required to adopt highly reliable means of contraception during participation and throughout long term follow up phases of studies after exposure to CAB and RPV LA.* *Females of reproductive potential also undergo regular pregnancy testing throughout study conduct to enable early discontinuation of study drugs once pregnancy is identified. However, it should be noted that CAB concentration could remain for prolonged periods despite discontinuation of CAB LA.*
Injection Site Reactions (ISRs)	With the current formulation of CAB 200 mg/mL clinical, experience to date has demonstrated ISRs occur in the majority of exposed participants treated with CAB LA but are generally CCI (Grade 1) or CCI (Grade 2) and include events of pain, tenderness, erythema, or nodule formation of several days' duration (median duration for individual events <1 week). Volumes up to 1 mL and 3 mL have been administered as single SC and IM injections	*Administration advice will be given to minimize risk of poor administration technique giving rise to injection site reactions. Similarly, the lateral thigh (vastus lateralis) has a lack of significant vasculature or nerves that could lead to complications of injections via this route. Study 208832 will evaluate the administration of CAB 200 mg/mL and RPV via the lateral thigh route and may*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product (IP) CAB [GSK 1265744]	
	(*gluteus medius*) respectively of CAB 200 mg/mL formulation [CAB IB 2021 ViiV Healthcare Document Number RPS-CLIN-004375]. The CAB 400 mg/mL LA formulation includes a different wetting agent; Poloxamer 338. Poloxamer 338 is a component of the rilpivirine LA formulation. There are extensive safety and tolerability data following IM administration of RPV. The CAB 400 mg/mL formulation containing Poloxamer 338, was tested in a GLP rat study to assess potential systemic toxicity of the new formulation including the novel excipient Poloxamer 338 and was found to be well tolerated. See section in supplemental IB [RPV IB, 2020].	*generate safety and PK data ahead of the commencement of study 212482 Cohort 3.* CCI  *A sentinel dosing strategy with four sentinel participants will be implemented for Part 2 when higher doses and larger volumes are being administered. Dosing of Cohort 5 and 6 will be staggered:*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product (IP) CAB [GSK 1265744]	
		following review of safety data from the sentinel participants (10 days post first injection), a further 7 participants will be randomized and have their first injection, and following a review of safety data from these 7 participants (10 days post first injection), the remaining 11 participants will receive the first injection. All participants in Part 2 will remain in clinic for 7 days (until Day 8) following each injection CCI [redacted]
Injections sites: *vastus lateralis* (IM lateral thigh injections and subcutaneous tissue (abdominal wall)	Intramuscular CAB injections into the thigh (*vastus lateralis)* have not previously been administered in the CAB development program. Similar to the ventrogluteal region, the *vastus lateralis* is free of major nerves and blood vessels. Therefore, it is expected to be a safe site for injections. The *vastus lateralis* is part of a large muscle group and can tolerate high volume injections of up to 5 ml [Rodger, 2000] in adults with lesser amounts being stipulated in younger participants or in those with less developed or atrophied muscle beds [Rodger, 2000]. Subcutaneous tissue is frequently used for the administration of medications and is considered safe for injections in particular due to the lack of significant vasculature or nerves. The tolerability and ISR profile of subcutaneous administration of CAB 200 mg/mL is broadly similar to that following IM injections albeit with limited numbers of participants receiving SC injections. The incidence of nodules and erythema was higher with SC versus IM administration however these were mild in severity	*Training of the appropriate technique will be provided to staff at the study centre and will be described in the study reference manual.* *Any participants experiencing a grade 3 or higher AE event prior to the follow-up phase will withdraw from the study and enter the follow-up phase if i) the AE is considered related to IP in the opinion of the investigator and sponsor and ii) the investigator and sponsor agree the subject should be withdrawn from the study* *Criteria for pausing recruitment or dosing of a cohort:* *If greater than 40% participants within a single cohort experience a local injection site reaction of at least grade 2 in severity once at least half of participants have received one or more injections.* *If ≥20% of injections given within a single cohort are followed by an injection site reaction of at least grade 3 in severity (once half of cohort participants have received one or more injections).*
Hypersensitivity Reactions (HSR)	Hypersensitivity reactions have been reported as uncommon occurrences with integrase inhibitors, including the closely related compound dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury.	*The risk of developing a hypersensitivity reaction post administration of IM CAB will be minimized by the use of a 4-week oral lead-in of oral CAB to determine individual safety and tolerability prior to the introduction of IM CAB.* *Clinical assessments, laboratory tests (including liver transaminases) and vital signs will be performed throughout this*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product (IP) CAB [GSK 1265744]	
	While there have been no clinical cases of hypersensitivity to CAB to date, there is a theoretical risk of systemic or severe hypersensitivity reactions with or without hepatic symptoms associated with use of IM or SC CAB. The long exposures anticipated after IM CAB injection may complicate the management of a drug hypersensitivity reaction in the event an HSR occurred.	*study (refer to the SoA Section 1.3). Results from these assessments may aid early detection of HSR.* *Oral CAB will be withdrawn immediately for cases with suspected HSR during the oral CAB lead-in phase and would not proceed to the injection phase. Participants in the injection phase would not receive further injections. During oral and IM CAB treatment, any HSR reactions that occur would be managed supportively.*
Relationship between CAB plasma concentration and QTc	In the Thorough QT study LAI117009 (n=40), oral CAB administration had no effect on cardiac repolarization at a supratherapeutic dose of 150 mg q 12 hours x 3 doses and was well-tolerated. The median Cmax was 22.5 μg/mL (95% CI: 21.1, 24.0). After baseline and placebo adjustment, the maximum time-matched mean QTcF for CAB was 2.62 msec (1-sided 95% upper CI: 5.26 msec). CAB did not prolong the QTc interval over 24 hours post dose.	*Increased ECG monitoring will occur in Part 2 (higher doses are being administered) to cover predicted tmax. The Bayesian probability of any participant exceeding the Cmax criteria of 22.5 μg/mL in Cohorts 5 and 6 will be calculated for each injection. Dose selection requires the Bayesian probability to be less or equal to 50% that anyone exceeds 22.5 μg/mL*
Drug-Drug Interactions (DDIs)	CAB (oral) and CAB LA should not be co-administered with some medicinal products Section 6.5. Please refer to study reference manual.	*All participants will be informed of prohibited medications throughout the study and updates provided as needed via the informed consent. Participants will be informed that they may be at risk for developing DDIs many weeks after discontinuing LA CAB.* *Participants receiving prohibited medications unable to stop or change to a permitted alternative medication will be excluded from the study.*
Inadvertent Intravenous Injection (Accidental Maladministration)	As with any intramuscular or subcutaneous injection, it is possible that CAB LA can be inadvertently administered intravenously instead of intramuscularly/subcutaneously possibly resulting in higher than expected concentrations of CAB shortly after injection and lower concentrations thereafter. This could be due to administrator error, improper injection technique and / or improper needle length used based on body	*Training will be provided regarding be provided to relevant staff regarding proper injection technique* *Should maladministration be suspected at any time (e.g. suspected under or overdose or inadvertent IV dosing), a post dose electrocardiogram (ECG), vital signs, or any other supportive testing may be obtained at the discretion of the investigator, and*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Investigational Product (IP) CAB [GSK 1265744]	
	type. The clinical consequences of overdose with CAB LA are currently unknown.	*the medical monitor will be notified. Laboratory samples for safety parameters will be closely monitored in all participants.* *Additionally, 2-hour post dose PK samples will be obtained at early timepoints for determination of CAB concentration and possible pharmacokinetic correlation with safety parameters such as ECG changes.* *Additionally, an unscheduled PK sample may be drawn approximately 2 hours post dosing for future evaluation of CAB concentrations.*
Acquisition of HIV and theoretical risk of CAB resistance in the presence of waning CAB concentrations	If a participant were to acquire HIV during the study or following completion of the study, there is a low theoretical risk of the development of CAB resistance in the presence of waning CAB concentrations	*Participants at increased risk for HIV will be excluded from the study.* *Participants will undergo HIV testing at baseline and during the study and at study completion. All participants will be advised regarding safer sex and the use of condoms during the study and participants will be advised regarding the long PK tail of GSK1265744 and the theoretical potential for emergence of HIV drug resistance to cabotegravir should they acquire HIV.*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Recombinant Human Hyaluronidase PH20 (rHuPH20)	
Spread of localized infection	rHuPH20 should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection.	*Training will be provided regarding be provided to relevant staff regarding proper injection technique.*
Hypersensitivity	Hypersensitivity, allergic and anaphylactic-like reactions have been associated with animal-derived hyaluronidases but have not been associated with rHuPH20.	*Subjects with a history of hypersensitivity to hyaluronidases are excluded.*
Inadvertent IV administration	In a study of healthy volunteers administered 10,000 U or 30,000 U of rHuPH20 intravenously, rHuPH20 had a half-life of less than 10 minutes and was well tolerated. There were no associated serious adverse effects [Printz, 2020].	*Training will be provided regarding be provided to relevant staff regarding proper injection technique.* *No mitigation activities are needed if there is suspected IV administration of rHuPH20.*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Recombinant Human Hyaluronidase PH20 (rHuPH20)		
Injection Site Reactions (ISRs)	rHuPH20 may cause ISRs. ISRs are mostly mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, oedema, induration, irritation, paraesthesia, numbness, and rash. Moderate ISRs occur less frequently, include burning, erythema, pain, and numbness (rHuPH20 IB, 2021). rHuPH20 may potentially alter the ISR profile of cabotegravir.	*Participants will be closely monitored for throughout the study.* *ISR-related criteria for pausing recruitment or dosing of a cohort as well as stopping criteria apply to Cohort 4h.* *A sentinel dosing strategy with four sentinel participants (two each with cabotegravir 200 mg/mL and cabotegravir 400 mg/mL formulation) in Cohort 4h as this will be the first time that cabotegravir and rHuPH20 will be administered together. Most AEs reported in clinical trials with rHuPH20 were mild, transient injection site reactions, including erythema. It is currently unknown if rHuPH20 may impact the ISR profiles of cabotegravir 200 mg/mL and cabotegravir 400 mg/mL formulations.*

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Venipuncture	Participants will be required to have blood samples taken. Risk of bruising, and rarely, infection	*Trained personnel will perform venipuncture.*
Risks of ECG pad removal	Some discomfort and rash may occur where the ECG pads are applied and subsequently removed.	*ECGs will be conducted by appropriately trained personnel and effort made to minimize contact time for application of the pads.*
Vasovagal reaction	Receiving injections can cause some participants to feel lightheaded or feel like they might pass out, or 'faint'. This reaction, called a 'vasovagal reaction', can occur with many medical procedures and resolves quickly.	*The participants are monitored and stay in the clinic for at least 24 hours after the injection for additional sampling and further observation.*

2.3.1.1. Other Clinically Relevant Information

Additional details concerning safety observations from clinical studies and for which a causal association has not been established or which are of minimal clinical significance may be found in the Investigator's Brochures [CAB IB 2021 ViiV Healthcare Document Number RPS-CLIN-004375; rHuPH20 IB, 2021]. Refer to 'Summary of data and guidance for the investigator'.

Seizure

Several cases of seizure have occurred during the CAB (200 mg/mL) program. These cases have had alternative explanations for their occurrence. Overall, there is not convincing evidence that cabotegravir exposure may be causally associated with seizure or with reduction of seizure threshold, due to the low frequency of reports, the confounders present in the cases received to date and lack of any pre-clinical signal or identified plausible mechanism. However, seizure and seizure-like events are considered as AEs of special interest for CAB. Participants with a prior history of seizure disorder will be excluded from study participation. Any cases of seizure or seizure like events will be reported within 24 hours of the event.

2.3.1.2. Non-Clinical Observations

Cabotegravir (200 mg/mL formulation) has undergone a comprehensive nonclinical toxicological evaluation in studies of appropriate design consistent with ICH requirements in the rat, monkey, mouse, and rabbit to support the clinical use of cabotegravir for the treatment of HIV infection. The CAB 400 mg/mL formulation was tested in a GLP rat study designed to assess local tolerability at the injection site when administered once per month for 3 months, and to assess potential systemic toxicity of the novel formulation containing Poloxamer 338. There were no cabotegravir-related effects on body weight or food consumption in rats. Injection site reactions included slight to marked oedema observed in both genders, slight to moderate erythema noted in females only and eschar (scabbing) observed in a small number of males and females. The ISRs were noted within 5 days of giving the injection, and, with time, decreased in incidence and severity, generally resolving at the next dosing occasion or by necropsy.

Non-clinical and clinical data regarding CAB plasma concentrations are discussed in Section 4.2.3. Non-clinical and clinical data regarding rHUPH20 are outlined in the IB [rHuPH20 IB, 2021].

2.3.2. Benefit Assessment

This is a study in healthy adult participants and as such there is no expected benefit to administration of CAB. Participation in this study may contribute to the process of developing new therapies for HIV. There may be benefit to participants from the medical evaluations and assessments which could identify conditions that the participant was previously unaware.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures to minimise the risk to participants in this study, the potential risks identified with GSK1265744, 400 mg/mL and 200 mg/mL formulations and rHuPH20 are well understood and are justified by the anticipated benefits that may be afforded in the future to people living with HIV.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	Primary
To describe the PK profiles of CAB 400 mg/mL formulation following multiple injections administered intramuscularly (*gluteus medius* or *vastus lateralis*) or subcutaneously (abdominal) in healthy adult participants	Summary measures to include: • Maximum observed plasma concentration (Cmax) [Injection 1 and 2] • Time of maximum observed plasma concentration (tmax) [Injection 1 and 2] • Area under the concentration – time curve for each injected dose from time zero to last quantifiable time point or 4 weeks following injection whichever is earlier (AUC0-t) • Trough concentrations (Cτ) at 4 weeks following first injection (or earlier if the second injection occurs at <4-week interval) and 4 weeks following the second injection • Apparent terminal phase half-life (t½) and absorption rate constant (KALA) [Injection 2]
To assess the relative bioavailability of a CAB 400 mg/mL formulation administered via different routes (i.e., IM (*vastus lateralis*), IM (*gluteus medius*) or SC routes)	• Pair-wise comparisons of geometric mean ratios of plasma trough concentrations (Cτ), Cmax, and Plasma AUC0-t [injection phase] for Cohort 1, 2, 3, 4, 4b, and 4h
To compare exposures after CAB 400 mg/mL formulation administered via different routes with historical data of CAB 200 mg/mL formulation administered IM (*gluteus medius*)	• Geometric mean ratios of plasma trough concentrations (Cτ) for Cohorts 1, 2, 3, 4, 4b, 4h, 5, and 6 (if conducted) compared to historical CAB 200 mg/ml data

Objectives	Endpoints
Safety	Safety
To assess safety and tolerability of CAB 400 mg/mL formulations following repeated intramuscular injections in the *gluteus medius, vastus lateralis* (lateral thigh) or subcutaneously (abdomen) of healthy adult participants To assess safety and tolerability of CAB 200 mg/mL with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants To assess safety and tolerability of CAB 400 mg/mL with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants	Safety and tolerability parameters including adverse events, clinical laboratory tests, and vital sign assessments
Secondary	Secondary
To assess the tolerability of CAB 400 mg/mL formulation following repeated intramuscular injections in the *gluteus medius*, *vastus lateralis* (lateral thigh) or subcutaneously (abdomen) of healthy participants To assess the tolerability of CAB 200 mg/mL formulation with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants To assess the tolerability of CAB 400 mg/mL formulation with rHuPH20 following a subcutaneous (abdominal)	Tolerability parameters (adverse events) and liver biochemistry abnormalities

Objectives	Endpoints
injection in healthy adult participants	
PK	PK
Secondary	Secondary
To describe the PK profiles of CAB 200 mg/mL and CAB 400 mg/mL formulations with rHuPH20 following a subcutaneous (abdominal) injection in healthy adult participants	Summary measures to include: • Maximum observed plasma concentration (Cmax) • Time of maximum observed plasma concentration (tmax) • Area under the concentration – time curve from time zero to last quantifiable time point or 4 weeks following the injection whichever is earlier (AUC0-t) • Trough concentrations (Cτ) through the Follow-up Phase • Apparent terminal phase half-life (t½) and absorption rate constant (KALA)
To describe the pharmacokinetic (PK) profiles of oral CAB 30 mg following daily administration in healthy adult participant	• Cmax • tmax • AUC(0-t) • C24 • Day 29 Cτ
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, double-blind (sponsor-unblind), active control, randomized, study to investigate the safety, tolerability and pharmacokinetics of repeat dose four-weekly (Q4W) and 12-weekly (Q12W) administration of long-acting CAB 400 mg/mL or CAB 200 mg/mL formulations. The data from active control (CAB 200 mg/mL) formulation in this study will be used for safety and tolerability comparisons only. These will be administered by HCPs intramuscularly (IM) or via subcutaneous (SC, abdominal) injections in healthy adult participants. We aim to recruit approximately 20% of women in this study.

The study will consist of:

- A 30-day Screening Period
- A 28-day oral lead-in (OLI), CAB 30 mg once daily with sparse PK sampling through Day 29
- A 7 to 14-day Washout Period (starting on Day 29)
- An Injection Phase
  - up to Week 8 (Injection 2 Day 28) in Part 1 Cohorts 1, 2, 3, 4 and 4b,
  - up to Week 4 (Injection Day 28) in Part 1 Cohort 4h and
  - up to Week 24 (Injection 2 Week 12) in Part 2 Cohorts 5 and 6 (if conducted)

- A 52-week Follow-up Phase post last injection or until CAB is no longer quantifiable (if this occurs prior to Week 52)

In circumstances where recruitment to or dosing of a cohort is paused, participants may be recruited or re-randomized (only prior to the injection phase) to subsequent cohorts if deemed appropriate by the investigator and sponsor.

If data following the conclusion of Part 1 or the interim data from Part 2 (12-week PK data from Cohort 5) warrants the assessment of alternative dose(s) and/or dosing schedule additional cohort(s) will be added.

4.1.1. Part 1

Participants will be enrolled sequentially into 3 cohorts (n=20 each). Participants will be recruited to Cohort 1 first, then to Cohort 2 and followed by Cohort 3. Participants will be randomized (9:1 Active vs Active Control [AC]) according to a pre-generated randomization schedule to receive:

- Cohort 1 - two IM injections of CAB 400 mg/mL or CAB 200 mg/mL (AC) formulations 4-weeks apart (600 mg and 400 mg respectively) in *gluteus medius*

- Cohort 2 - two subcutaneous injections of CAB 400 mg/mL formulation 4-weeks apart (600 mg and 400 mg respectively) or CAB 200 mg/mL (AC, 300 mg and 200 mg respectively) in the abdomen.

  The VSLC agreed to reduce the dose of the second injection (see Section 6.2.1).

- Cohort 3 – two IM injections of CAB 400 mg/mL or CAB 200 mg/mL (AC) formulations 4-weeks apart (600 mg and 400 mg respectively) lateral thigh/*vastus lateralis*.

  The STR agreed to reduce the dose of the first injection for the remaining Cohort 3 participants (see Section 6.2.1).

Cohort 4 (optional) - the requirement for an optional Cohort 4 and determination of the dose and dosing schedule will be determined based on an interim review of the safety and tolerability data from Cohorts 1-3 and PK data through Week 4 from Cohorts 1-2. This determination will be undertaken by the Study Team safety & PK Review (STR). This will be based on the comparison to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 with the aim of selecting a safe dose predicted to achieve approximately 95% of dosed participants having trough concentrations higher than the Phase 3 benchmark. Active control participants will receive CAB 200 mg/mL matched to the volume of CAB 400 mg/mL if administered subcutaneously. Should Injection 1 be administered via the IM route, active control participants will receive CAB 200 mg/mL matched on dose to CAB 400mg/mL. Note: A minimum of 15 participants in each cohort are required to have evaluable data for both injections.

At their meeting on 22 December 2020, the STR agreed to conduct Cohort 4 (see Section 6.2.1).

Cohort 4b – two subcutaneous injections of CAB 400 mg/mL formulation 4-weeks apart (each 300 mg) CCI [redacted]

Participants (n=24) will be randomized in equal numbers according to a pre-generated randomization schedule to one of two sequences (i.e. 12 per sequence) of two treatments to be administered along with Injection 1 and Injection 2, respectively (see Section 1.2 Schema Part 1 [Cohort 4b]).

Cohort 4h – one subcutaneous injection in the abdomen with rHuPH20 followed by CAB 400 mg/mL formulation (400 mg) or CAB 200 mg/mL (400 mg). Instructions regarding drug preparation and administration are provided in the pharmacy manual.

Participants will be randomized to receive 5000 U of rHuPH20 followed by either CAB 200 mg/mL or CAB 400 mg/mL formulations at a dose of 400 mg (2 mL and 1 mL, respectively). Four sentinel participants (two each administered CAB 200 mg/mL and CAB400 mg/mL formulations) will be followed clinically for 10 days after dose administration and if there are no significant safety concerns upon a 10-day review of safety data, the remaining 16 participants will be dosed with rHuPH20 plus either CAB 200 mg/mL or CAB 400 mg/mL.

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the Sponsor in consultation with the investigator.

4.1.2. Part 2

Part 2 will commence once data (trough concentrations (Cτ) and plasma AUC_{0-t} up to and including Week 8 following Injection 1 from all participants in Cohort 1, and available safety and tolerability collected from each cohort 1-3) are reviewed and compared to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program. The first injection in Part 2 Cohort 5 will be administered once safety and tolerability data observed within the first ten days after the first injection for at least 50% of Cohort 4 participants (n=10) have been reviewed by the STR. If pausing criteria due to ISRs (see Section 7.1) are met in Cohort 4, Cohort 5 will be paused until further discussion. The determination of the dose and dosing schedule will be governed by a Study Team safety & PK Review (STR) with the aim of selecting a safe dose predicted to achieve approximately 95% of dosed participants having trough concentrations higher than the Phase 3 benchmark.

The requirement for an optional Cohort 6 will be based upon a review of the safety, tolerability and PK data from Cohort 5 (12 weeks after injection 1) and available safety, tolerability and PK data from Cohorts 1-4 and comparison to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program. This determination will be undertaken by the STR and will be guided by the predicted proportion of participants exceeding the phase 3 (CAB 200 mg/mL) trough concentration benchmark in simulation models and the ISR profile.

Participants in Cohorts 5 and 6 (n=22 each) will receive two IM injections 12 weeks apart, via the *gluteus medius*. Participants randomized to the active arm in Cohort 5 will receive ≤1200 mg (3 mL) of the CAB 400 mg/mL formulation. Participants randomized to the active arm in Cohort 6 will receive ≤2000 mg (5 mL) of the CAB 400 mg/mL formulation. A minimum of 16 participants in each cohort are required to have evaluable data for both injections.

The first four subjects enrolled in each cohort will serve as sentinel participants with three receiving CAB 400 mg/mL formulation (dose up to 1200 mg based upon data from Part 1) and one receiving active control (based on 3:1 randomization). These sentinel participants will be followed clinically for 10 days after dose administration to monitor the emergence of adverse events. If there are no significant safety concerns upon 10-day review of safety data (e.g. vital signs, ECGs, and adverse events) for the sentinel participants, the remaining participants will subsequently be treated with either CAB 400 mg/mL formulation (n=17) or AC (n=1) based on a 17:1 randomization. Dose administration for these remaining participants (n=18) will be staggered:

- a further 7 participants will be randomized and have their first injection.
- Following a review of safety data from the initial 7 participants 10 days post first injection, the remaining 11 participants will receive their first injection.
- These remaining participants may start the OLI phase prior to the 10-day reviews of safety data but they may only be randomized and proceed to the injection phase following the relevant safety review and if there are no significant safety concerns. Intramuscular dosing of active control (CAB 200 mg/mL) will be matched to the volume of CAB 400 mg/mL formulation administered via the *gluteus medius*.

The dose of the second injection in Cohort 5 will be guided by safety and PK data when ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments.

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the Sponsor in consultation with the investigator.

4.1.3. Screening

All participants will undergo a screening visit within 30 days of the first dose of the oral lead-in. Participants may be rescreened once. Participants who are enrolled into the trial and subsequently withdrawn from the study, for any reason, may not be re-screened. Participants may continue to the oral lead-in phase as soon as all eligibility requirements have been met. See Appendix 8 for permissible procedures during the COVID-19 pandemic (Section 11.8).

4.1.4. Oral Lead-in Phase

Participants that are eligible to participate will return to the clinic on Day 1 of the OLI phase and receive their first oral dose of CAB 30 mg after the completion of all pre-dose assessments. Participants will undergo assessments as described in the Schedule of Activities (SoA). Participants will be dispensed a sufficient supply of oral CAB tablets to complete 25 days of once daily dosing at home and be counselled to take their dose at approximately the same time each day.

On Day 14 of the OLI phase, the participants will return to the clinic. A pre-dose PK sample will be collected. In addition, this visit will include assessment of safety, tolerability, and participant adherence to study drug. Participants should bring their supply of oral CAB to the Day 14 visit to have drug accountability performed. Participants will receive Day 14 dose at the clinic. See Appendix 8 for permissible procedures during the COVID-19 pandemic (Section 11.8).

Participants will return to the clinic on Day 29, within 24 hours of Day 28 last dose, for PK sample collection, to have drug accountability, and all assessments performed as described in the SoA. The participants will begin a 7-14-day washout period (starting on Day 29), during which no CAB will be administered.

4.1.5. Washout Period and Injection Phases

A 7 to 14-day Washout Period (starting on Day 29) will occur prior to participants returning to the clinic to initiate the injection phase. The washout period may be extended if deemed necessary by the investigator and sponsor. See Appendix 8 for permissible procedures during the COVID-19 pandemic (Section 11.8).

The Part 1 injection phase (Cohorts 1, 2 and 3) will consist of all participants receiving an initial injection on Injection 1 Day 1 of CAB 400 mg/mL as loading dose (600 mg, 1.5 mL) followed by second injection for maintenance dose (400 mg; 1 mL) at Week 4/Injection 2 Day 1 (±3 days). Two participants in cohorts 1 and 3 will receive 3 mL and 2 mL of CAB 200 mg/mL injections as first and second injections, respectively. Two participants in Cohort 2 will receive CAB 200 mg/mL; the volume will be matched to the volume of CAB 400 mg/mL administered subcutaneously in Cohort 2.

The requirement for an optional Cohort 4 and determination of the dose and dosing schedule will be determined based on a review of the safety and tolerability data and any available PK data from Cohorts 1-3. This determination will be undertaken by the STR and will be based on the comparison to historical PK data of the CAB 200 mg/mL formulation from the Phase 2/3 program.

The Cohort 4b injection phase will consist of an initial subcutaneous injection on Injection 1 Day 1 of CAB 400 mg/mL (300 mg; 0.75 mL) followed by a second subcutaneous injection of CAB 400 mg/mL (300 mg; 0.75 mL) at Week 4/Injection 2 Day 1 (±3 days). CCI [redacted]

The Cohort 4h injection phase will consist of a single subcutaneous injection on Injection Day 1 with rHuPH20 (5000 U) followed by CAB 400 mg/mL (400 mg; 1 mL) or CAB 200 mg/mL (400 mg; 2 mL).

The Part 2 Cohort 5 injection phase will consist of participants receiving two IM gluteal injections of CAB 400 mg/mL on Injection 1 Day 1 and Week 12/Injection 2 Day 1 visits. The determination of the dose and dosing schedule for cohort 5 will be based on safety and pharmacokinetic endpoints from Cohort 1 and any available data from Cohorts 2-4 and historical PK data of the CAB 200 mg/mL formulation. This will be governed by

a Study Team safety & pk Review (STR) but will not exceed a dose of 1200 mg (3 mL). Active control participants will receive a matching volume of CAB 200 mg/mL formulation.

The requirement for an optional Cohort 6 in Part 2 will be based upon a review of the safety, tolerability and PK data from Cohort 5 (12 weeks after injection 1 in Cohort 5) and the available safety, tolerability and PK data from Cohorts 1-4 and comparison to historical PK data of the CAB 200 mg/mL formulation. This determination will be undertaken by the STR but will not exceed a dose of 2000 mg (5 mL).

Injection 1 in Cohorts 5 and 6 will be followed by PK sampling as per the SoA through Week 4. The participants would be monitored for safety and tolerability and plasma PK samples will be collected at Weeks 6, 8 and 10. The second IM injection would be administered at Week 12, followed by PK sampling through Week 24, as per the SoA.

4.1.6. Follow-up/Withdrawal Visit

Because of the long acting PK profile of CAB 400 mg/mL and 200 mg/mL LA, every effort should be made to bring participants back over the 52-week follow-up phase after the last injection.

Part 1, all participants, who received CAB 400 mg/mL or 200 mg/mL LA injections, will return to clinic for safety and PK assessments at Weeks 4, 8, 12, 20, 28, 36, 44 and 52 post last IM and SC injection or until the drug level of CAB is below the level of quantification if this occurs prior to Week 52.

Part 2, Cohort 5/6 participants, who received CAB 400 mg/mL or CAB 200 mg/mL LA injections, will return to clinic for safety and PK assessments at Weeks 12, 24, 40 and 52 post last injection or until the drug level of CAB is below the level of quantification if this occurs prior to Week 52.

If a participant is withdrawn prior to receiving any injection, then a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB. If a participant is withdrawn or disqualified from the study after receiving at least one injection of CAB LA, because of the long acting PK profile of CAB, every effort should be made to bring the participant back in for the 52 weeks of safety and PK assessments following the last injection at weeks post injection as outlined in the SoA or until the drug level of CAB is below the level of quantification if this occurs prior to Week 52. Participants who terminate before week 52 post last injection will be asked to return to the site for a withdrawal visit.

4.2. Justification for Dose

4.2.1. Oral Dose

The risk of developing a hypersensitivity reactions (HSRs) post administration of parenteral CAB will be minimized by the use of a 4-week oral lead-in of oral CAB. In the event of a suspected HSR participants would not receive parenteral dosing with CAB. The management of participants with an HSRs following receipt of drugs with a long

half-life may be challenging. HSR have been reported as uncommon occurrences with integrase inhibitors, including the closely related compound dolutegravir to cabotegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. The time of onset of HSR reactions supports the proposed duration of the OLI with the majority of HSRs occurring within the first 28 days of exposure to a drug.

During the oral lead-in (OLI) phase of this study, oral formulation of CAB will be administered to assess safety and tolerability in each participant prior to injection with CAB 400 mg/mL or 200 mg/mL LA. CAB 10, 30, and 60 mg QD doses have been administered orally to HIV-1 infected participants in Phase 2b studies. In these studies, all three oral CAB doses demonstrated similar efficacy at the week 48 primary endpoint. However, 30 mg dose was selected as OLI for all CAB LA studies, as it delivered higher steady-state exposures than predicted for the monthly or every 2-month regimen. Therefore, CAB 30 mg will be used as the OLI dosing in the present study as this dose is predicted to achieve sufficiently high exposures to assess safety and tolerability during a short OLI prior to IM administration of CAB LA injectable formulations. The PK collected during the OLI phase will be utilized along with the data from LA injection phase to precisely estimate PK parameters using a robust population PK (PopPK) model. A window of 7 to 14 days from Day 29 (covering ~5-9 half-lives) will be used for a washout period prior to LA injection accounting for variability in half-life in participants. This washout period would prevent plasma concentrations after oral administration from being mixed with plasma concentrations on Day 1 after LA IM/SC injections in Part 1 and/or Part 2 of the study. The washout period may be extended if deemed necessary by the investigator and sponsor. Also see Appendix 8 for permissible procedures during the COVID-19 pandemic (Section 11.8).

4.2.2. Long Acting Injectable Dose

This study will evaluate repeat dose four-weekly (Q4W) or 12-weekly (Q12W) administration of long-acting CAB 400 mg/mL or CAB 200 mg/mL formulations administered either intramuscularly into *gluteus medius* or lateral thigh (*vastus lateralis*) muscle or subcutaneously into abdomen. Currently CAB LA 600 mg (3 mL of 200 mg/mL nanomilled formulation) IM is the largest CAB LA dose that has been administered by a single injection. Previously, a higher dose (800 mg) have been administered as two split injections (2 x 400 mg each injection with 2 mL of 200 mg/mL nanomilled formulation) given simultaneously at two separate injection sites. The two split injection approach resulted in faster rate of absorption due to increased available surface area for absorption. Thus far, in various clinical studies safety, efficacy, and tolerability has been established for CAB LA 600 mg IM administered every 4 weeks (Q4W) and every 8 weeks (Q8W) in HIV infected subjects (201585 [ATLAS]), 207966 [ATLAS-2M]) and in pivotal PrEP studies in healthy participants at high risk of HIV infection (HPTN083 and HPTN084). Therefore CAB LA 600 mg IM (loading dose)/400 mg IM (maintenance dose) was selected for Q4W cohorts in Part 1 of this study.

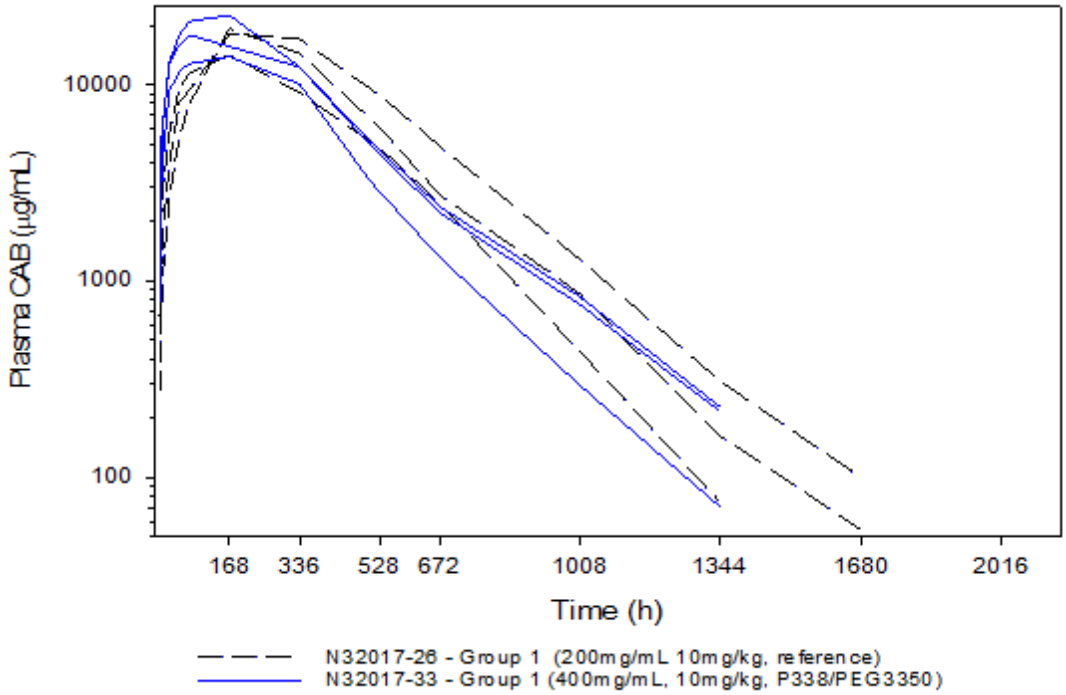
CAB 400 mg/mL LA is a new formulation in development with the potential to enable administration of larger doses and less frequent administration. The PK and tolerability of this new formulation will be evaluated in this study.

Preclinical studies were conducted in rats with original nanomilled formulation of 200 mg/mL (Study N32017-26) and new nanomilled formulation of 400 mg/mL (Study N32017-33) containing P338 and PEG3350 excipients. PK data were collected after intramuscular administration of 10 mg/kg dose from each formulation. Table 1 summarizes the absorption rate constant (KALA) and terminal phase half-life from both studies.

Table 1 Comparison of PK parameters in rats after IM administration of 10 mg/kg using 200 mg/mL and 400 mg/mL nanomilled formulations

PK Parameter	Rat	Formulations	
		PS20/PEG3350 – 200 mg/mL	P338/PEG3350 – 400 mg/mL
AUClast (h*µg/mL)	1	7580	8570
	2	5920	7400
	3	9220	5590
	Mean	7574	7186
C_{max} (µg/mL)	1	19.3	22.4
	2	14.2	17.8
	3	18.1	13.8
	Mean	17.2	18.0
KALA (1/h)	1	0.00418	0.00362
	2	0.00485	0.00347
	3	0.0039	0.00435
	Mean	0.00431	0.00381
$t_{1/2}$ (h)	1	166	191
	2	143	200
	3	178	160
	Mean	162	182

Figure 1 Comparison of individual PK profiles from rats after IM administration of 10 mg/kg using 200 mg/mL and 400 mg/mL nanomilled formulations



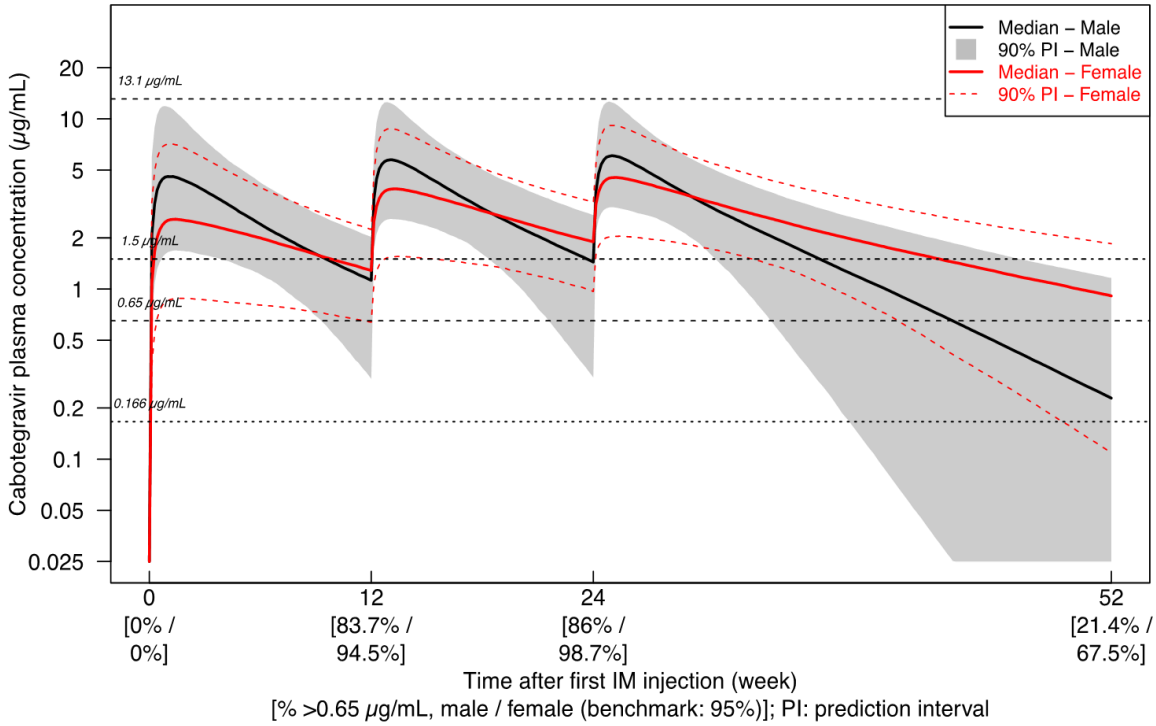
The 400 mg/mL formulation was tested in a GLP rat study designed to assess local tolerability at the injection site when administered once per month for 3 months, and to assess potential systemic toxicity of the novel formulation containing Poloxamer 338. There were no cabotegravir-related effects on body weight or food consumption in rats. Injection site reactions included slight to marked oedema observed in both male and female animals, slight to moderate erythema noted in females only and eschar (scabbing) observed in a small number of males and females. The ISRs were noted within 5 days of giving the injection, and, with time, decreased in incidence and severity, generally resolving at the next dosing occasion or by necropsy.

A comparison of individual PK profiles from both studies (Figure 1) shows that slopes of the terminal phase which represent long-acting absorption are overlapping indicating similar absorption rates. Based on this information, LA IM absorption rate in the CAB PopPK model was assumed to be same for both nanomilled formulations. The CAB PopPK model has been updated with PK data from pivotal Phase 3 studies (FLAIR and ATLAS) significantly increasing the data in the population PK dataset (N=1647 subjects). Simulations based on the updated PopPK model have been conducted to evaluate several potential dose and dosage regimens with the new formulations [GSK Document Number 2019N421607_00].

An example of a 1200 mg IM dose simulation (every 12 weeks) is presented here for illustration. Simulated 5th percentile trough concentrations were benchmarked against the phase 3 (CAB200 mg/mL) 5th percentile trough concentrations (0.65 µg/mL) for evaluation purposes.

Figure 2 shows that after initial injection of 1200 mg IM dose in males, the 5th percentile of trough concentration at Week 12 is slightly below the phase 3 benchmark (0.65 µg/mL). However, in a female only population (Figure 2), the 5th percentile of trough concentrations after initial injection was at the Phase 3 benchmark and slightly above the Phase 3 benchmark after second injection due to accumulation.

Figure 2 Predicted Median (90% PI) CAB Plasma Concentration-Time Profile in Male and Female Population Following Repeated Dosing of 1200 mg IM Injections Every 12 Weeks in *Gluteus Muscle*



As per Section 4.1, the determination of the dose and dosing schedule for Cohorts 4, 5 and 6 will be made by the STR based upon the PK and safety profile from earlier cohorts and historical CAB 200 mg/mL formulation data with the aim of selecting a safe dose predicted to achieve approximately 95% of dosed participants having trough concentrations higher than the Phase 3 benchmark.

In summary, the above simulations support considering a dosage regimen of IM 1200 mg or higher in Cohort 5 pending the results from earlier cohorts. A planned interim analysis of Cohort 5 will help inform the need for Cohort 6 as outlined in Section 4.1. Pharmacokinetic data obtained in this study from Q4W cohorts will be used in conjunction with current PopPK model to inform appropriate dose for Q12W cohorts in Part 2 of the study.

The impact of rHuPH20 on the pharmacokinetics of CAB 200 mg/mL has been investigated in rats [GSK Document Number 2021N479337]. A single SC injection of CAB (5 or 10 mg/kg) was dosed to rats with and without prior administration of rHuPH20. The systemic exposure of CAB, as defined as AUC0-t and Cmax, was generally similar with and without administration of rHuPH20 (3000 U), with the

respective mean CAB half-life values being 360 and 330 hours (10 mg/kg CAB) and 180 and 200 hours (5 mg/kg CAB).

The doses of the CAB 400 mg/mL and CAB 200 mg/mL formulations administered in Cohort 4h were selected based on PK and safety data from Cohorts 1-4 irrespective of route of administration.

4.2.3. rHuPH20

The pharmacological effects of rHuPH20 are limited to the site of injection with no measurable systemic absorption at doses up to 30,000 U. The dose/concentration of rHuPH20 depends on the viscosity and volume of the solution to be injected. The approved monoclonal antibodies co-formulated with rHuPH20 have a viscosity of ~5 cP and volumes up to 15 mL per injection and utilize concentrations of 2000 U/mL of rHuPH20. Taking into consideration the viscosity of the suspensions of CAB 200 mg/mL (10 cP) and CAB 400 mg/mL (25 cP) and the respective injection volumes of ~2 mL and ~1 mL a dose of rHuPH20 of 5000 U is considered an appropriate dose for both.

4.2.4. Rationale Supporting Cmax criteria in Part 2

Across the cabotegravir 200 mg/mL formulation program, no apparent relationship between the frequency and grade of AEs and CAB plasma concentrations following either oral or LA dosing in clinical studies has been identified. In the LATTE study (LAI116482) no apparent relationship between AE frequency and the dose of cabotegravir was observed. In this study, following oral CAB 60 mg once daily over 96 weeks the observed geometric mean Cmax was 13.1 µg/mL (range: 7.3 – 24.5 µg/mL; 95% CI: 9.9, 17.5) (ViiV Healthcare Document Number 2014N216014_00). This is the highest observed exposure in oral CAB long-term studies.

In the thorough QT/QTc (TQT) study (Study LAI117009), the observed geometric mean Cmax was 22.5 µg/mL (95% CI: 21.1, 24.0) following a supratherapeutic dose of oral CAB 150 mg (3 doses in total, twice daily) [CAB IB 2021 ViiV Healthcare Document Number (Section 5.2.11.1); ViiV Healthcare Document Number RPS-CLIN-004375]. This supratherapeutic dose had no effect on cardiac repolarization and there were no other safety findings.

Across the cabotegravir 200 mg/mL formulation Phase 2b and 3 studies high CAB plasma concentrations up to 104 µg/mL, consistent with partial intravenous. administration have been observed in 17 subjects following IM injections. No specific AEs were identified in these subjects.

Across the non-clinical program, the no-observed-adverse-effect level (NOAEL) mean Cmax was 34.6 µg/mL in 39-week monkey oral CAB toxicity study.

These data support use of 22.5 µg/mL as a Cmax criteria for dose selection in Part 2 given the short duration of Cmax following IM administration based on simulations (Figure 2). The dose selection and dose escalation in Cohorts 5 and 6 of Part 2 will be based on the Bayesian predictive probability of Cmax in any single participant (out of

n=20) exceeding 22.5 µg/mL will be ≤50% (Section 10.4.6).

4.3. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
3. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included if the investigator determines and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. A single repeat of a procedure or lab parameter is allowed to determine eligibility.
4. Participants who are negative on two consecutive tests for SARS-CoV-2, performed at Screening and within 5 days (ideally within 24 hours) of admission to the Phase I unit, using an approved molecular test (PCR) or an immunological test for a viral antigen.

Weight

5. Body weight ≥40 kg and body mass index (BMI) within the range 18 to 32 kg/m^2 (inclusive).

Sex

6. Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and through the follow-up phase after the last dose of study intervention:

- Refrain from donating sperm.

Female Participants:

a) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   I. Is not a woman of childbearing potential (WOCBP)

   OR

   II. Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and through the follow-up phase after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

   III. A WOCBP must have a negative highly sensitive (Appendix 2) pregnancy test (urine or serum as required by local regulations) within the 30 days before the first dose of study intervention.

   IV. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

b) Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

c) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Signs and symptoms which in the opinion of the investigator are suggestive of COVID-19 (i.e. fever, cough etc) within 14 days of inpatient admission
2. Contact with known COVID-19 positive person/s in the 14 days prior to inpatient admission
3. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data
4. Abnormal blood pressure as determined by the investigator.
5. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN)
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
8. QTc >450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. Participants will be excluded if the average QTc interval from triplicate ECGs is >450 msec.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
9. A known hypersensitivity to hyaluronidases (Cohort 4h only)
10. The participant has an underlying skin disease or disorder (i.e. infection, inflammation, dermatitis, eczema, drug rash, drug allergy, psoriasis, food allergy, urticaria) that would interfere with assessment of injection sites.
11. Current or anticipated need for chronic anti-coagulation with the exception of the use of low dose acetylsalicylic acid (≤325 mg) or hereditary coagulation and platelet disorders such as haemophilia or Von Willebrand Disease.
12. Participants considered to have insufficient musculature to allow safe administration of CAB 400 mg/mL (*gluteus medius* or *vastus lateralis*) in the opinion of the investigator will be excluded.

13. History of ongoing or clinically relevant seizure disorder within the previous 2 years, including participants who have required treatment for seizures within this time period. A prior history of seizure, with a seizure free period of at least 2 years, off anti-epileptics, may be considered for enrolment if the investigator believes the risk of seizure recurrence is low. All cases of prior seizure history should be discussed with the medical monitor prior to enrolment.
14. History of or on-going high-risk behaviours that may put the participant at increased risk for HIV acquisition in the opinion of the investigator. This includes participants in HIV discordant relationships, or men who report current or prior unprotected anal sex with other men and those reporting prior or current injecting drug use.

Prior/Concomitant Therapy

15. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

Prior/Concurrent Clinical Study Experience

16. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
17. The participant has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
18. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

Diagnostic assessments

19. Presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment.
20. A positive pre-study drug/alcohol screen.
21. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination except for QTc considerations where triplicate is required):

	Males	**Females**
Heart rate	<45 or >100bpm	<50 or >100bpm
PR Interval	<120 or >220 msec	
QRS duration	<70 or >120 msec	
QTc interval	>450 msec	

Note: A heart rate from 100 to 110 bpm can be rechecked by ECG or vitals within 30 minutes to verify eligibility.

22. Evidence of previous myocardial infarction (does not include ST segment changes associated with re-polarization).

23. Any conduction abnormality (including but not specific to left or right complete bundle branch block, atrioventricular [AV] block [2nd degree or higher], Wolff-Parkinson-White [WPW] syndrome).
24. Sinus Pauses > 3 seconds.
25. Any significant arrhythmia which, in the opinion of the Investigator OR GSK/ViiV Healthcare Medical monitor, will interfere with the safety for the individual participant.
26. Non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats).
27. Positive human immunodeficiency virus (HIV) antibody/antigen test (HIV-1 ± HIV-2). Participants will be advised regarding safer sex. In the event a participant acquires HIV during the course of the study they will be required to withdraw from the study and will be referred urgently to an HIV treatment centre for further management.
28. Regular use of known drugs of abuse

Other Exclusions

29. Regular use of tobacco- or nicotine-containing products within 3 months prior to screening.
30. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
31. Participants with a history of intolerance to or with contraindications to the use of CCI [redacted] will be excluded from participation in Cohort 4b
32. Regular alcohol consumption within 6 months prior to the study defined as:

a) An average weekly intake of >14 units for males or >7 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.

33. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.
34. The participant has a tattoo or other dermatological condition overlying the location of injection or a prior history of silicone implants (gluteal) which may interfere with interpretation of injection site reactions or administration of CAB LA.

5.3. Lifestyle Considerations

An overnight fast is preferred prior to screening laboratory assessments; however, a minimum of a 6 hour fast is acceptable. Otherwise, food and drink can be given ad libitum throughout the course of the trial. At visits where participants will be in the clinic for multiple hours, meals will be provided by the study site (in the form of a boxed lunch or card for use at the site cafeteria).

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices during oral lead in period through Day 29 PK collection.

5.3.2. Alcohol

Participants will abstain from alcohol for 48 hours prior to initiating oral dosing and prior to the injection. Participants will abstain from alcohol for 48 hours prior to the collection of the pharmacokinetic sampling and clinical laboratory tests during each session.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

Participants will be advised regarding the long PK tail of GSK1265744 and the potential for emergence of HIV drug resistance to cabotegravir should individuals acquire HIV. All participants will be advised that the use of condoms for 12 months following the last injection or until the plasma concentration of GSK1265744 falls below the lower limit of quantification if this occurs prior to week 52 is advisable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Participants should be assigned a new participant number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

6.1.1. Formulations of CAB

6.1.1.1. Cabotegravir Tablets (CAB)

CAB is manufactured by GlaxoSmithKline and is formulated as white to almost white oval shaped film coated 30 mg tablets for oral administration, packaged in high density polyethylene (HDPE) bottles with desiccant and child-resistant closure that include an

induction seal. CAB tablets will be packaged in bottles of 30 tablets. Participants must keep all investigational product (IP) in its original pack container. GSK will notify sites if and when data are available to support the use of pill boxes. The recommended storage conditions, and expiry date where required, are stated on the product label.

CAB Tablet is composed of cabotegravir sodium, lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate, and white film-coating. The white film-coating contains hypromellose, titanium dioxide and polyethylene glycol.

6.1.1.2. Cabotegravir Injectable Suspension (CAB 400 or CAB 200)

GSK1265744 400 mg/mL (CAB 400) and GSK1265744 200 mg/mL (CAB 200) are manufactured by GlaxoSmithKline and are sterile white to slightly pink suspensions containing a sterile white to slightly pink suspension containing either 400 mg/mL or 200 mg/mL of GSK1265744 as free acid for administration by intramuscular (IM) injection or Subcutaneous (SC) Injection. The product is packaged in a glass vial with a stopper and aluminum seal. The glass vial is a clear vial at the time of filling the suspension, and the vial becomes brown upon sterilization by gamma radiation.

Each vial is for single-dose use containing a withdrawable volume of 2.0 mL and does not require dilution prior to administration. Each vial is packaged in a 1x vial carton. The recommended storage conditions, and expiry date where required, are stated on the product label.

ARM Name	ACTIVE	ACTIVE CONTROL/ACTIVE (Cohort 4h)	ORAL LEAD IN (OLI)	ACTIVE (Cohort 4h)
Intervention Name	Cabotegravir	Cabotegravir	Cabotegravir Sodium	rHuPH20 (see Section 6.1.3)
Type	Drug	Drug	Drug	Biologic
Dose Formulation	Injectable Suspension	Injectable suspension	Tablet	Solution for injection
Unit Dose Strength(s)	400 mg/ml	200 mg/mL	30 mg	1 mg/mL, 0.5mL fill (enzyme activity approximately 55,000U per vial
Dosage Level(s)	400 mg – 2000 mg	200 mg – 1000 mg	30 mg	5000 U
Route of Administration	IM injection, SC Injection	IM Injection, SC Injection	oral	SC injection
Use	experimental	experimental	experimental	experimental

ARM Name	ACTIVE	ACTIVE CONTROL/ACTIVE (Cohort 4h)	ORAL LEAD IN (OLI)	ACTIVE (Cohort 4h)
Intervention Name	Cabotegravir	Cabotegravir	Cabotegravir Sodium	rHuPH20 (see Section 6.1.3)
Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product NIMP	IMP (Cabotegravir)	IMP (Cabotegravir)	IMP (Cabotegravir Sodium)	IMP (rHuPH20)
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor.	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in a vial in a 1x vial carton. Each vial/carton will be labelled as required per country requirement.	Study Intervention will be provided in a vial in a 1x vial carton. Each vial/carton will be labelled as required per country requirement.	Study Intervention will be provided in a high-density polyethylene (HDPE) bottle. Each bottle will be labelled as required per country requirement.	Study intervention will be supplied in a clear glass vial. Each vial will be labelled as required per country.
Current/Former Name(s) or Alias(es)	GSK1265744	GSK1265744	GSK1265744	rHuPH20

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[redacted]

6.1.3. Recombinant human hyaluronidase PH20 (rHuPH20)

Participants in Cohort 4h will receive rHuPH20 (5000 U) followed by CAB 200 mg/mL or 400 mg/mL formulation via subcutaneous injection via a single butterfly needle (also see Section 6.1.1.2). Due to a dead volume of 0.331 mL in the butterfly tube, a larger volume of CAB 200 mg/mL or CAB 400 mg/mL formulation will be required. Therefore, 1.4 mL of CAB 400 mg/mL and 2.4 mL of CAB 200 mg/mL will be used for injection, and the exact doses of CAB 400 mg/mL and CAB 200 mg/mL administered will be 427.6 mg (1.069 mL) and 413.8 mg (2.069 mL), respectively. Guidance regarding test drug preparation and administration is outlined in the pharmacy manual and drug administration instruction.

rHuPH20 will be supplied as ENHANZE™ Drug Product (EDP). EDP (rHuPH20) Solution for Injection, 1 mg/mL (110,000 U/mg), is supplied as a clear, colorless sterile liquid, packaged in a clear glass 2 mL vial, with a rubber stopper and aluminum over seal. Each vial of EDP contains 0.5 mL of recombinant human hyaluronidase (rHuPH20).

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.2.1. Dosage and Administration

All participants will be assigned treatment with Oral CAB 30 mg once daily for 4 weeks during the Oral Lead In phase. Regardless of treatment arm assignment, the investigator should instruct all participants on the importance of treatment adherence. Participants will be recruited to Cohort 1 first, then to Cohort 2 and followed by Cohort 3. In circumstances where recruitment to or dosing of a cohort is paused, participants may be recruited to subsequent cohorts and re-randomized (only prior to the injection phase), if deemed appropriate by the investigator and sponsor. Dosing is outlined in Table 2 below.

Table 2 Dosage and Administration

Oral Lead-In	
OLI Days 1 to 28	Take 1 tablet CAB 30 mg once daily. *Should be taken with or without a meal once daily at approximately the same time each day.*
7-14 Day Washout Period (from Day 29)	
Part 1	
First Injection (Loading Dose)	
Cohort 1	Receive CAB 600 mg given as 1 x 1.5 mL CAB 400 mg/mL formulation or 600 mg as 1 x 3 mL CAB 200 mg/mL IM gluteal injection
Cohort 2	Receive CAB 600 mg given as 1 x 1.5 mL CAB 400 mg/mL formulation or 300 mg as 1 x 1.5 mL CAB 200 mg/mL subcutaneous abdominal injection
Cohort 3	Receive CAB 600 mg given as 1 x 1.5 mL CAB 400 mg/mL formulation or 600 mg as 1 x 3 mL CAB 200 mg/mL IM lateral thigh injection The STR agreed[9]: Receive CAB 400 mg given as 1 x 1 mL of CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM lateral thigh injection
Cohort 4	Optional cohort. Receive CAB 400 mg/mL formulation (to a maximum of 1200 mg/3 mL if given IM or 600 mg/1.5 mL if given SC) or matched volume of CAB 200 mg/mL formulation if SC, and matched dose if IM. Dose determination by STR

[9] At their meeting on 22 December 2020, the STR agreed to reduce the dose of the first injection for remaining Cohort 3 participants based on interim PK data from Cohorts 1 and 2.

1

	The STR agreed[10]: Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM gluteal injection
Cohort 4b	Receive CAB 300 mg given as 1 x 0.75 mL CAB 400 mg/mL formulation subcutaneous abdominal injection[11]
Cohort 4h	Receive 5000 U of rHuPH20 followed by CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 1 x 2 mL CAB 200 mg/mL given as subcutaneously abdominal injection (sequential administration).[12]
Second Injection (Week 4 ± 3 days, see Appendix 8 [Section 11.8] for permissible procedures during the COVID-19 pandemic)	
Cohort 1	Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM gluteal injection
Cohort 2	Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 200 mg as 1 x 1 mL CAB 200 mg/mL subcutaneous abdominal injection The VSLC agreed[13]: Receive CAB 200 mg given as 0.5 mL CAB 400 mg/mL formulation or 100 mg as 1 x 0.5 mL CAB 200 mg/mL subcutaneous abdominal injection
Cohort 3	Receive CAB 400 mg given as 1 x 1 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM lateral thigh injection
Cohort 4	Optional cohort. Receive CAB 400 mg/mL formulation (to a maximum of 1200 mg/3mL if IM or 600 mg/1.5mL if SC) or matched volume of CAB 200 mg/mL formulation if SC, and matched dose if IM. Dose determination by STR

[10] At their meeting on 22 December 2020, the STR agreed to conduct Cohort 4.

CCI [redacted]

[12] rHuPH20 and CAB will be injected via a single butterfly needle. Due to a dead volume of 0.331 mL in the butterfly tube, a larger volume of CAB 200 mg/mL or CAB 400 mg/mL formulation will be required. Therefore, 1.4 mL of CAB 400 mg/mL and 2.4 mL of CAB 200 mg/mL will be used for injection and the exact doses of CAB 400 mg/mL and CAB 200 mg/mL administered will be 427.6 mg (1.069 mL) and 413.8 mg (2.069 mL), respectively.

[13] At the VSLC meeting on 13 November 2020, it was agreed to modify the conduct of Cohort 2 based upon interim PK and safety data.

1

	The STR agreed[14]: Receive CAB 200 mg given as 1 x 0.5 mL CAB 400 mg/mL formulation or 100 mg as 1 x 0.5 mL CAB 200 mg/mL subcutaneous abdominal injection
Cohort 4b	Receive CAB 300 mg given as 1 x 0.75 mL CAB 400 mg/mL formulation subcutaneous abdominal injection[10]
Part 2	
First Injection	
Cohort 5	Day 1 receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose 1400 mg/3.5 mL IM). Dose determination by STR. The STR agreed[15]: Receive CAB 800 mg given as 1 x 2 mL CAB 400 mg/mL formulation or 400 mg as 1 x 2 mL CAB 200 mg/mL IM gluteal injection
Cohort 6	Optional Cohort. Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of <2000 mg/5 mL IM). Dose determination by STR.
Second Injection (Week 12 ± 3 days, see Appendix 8 [Section 11.8] for permissible procedures during the COVID-19 pandemic)	
Cohort 5	Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of 1400 mg/3.5 mL IM). Dose determination by STR. The STR agreed[16]: Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of 1200 mg/3 mL IM)

[14] At their meeting on 22 December 2020, the STR agreed to conduct Cohort 4.

[15] At their meeting on 4 February 2021, the STR agreed to conduct Cohort 5 evaluating two Q12W injections of CAB 400 mg/mL 12 weeks apart (n=20, first injection 800 mg, 2 mL IM *gluteus medius* and second injection informed by safety and PK data 4 weeks after injection 1) or two Q12W injections of CAB 200 mg/mL 12 weeks apart as active controls (n=2, first injection 400 mg, 2 mL IM *gluteus medius* and second injection matched on volume to CAB 400 mg/mL IM *gluteus medius*).

[16] At their meeting on 4 February 2021, the STR agreed to conduct Cohort 5 evaluating two Q12W injections of CAB 400 mg/mL 12 weeks apart (n=20, first injection 800 mg, 2 mL IM *gluteus medius* and second injection informed by safety and PK data 4 weeks after injection 1) or two Q12W injections of CAB 200 mg/mL 12 weeks apart as active controls (n=2, first injection 400 mg, 2 mL IM *gluteus medius* and second injection matched on volume to CAB 400 mg/mL IM *gluteus medius*). The dose of the second injection will be guided by safety and PK data when ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments.

Cohort 6	Optional Cohort. Receive CAB 400 mg/mL formulation as an IM gluteal injection or matched volume CAB 200 mg/mL (maximum dose of <2000 mg/5 mL IM). Dose determination by STR.

6.3. Measures to Minimize Bias: Randomization and Blinding

This will be a double-blind study with participants and investigators blinded to randomized treatment assignments with the following exception: due to the difference in concentrations of CAB 400 mg/mL and 200 mg/mL, an unblinded pharmacist at the site will prepare the blinded drug product, and the blinded drug product will be administered by site staff not involved with assessments. CCI [redacted]

The sponsor will be unblinded (meaning some staff may have access to unblinded data). For details of the blinding approach, refer to the SRM.

Subjects will be assigned to study treatment in accordance with the central randomization schedules generated by the Sponsor or their delegate, prior to the start of the study, using the GSK-validated randomization software RANDALL NG. Randomization and study treatment assignment will be facilitated by the interactive response technology (IRT) through the central Randomization and Medication Ordering System Next Generation (RAMOS NG). Each participant scheduled to receive study drug will receive a treatment allocation number when randomized. Study treatment will be administered at the study visits summarized in the SoA.

For each cohort (excluding Cohort 4b), the project physician lead at VH and lead project programmer at GSK will be unblinded to randomized treatment assignments once all subjects in the cohort have completed their injection phase visits (i.e. Week 8 [Injection 2 Day 28] assessments for Part 1 Cohorts, and Week 24 [Injection 2 Week 12] assessments for Part 2 Cohorts).

GSK's Clinical Pharmacology Modelling & Simulation (CPMS) staff will be unblinded when all participants in Cohort 1 and 2 complete Week 4 (Injection 1 Day 28/Injection 2 Day 1) assessments, respectively, when 50% of participants in Cohort 4 complete Week 8 (Injection 2 Day 28) assessments, when all participants in Cohort 3 complete Week 8 (Injection 2 Day 28) assessments, when 50% of participants in Cohort 5 complete Injection 1 Week 4 assessments, and when all participants in Cohort 6 complete Week 24 (Injection 2 Week 12/Week 12 follow-up) assessments.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

For STR meetings, PK data will be reviewed by treatment arm using scrambled subject identifiers to conceal randomized treatment assignments for subjects with on-going injection phase participation. Safety and tolerability data for a cohort will not be reviewed by treatment arm until all subjects in the cohort have completed the injection phase visits. For the preliminary interim analysis when ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments (see Section 10.5), the analysis and presentation of PK results will be limited to data obtained from the first 9 active treatment and first active control participants based on timing of first injection (this will mask whether 2 vs 1 active control participants will have completed Week 4 assessments at the time of the interim analysis). Additional randomization details are provided in Section 4.1.1 and Section 4.1.2.

6.4. Study Intervention Compliance

- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.
- When participants self-administer study intervention(s) at home, compliance with CAB will be assessed by direct questioning, counting returned tablets/capsules, etc. during the site visits and documented in the source documents and CRF.
- A record of the number of CAB tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Permitted Medications and Non-Drug Therapies

Participants must abstain from taking prescription drugs within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start

of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants must abstain from taking non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until the last PK sample collected on Week 8 (injection phase)/Week 4 following last injection (for Cohorts 1-4 and 4b and for Cohort 4h until the last PK sample collected on Week 4 (injection phase)/Week 4 following the injection) or Week 24 (injection phase)/Week 12 following last injection (for Cohorts 5-6), unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/Acetaminophen at doses of ≤2 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

Non-opioid analgesics CCI [redacted] or acetaminophen may be used for prophylaxis (up to 24 hours prior to an injection) as well as treatment of injection site reactions as per the first step (mild pain) of the WHO analgesic ladder (Miller, 2004). Weak opioids (e.g. hydrocodone, codeine, tramadol) with or without non-opioid analgesics may be used on a case-by-case basis by the investigator in consultation with the Medical Monitor.

CCI [redacted]

CCI [redacted]

Antacid use (CAB oral administration only):

Antacid products containing divalent cations (e.g., aluminium, calcium and magnesium) must be taken at least 2 hours before or at least 4 hours after CAB.

Topical creams:

Topical creams should not be applied to the anterior chest wall on the day of scheduled ECGs such that this would impact upon performing ECGs.

COVID-19 vaccines:

Any active trial participant who has access via local guidelines to a COVID-19 vaccine that has received emergency, conditional, or standard market authorization may receive that vaccine, if requested.

6.5.2. Prohibited Medications and Non-Drug Therapies

For participants receiving **either formulation** of CAB, the following medications could significantly decrease the levels of CAB due to enzyme induction and therefore must not be administered concurrently:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampicin / Rifampin
- Rifapentine
- St. John's wort (*Hypericum perforatum*)

Use of anticoagulation agents greater than 14 days are prohibited and systemic anticoagulation on the day of an IM injection should be avoided where possible.

6.6. Dose Modification

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during the study beyond what is allowed within the protocol or directly approved by the study Medical Monitor. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct.

6.7. Intervention after the End of the Study

Participants will not receive any additional treatment from GSK/ViiV Healthcare after completion of the study because only healthy participants are eligible for study participation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants may voluntarily withdraw from the study at any time and for any reason. Site investigators and study staff may withdraw participants before their scheduled termination visit for safety, behavioural, or administrative reasons, or if the participants are unable or unwilling to comply with study procedures. The reasons for withdrawals will be recorded in the participants' study records. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

During the oral lead-in period, early withdrawal on medical grounds will occur if the participant develops a grade 3 or higher AE that is judged by the investigator to be related

directly to the study product (see Appendix 3 and Appendix 4 for definitions and grading of severity of adverse events), or any AE that is deemed clinically significant by the investigator and is judged by the investigator to be related directly to the study product.

For liver-related stopping criteria, please refer to Section 7.1.1.

During the oral lead or injection phase additional pre-specified reasons for discontinuing a participant from the study (or, at minimum, discontinuing administration of study product and continuing safety evaluations) include:

- Pregnancy (please see Section 8.3.5)
- Protocol deviation
- Non-compliance
- Participant withdraws consent
- Participant lost to follow-up
- Investigator discretion
- Sponsor discontinues study

During the injection phase of the study reasons for discontinuing study intervention for a participant are outlined below:

- Any participants experiencing a grade 3 or higher AE event prior to the follow-up phase will withdraw from study intervention and enter the follow-up phase if i) the AE is considered related to IP in the opinion of the investigator and sponsor and ii) the investigator and sponsor agree the subject should be withdrawn from study intervention or
- Any participant developing a grade 3 or higher laboratory abnormality (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride or CPK increase) prior to the follow-up phase and the investigator and sponsor agree the participant should be withdrawn from study intervention or
- Any participant developing a grade 2 or higher rash with concurrent fever, AST/ALT elevation or eosinophilia prior to the follow-up phase will be withdrawn from study intervention.

During the injection phase of the study, reasons for pausing recruitment or dosing of a cohort following review of safety data or Study Team Review are outlined below. Approval to recommence recruitment to or dosing of a cohort following a pause would be given by the ViiV Healthcare Safety and Labelling Committee (VSLC). In the event of a pause of dosing in the injection phase, the washout period may be extended if deemed necessary by the investigator and sponsor.

- 25% of participants receiving GSK1265744 have a grade 3 or higher AE or laboratory abnormality (with the exception of asymptomatic Grade 3 or higher cholesterol, triglyceride or CPK increase) prior to the follow-up phase or a ≥ Grade 2 rash with concurrent fever, AST/ALT elevation or eosinophilia prior to the follow-up phase, where the AEs are considered related to IP in the opinion of the investigator and sponsor.

- If greater than 40% of injections administered within a single cohort are followed by a local injection site reaction of at least grade 2 in severity (once half of cohort participants have received one or more injections).[17]
- If ≥20% of injections given within a single cohort are followed by an injection site reaction of at least grade 3 in severity (once half of cohort participants have received one or more injections).[17]
- If liver chemistry stopping criteria (see Section 7.1.1) are met in a participant in Cohort 5/6.
- If a Cohort 5/6 participant has abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.
- If a Cohort 5/6 participant develops a grade 2 or higher rash with concurrent fever, AST/ALT elevation or eosinophilia prior to the follow-up phase and is withdrawn from study intervention.

During the long acting phase of the study reasons for stopping the study following Study Team Review are outlined below:

There is a participant death assessed as related to study drug by the principal investigator and sponsor.

If a participant is withdrawn prior to receiving the CAB LA injection, a follow-up/withdrawal visit should be scheduled 10-14 days after the last oral dose of CAB. If study intervention is definitively discontinued during the injection phase, the participant will remain in the study and be followed 52-weeks post last injection per the SoA or until CAB is undetectable for appropriate procedures, including blood plasma PK sampling, and safety evaluations, and will not be removed from the study for medical reasons, unless they withdraw consent to continue participation.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology ([across oral and injection phases] in alignment with the FDA premarketing clinical liver safety guidance).

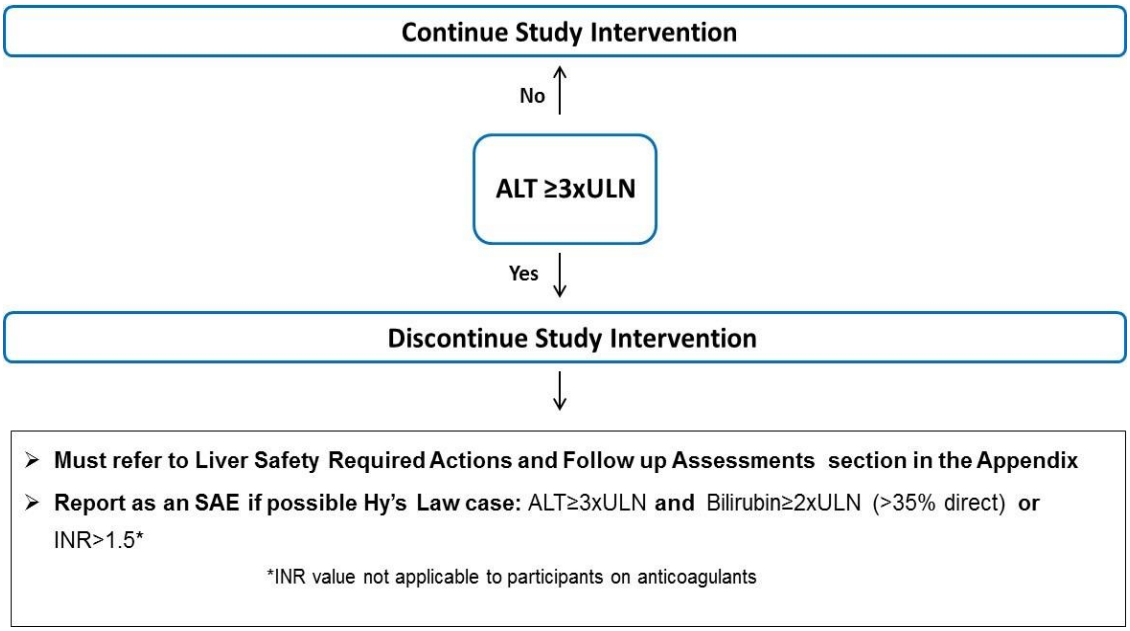
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study intervention for abnormal liver tests is required when:

[17] Where a cohort includes administration via different routes, the ISR data will be considered by each route of administration.

- a participant meets one of the conditions outlined in the algorithm
- in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Appendix 6 for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the same formula must continue to be used for that participant for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on the average of triplicate QTc values ECG readings obtained over a brief (less than 6 minutes) recording period (see Section 8.2.3).

A participant that meets either bulleted criteria below will be withdrawn from study intervention.

- QTc >500 msec
- QTc increase from baseline >60 msec

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

If these assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

  - 12-lead ECG
  - vital signs
  - blood draws.

- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- In Cohort 4b, participants will receive a topical NSAID or a topical steroid (high potency) as per the randomization schedule. These will be applied on Day -1 through to Day 5 after each subcutaneous abdominal injection.

8.1. Efficacy Assessment

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA Section 1.3.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.2.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. 12-lead ECGs will be performed with the subject in a supine/semi-supine position having rested in this position for at least 5 minutes beforehand. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 6 minutes.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- **Screening for SARS-CoV-2**: Study participants will be monitored at Screening and daily while inpatients for COVID-19 symptoms. Investigator(s) should utilise the World Health Organization (WHO) Case Definitions to classify COVID-19 cases [World Health Organization, 2020]. While outpatients, participants should report to the unit any symptoms suggestive of COVID-19. All participants who experience symptoms suggestive of COVID-19 should be isolated in the unit or at home and tested for SARS-CoV-2 using an approved molecular test (PCR) or an immunological test for a viral antigen. The investigator should consider any participant testing positive for SARS-CoV-2 being discontinued from study drug if COVID-19 symptoms are moderate to severe. Appropriate contact tracing for all participants testing positive will be performed within the unit. This should be done in accordance with local legislation and guidelines. Appropriate follow up should be implemented for participants who discontinue the study due to COVID-19.

8.2.5. Suicidal Ideation and Behaviour Risk Monitoring

Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

8.2.6. Assessment of Injection Site Reactions

Injection Site Reaction examination will include an assessment of pain (or tenderness), pruritis, warmth, infections, rash, erythema (or redness), swelling (or induration), and nodules (granulomas or cysts). Digital photographs will be documented on all participants who have an injection site reaction that are considered more serious by the principal investigator (PI), e.g. Grade 2 or above or if persistent beyond 2 weeks.

Injection site erythema/redness or swelling/induration will be evaluated and graded using the greatest measured surface area (as well as impact with usual social and functional activities) as per DAIDS and data regarding the size of these injection site reactions recorded at each ISR assessment. The greatest width and length of these injections site reactions should be recorded in the CRF at each ISR assessment (Cohorts 4, 5 and 6). If the grade of an ISR changes over time, each change will also be recorded in the CRF. See Section 11.7 The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE Grading Table”).

8.2.6.1. Diary Cards

Participants will complete a diary card following each injection. This allows participants to record and score the severity of any reactions as well as record any action taken such as use of analgesic medication prophylactically or following the injection. Participants will also be asked to collect their temperature daily for 14-days following each injection. Concomitant medication will be recorded in the CRF.

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8.2.6.3. CCI [redacted]

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8.2.6.4. CCI [redacted]

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8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 11.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures,

invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.

- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, non-serious AEs such as ISRs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority,

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the last follow up visit.
- If a pregnancy is reported, the investigator should inform GSK within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- If a participant should become pregnant during the oral lead-in phase, the study product will be immediately discontinued, and the participant will continue to be followed for safety evaluations every 4-5 weeks until the pregnancy outcome is reached, at which point the participants will be terminated from the study. If a participant should become pregnant at any time point after the IM CAB LA injection has been received, she will continue on study and will receive the appropriate safety follow-up evaluations per the SoA.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For the oral lead in period of this study, any tablet intake exceeding a total daily dose of 30 mg will be considered an overdose.

For the injection phase of the study, any dose of CAB 400 mg/mL and CAB 200 mg/mL LA above those specified for each cohort in this protocol and/or selected by the STR for a cohort will be considered an overdose.

GSK/ViiV Healthcare does not recommend specific treatment other than supportive care for an overdose.

- The investigator will use clinical judgement to treat any overdose. Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 52 weeks following the last injection or until CAB can no longer be detected systemically.

- Obtain a plasma sample for PK analysis as soon as possible if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of CAB as specified in the SoA.

- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of CAB. Genetic analyses will not be performed on these plasma samples.
- **Permitted sampling window for the OLI phase:**

Plasma PK Assessment	**Permitted Sampling Window**
Day 1 (1 h)	±15 min
Day 1 (2 h)	±15 min
Day 1 (3 h)	±15 min
Day 1 (4 h)	±15 min
Day 1 (6 h)	±30 min
Day 1 (8 h) (Cohorts 5 and 6 only)	±1 h
Day 1 (12 h) (Cohorts 5 and 6 only)	±1 h
Day 2 (24 h)	±4 h (i.e. 20-28 h from Day 1 dose)

Plasma PK Assessment	**Permitted Sampling Window**
Day 14	±1 day
Day 29	20-28 h from Day 28 dose

Permitted sampling window for the injection phase is provided in the SoA.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

A 6 mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Plasma samples will be collected for storage (pre-dose, Day 14 and Day 28). It is considered unlikely that recombinant human protein rHuPH20 induces an anti-drug antibody (ADA) response in healthy volunteers after a single dose, particularly at low doses. Immunogenicity analysis will be performed on these stored samples if there are safety events suggestive of immune-mediated reactions. Please refer to the SRM for additional instructions regarding storage and processing of these samples.

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9. PHARMACOKINETIC METHOD OF ANALYSES

The department of Clinical Pharmacology Modelling & Simulation (CPMS) will be responsible for the PK analysis of data from Parts 1 and 2.

PK analysis of the plasma CAB concentration-time data will be conducted using non-compartmental methods with WinNonlin (Version 6.3 or higher). Actual sampling and dosing times as recorded in CRF will be used for analysis. From the plasma concentration-time data, the following pharmacokinetic parameters from the oral phase will be determined, as data permit: AUC(0-t), Cmax, tmax, Day 1 C24, and Cτ. From the plasma concentration-time data, the following pharmacokinetic parameters from the injection phase will be determined, as data permit: AUC0-t, Cτ, Cmax, tmax, half-life ($t_{½}$), and absorption rate constant (KALA).

Plasma CAB concentration data will be presented in graphical and/or tabular form and will be descriptively summarized by treatment and cohort.

Population PK analyses using non-linear mixed effects modelling software NONMEM (ICON; Hanover, MD) may be done with the data from the study in conjunction with previous data to inform dose/dosage regimen for CAB 400 mg/mL formulation in Part 1 (Cohorts 4 and 4b) and Part 2 of the study.

Details of PK analyses and simulations will be provided in the report and analysis plan (RAP) separately.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

This study is primarily designed to describe the PK profile of CAB 400 mg/mL injection administered in different routes. No formal hypothesis will be tested.

10.2. Sample Size Determination

In Part 1, 80 participants in Cohorts 1-4 will be randomly assigned study intervention (CAB 400 mg/mL or AC CAB 200 mg/mL), 24 participants in Cohort 4b will receive study intervention with CAB 400 mg/mL, and approximately 20 participants in Cohort 4h will be randomly assigned study intervention rHuPH20 with CAB 400 mg/mL or CAB 200 mg/mL, such that approximately 93 evaluable participants will be receiving CAB (15 in each of Cohorts 1-4 and Cohort 4h, 18 in Cohort 4b). In Part 2, 22-44 participants will be enrolled to Cohort 5 and 6 (if conducted) and randomly assigned study intervention (CAB 400 mg/mL or AC CAB 200 mg/mL) such that approximately 16 evaluable participants receiving CAB from each cohort complete the study.

With the determined sample size, certain statistical precision can be achieved when estimating PK trough concentrations using sample geometric mean trough concentration as shown below in Table 3:

Table 3 Statistical Precision When Estimating PK Trough Concentration

Exp. Arm	Time Point	Assumptions*			Precision+ when estimating trough Concentration 90%CI	
		Mean (LgConc.)	SD (LgConc.)	True Geo. Mean (To be observed)		
Cohorts 1-4: 600 mg - >400 mg Q4W (N=15)	Week 4	0.3291	0.66079	1.3898	1.0290	1.8769
	Week 8	0.6123	0.47376	1.8446	1.4871	2.2881
Cohort 4h: 400 mg Q4W (N=8)	Week 4	0.3292	0.66079	1.3898	0.8927	2.1636
Cohorts 5/6: 1200 mg Q3M (N=16)	Week 12	0.0311	0.59603	1.0316	0.7944	1.3395
	Week 24	-1.3837	1.11507	0.2507	0.1538	0.4086

*Assumptions for Q4W arm were from pooled PK Trough data from FLAIR (Study 201584) and ATLAS (Study 201585) i.e. 1.44 μg /mL; assumptions for Q3M were from simulated PK Trough data from a single 1200 mg dose in 80% male and 20% female.
+Precisions were calculated based on t-distribution.

In addition, the bioavailability of CAB 400 mg/mL formulation administered IM to *gluteus medius* will be assessed relative to IM administration to lateral thigh or SC administration to abdomen from Q4W cohorts of Part 1. Additionally, Cτ following

CAB 400 mg/mL formulation administration in Part 1 will be compared to historical PK data of CAB 200 mg/mL using cross-study comparisons.

Table 4 Statistical Precision When Estimating Ratio of PK Trough Concentration

Exp. Arm	Time Point	Assumptions*			Precision+ for estimating Ratio of Trough Concentration		
		CVb%	SD (LgConc.)	Ratio of Geo. Mean Concentration (To be observed)	Half Width of (ΔLg Conc).	90% CI for Ratio	
Cohorts 1-4: CAB 400 mg/ml (N=15)/ Historical CAB 200 mg/ml (N=579)	Week 4	74%	0.66079	0.7	0.28470	0.5266	0.9306
				0.8		0.6018	1.0635
				0.9		0.6770	1.1964
				1.0		0.7522	1.3294
				1.1		0.8275	1.4623
				1.2		0.9027	1.5952
				1.3		0.9779	1.7282
Cohort 4h: CAB 400 mg (N=8)/ Historical CAB 200 mg/ml (N=579)	Week 4	74%	0.66079	0.7	0.387538	0.4751	1.0313
				0.8		0.5430	1.1787
				0.9		0.6109	1.326
				1.0		0.6787	1.4733
				1.1		0.7466	1.6207
				1.2		0.8145	1.768
				1.3		0.8823	1.9154
Cohorts 1-4: CAB 400 mg/ml (N=15) / Historical CAB 200 mg/ml (N=577)	Week 8	50%	0.47376	0.7	0.20413	0.5707	0.8585
				0.8		0.6523	0.9812
				0.9		0.7338	1.1038
				1.0		0.8154	1.2265
				1.1		0.8969	1.3491
				1.2		0.9784	1.4717
				1.3		1.0600	1.5944

* CVb%, SD (Lg Conc) is from pooled Cabotegravir trough concentration data from ATLAS and FLAIR studies
+Precisions were calculated based on t-distribution.

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10.3. Populations for Analyses

The following populations are defined:

Population	Description
Screened	All participants who were screened for eligibility.
Enrolled	All participants who passed screening and entered the study. *Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study.*
Randomized	All participants who were randomly assigned to treatment in the study.
Safety Population	All participants who received at least one dose of study treatment (oral or injection). This population will be based on the treatment the participant received. The Safety population will be used for Safety analyses and summarization of baseline/demographic characteristics.
Pharmacokinetic	All participants in the Safety population who received study treatment and had at least 1 non-missing PK assessment (non-quantifiable [NQ] values will be considered as non-missing values). *Note: PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded.*

10.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Further technical details of the planned statistical analyses will be provided in the reporting and analysis plan (RAP). PopPK model-based simulations on proportions of participants achieving the clinical target will be described in a separate CPMS RAP.

10.4.1. General Considerations

Pharmacokinetic analysis that involves PK modelling to produce the PK parameters will be the responsibility of the Clinical Pharmacology Modelling & Simulation department within GlaxoSmithKline. Statistical analyses of the pharmacokinetic concentration and pharmacokinetic parameters and all other clinical data including safety and demographic data will be the responsibility of Clinical Statistics & Programming, GlaxoSmithKline.

10.4.2. Primary Endpoints

The primary endpoints are injection phase PK parameters including Cmax, tmax, Cτ, AUC0-t, terminal phase half-life($t_{1/2}$) and absorption rate constant (KALA) for each cohort. The PK Parameter Population will be used for the analyses of these endpoints.

Following $\log_e$-transformation, the PK parameters will be summarized by treatment and time period if applicable. Summary statistics (such as mean, standard deviation, median, min, max) will be produced for the $\log_e$-transformed PK parameters. The Summary statistics will also be back-transformed to the original scale to produce geometric mean and between participant coefficient variation (CVb).

In addition, the primary analyses will also include the following assessments based on geometric mean ratios:

- Pair-wise comparisons between Cohorts 1, 2, 3, 4, 4b, and 4h for CAB 400 mg/mL plasma trough concentrations (Cτ), Cmax and AUC0-t at Week 4 (Injection 1 Day 28) and Week 8 (Injection 2 Day 28) where administered via different routes;
- CAB 200 mg/mL plasma trough concentrations (Cτ) at Week 4 (Injection 1 Day 28) for Cohorts 4h compared to historical CAB 200 mg/mL data (Week 8 Cτ following first injection at Week 4b in ATLAS/FLAIR);
- CAB 400 mg/mL plasma trough concentrations (Cτ) at Week 4 (Injection 1 Day 28) for Cohorts 1, 2, 3, 4, 4b and 4h compared to historical CAB 200 mg/mL data (Week 8 Cτ following first injection at Week 4b in ATLAS/FLAIR);
- CAB 400 mg/mL plasma trough concentrations (Cτ) at Week 8 (Injection 2 Day 28) for Cohorts 1, 2, 3, 4, and 4b compared to historical CAB 200 mg/mL data (Week 12 Cτ following second injection at Week 8 in ATLAS/FLAIR);
- CAB 400 mg/mL plasma trough concentrations (Cτ) at Week 12 (Injection 1 Week 12) for Cohorts 5 and 6 (if conducted) compared to historical CAB 200 mg/mL data (Week 8 Cτ following first injection at Week 4b in ATLAS/FLAIR).

Relative bioavailability assessments using pair-wise comparisons between cohorts in the current study may be done with dose-normalized PK parameters if the doses administered are different in different cohorts.

Following log transformation, PK concentration or PK parameters will be separately analyzed using a linear regression model with fixed effect terms for the treatment. Point estimates and corresponding 90% confidence intervals will be constructed for the differences (CAB 400 mg/mL – CAB 200 mg/mL). The point estimates and their 90%

confidence intervals will then be transferred back to provide point estimates and 90% confidence intervals on the original scale.

10.4.3. Safety Endpoints

The safety endpoints are safety and tolerability parameters including adverse events, clinical laboratory tests, vital sign assessments. Liver biochemistry abnormalities are included as secondary endpoints. The Safety Population will be used for the analyses of the safety endpoints. Participants on active control CAB 200 mg/mL will also be combined as a single group for the analysis. Safety data will be presented in tabular and/or graphical format and summarized with descriptive statistics according to GSK's Integrated Data Standards Library (IDSL) standards.

10.4.4. Secondary Endpoints

The secondary endpoints are tolerability parameters including patient reported outcome measures and liver biochemistry abnormalities. Participants on active control CAB 200 mg/mL will also be combined as a single group for the analysis. The Safety Population will be used for the analyses for these endpoints. The secondary endpoints data will be presented in tabular and/or graphical format and summarized with descriptive statistics according to GSK's IDSL standards.

The secondary endpoints for the PK parameters following oral administration (i.e., AUC0-t, Cmax, tmax, Day 1 C24, and Cτ) will be presented in tabular and/or graphical format and summarized with descriptive statistics according to GSK's IDSL standards.

10.4.5. Exploratory Endpoints for Cohort 4b and Other Cohorts

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10.4.6. Bayesian Predictive Probability for Cohort 5 and 6 Dose Selection

A Bayesian predicted probability ≤50% that any participant's Cmax will exceed a criteria of 22.5 µg/mL following dose escalation is used to support dose selection for Cohort 5 and 6. See Section 4.2 for additional considerations for the determination of the dose and dosing schedule, and Section 4.2.3 for rationale supporting the Cmax criteria of 22.5 µg/mL.

Cmax for Cohort 5 Injection 1 will be extrapolated from observed concentrations in Cohort 1 under the assumption of dose proportionality, using the following Bayesian model (with non-informative prior distributions for the model parameters):

$$y_i = \theta_1 + d_i + \varepsilon_{ij} \quad [1]$$

Where is y_{ij} is the logarithm of Cmax for *i*-th participant; d_i, is the logarithm of the dose received by the *i*-th participant, $\hat{\theta}_1$, is the population intercept, ε_i is random error of *i*-th participant (assumed to be normally distributed with mean 0).

Cmax for Injection 2 in Cohort 5 will be extrapolated from observed values in Cohort 1 following each injection and in Cohort 5 following injection 1 (for at least 50% of participants completing Week 4 assessments), using the following Bayesian mixed effects model [Whitehead, 2001] (with non-informative prior distributions for the model parameters):

$$y_{ij} = \theta_1 + \theta_2 d_{ij} + s_i + \varepsilon_{ij} \quad [2]$$

where is y_{ij} is the logarithm of Cmax for the *j*-th observation on the *i*-th participant; d_{ij}, is the logarithm of the *j*-th dose received by the *i*-th participant. $\hat{\theta}_1$ *and* $\hat{\theta}_2$, are the population intercept and slope, respectively, and s_i is the random effect of *i*-th participant and ε_{ij} is random error of *i*-th participant in *j*-th dose (assumed to be mutually independent, normally distributed random variables with mean 0). A similar modelling approach will be used for Cohort 6, if conducted.

Based on the above models, the Bayesian predictive probability for injection 1 and injection 2, respectively, following dose escalation is calculated according to the following MCMC procedure:

1. For each iteration, obtain a random sample of model parameter values from the posterior parameter distribution estimated from the Bayesian model above:
   - $\hat{\theta}_1,\ \hat{\sigma}$ $(the\ estimated\ standard\ deviation\ of\ \varepsilon_i)\ for\ model$ [1], or
   - $\hat{\theta}_1, \hat{\theta}_2, \hat{s}_i\ (i, 2, \ldots 28), \hat{\sigma}$ $\left(the\ estimated\ standard\ deviation\ of\ \varepsilon_{ij}\right)\ for\ model$ [2]
2. For each of n=20 new participants, obtain a random sample for the predicted Cmax values corresponding to log-dose *d* from the following Normal distribution (*mean, variance*):
   - $N(\hat{\theta}_1 + d,\ \hat{\sigma}^2)$ for model [1], or
   - $N(\hat{\theta}_1 + \hat{\theta}_2 * d + \hat{s}_i, \hat{\sigma}^2)$ for model [2]
3. Repeat steps 1 and 2 for 100,000 iterations;
4. Count the number of iterations N in which any of the predicted Cmax values exceed the criteria of log (22.5);
5. The Bayesian predictive probability is calculated as $\frac{N}{100000}$.

The selected Cohort 5 Injection 1 dose of 800 mg had a calculated Bayesian predicted value of 3.9%, which met the ≤50% criterion for dose escalation. The same approach will be applied to Cohort 6 if conducted.

10.5. Planned Analyses

The following 13 preliminary analyses will be conducted for STR review:

1. When all participants in Cohort 1 complete Week 8 (Injection 2 Day 28/Week 4 follow-up) assessments (*results of this analysis will determine Cohort 5 dose and dosing schedule*);

2. When all participants in Cohort 1 & Cohort 2 complete Week 4 (Injection 1 Day 28/Injection 2 Day 1) assessments (*results of this analysis will determine if optional Cohort 4 will proceed and the dose/dosing schedule*);

3. When all participants in Cohort 2 complete Week 8 (Injection 2 Day 28/Week 4 follow-up) assessments;

4. When ≥50% participants in Cohort 4 complete Injection 1 Day 10 assessments following Injection 1, data on injection site reactions will be reviewed prior to proceeding with Cohort 5 Injection 1;

5. When 50% participants in Cohort 4 complete Week 8 (Injection 2 Day 28) assessments PK and safety data will be reviewed;

6. When all participants in Cohort 3 & Cohort 4 complete Week 8 (Injection 2 Day 28/Week 4 follow-up) assessments;

7. When all participants in Cohort 4b complete Week 8 (Injection 2 Day 28) assessments, PK and safety data will be reviewed;

8. When ≥50% participants in Cohort 4h complete Week 4 (Injection Day 28) assessments, PK and safety data will be reviewed;

9. When all participants in Cohort 4h complete Week 4 (Injection Day 28) assessments, PK and safety data will be reviewed;

10. When ≥50% participants in Cohort 5 complete Injection 1 Week 4 assessments, the safety and PK data will be used to determine the dose for Injection 2;

11. When all participants in Cohort 5 complete Week 12 (Injection 1 Week 12 /Injection 2 Day 1) assessments (*results of this analysis will determine if optional Cohort 6 will proceed and the dose/dosing schedule*);

12. When all participants in Cohort 5 complete Week 24 (Injection 2 Week 12/Week 12 follow-up) assessments;

13. When all participants in Cohort 5 & Cohort 6 (if conducted) complete Week 24 (Injection 2 Week 12/Week 12 follow-up) assessments.

The timing or number of preliminary analyses above may be modified based upon emerging data, for example if the planned dosing for a cohort is modified following an STR review due to safety pausing criteria described in Section 7.1 being met, the timing

of the analysis may be modified accordingly.

A further unblinded preliminary analysis will be conducted when all participants in Part 1 Cohorts 1, 2, 3, 4 complete the 8-week Injection Phase to support an abstract submission of key results to a scientific conference.

At least two formal analyses will be conducted:

1. Injection Phase complete: when all participants in Part 1 Cohorts 1, 2, 3, 4 and 4b complete the 8-week Injection Phase, all Cohort 4h participants complete the 4-week Injection Phase and all participants in Part 2 complete the 24-week Injection Phase.
2. End of Study: when all subjects complete the 52-week Follow-up Phase in Part 1 and Part 2.

The Injection Phase complete and End of Study formal analyses will be described in separate clinical study reports.

Each contributing cohort will be unblinded for the purpose of conducting the above formal analyses (after all participants in the cohort complete the injection phase); however, participants and investigators will remain blinded to treatment allocation until each participant in the cohort completes the 52-week Follow-up Phase.

If the recruitment time is prolonged, a formal unblinded interim analysis of data from Cohort 4b and/or Cohort 4h (i.e. prior to all participants in the cohort completing the injection phase) may be conducted to support timely dissemination of study results. The decision to conduct an interim analysis and planned analyses will be documented before unblinding treatment allocations. To minimise bias, the interim results will not be shared with any participants and investigators. However, when investigators are identified as authors of a potential conference presentation of interim results, those investigators and the other co-authors will have access to the interim results prior to its presentation. No other investigators will have knowledge of these data prior to the last participants completing their last visits for the injection phase. An interim analysis abstract may be submitted to a conference for consideration only if the conference convenes after all data collection for the injection phase has been completed. In order to avoid inflation of type I error, no formal statistical analyses evaluating treatment comparisons will be performed for the interim analysis.

Once all participants in Cohort 1 complete 8 weeks post-injection 1, PK (trough concentrations [$C\tau$] and Plasma AUC0-t), safety and tolerability data will be reviewed along with any safety and tolerability data available at this time from Cohorts 2-3 to determine the dose and dosing schedule for cohort 5 in Part 2. This will be determined by the STR with the aim of selecting a safe dose predicted to achieve approximately 95% of dosed participants having trough concentrations higher than the Phase 3 benchmark for future efficacy studies.

An interim analysis will be performed once all participants in Cohort 1 and Cohort 2 complete their Week 4 assessments post-injection 1. This interim analysis will inform the need for optional Cohort 4 and its dose/dosing schedule and will be based upon review of PK data and all available safety and tolerability data.

An interim analysis for Cohort 5 of PK and safety data up to 4 weeks after the first injection (≥50% participants) and 12 weeks after the first injection, including a review of available PK, safety and tolerability data from cohorts 1-5, will be undertaken to determine the dose for Injection 2 in Cohort 5 and to determine the need for and dose/dosing schedule for Cohort 6, respectively.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATION REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

11.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

GSK/ViiV Healthcare (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about CAB or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the CAB approved for medical use or approved for payment coverage.

11.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant

reports and will have the opportunity to review the complete study results at a ViiV Healthcare/GSK site or other mutually agreeable location.

- ViiV Healthcare/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- ViiV Healthcare/GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with ViiV Healthcare/GSK Policy.
- ViiV Healthcare/GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

11.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Monitoring Plan.

11.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

GSK/ViiV Healthcare or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK/ViiV Healthcare. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

11.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 5 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
- Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at per the SoA during intervention
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Testing for SARS-CoV-2 as per protocol should be undertaken using PCR laboratory testing. Sponsor approval is required for the use of non-PCR based tests for SARS-CoV-2 in the protocol.

Table 5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	CPK
Coagulation tests	PT	PTT	INR	Coagulation tests
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine, alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Highly sensitive [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • Serology [(HIV antibody (laboratory or point of care test), hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			

Laboratory Assessments	Parameters
	• SARS-CoV-2 molecular test (PCR) or an immunological test for a viral antigen. Tests not using PCR technology require Sponsor approval if they are being considered for SARS-CoV-2 testing as per protocol • Immunogenicity assessments of plasma storage samples if there are safety events suggestive of immune-mediated reactions to rHuPH20.

NOTES:

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

Results in death

Is life-threatening
The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
Is associated with liver injury and impaired liver function defined as: • ALT ≥3xULN and total bilirubin* ≥2xULN (>35% direct), or • ALT ≥3xULN and INR** >1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3xULN and total bilirubin ≥2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

11.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to GSK.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK/ViiV Healthcare to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

11.3.4. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor and SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor and the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

11.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

35. Premenarchal
36. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
37. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

11.4.2. Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

11.4.3. Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- The initial information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

  Any female participant who becomes pregnant in OLI phase: will discontinue study intervention and will not receive IM injections.

  If participant gets pregnant after receiving injection(s), the participant should be followed up for safety evaluations per the SoA.

11.5. Appendix 5: Genetics

Use/analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to CAB. They may also be used to develop tests/assays including diagnostic tests) related to CAB and other medicines used to treat or prevent HIV infection. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to CAB or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on CAB (or study interventions of this class) and other medicines used to treat or prevent HIV infection continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

11.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology

Phase 1 liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or <u>international normalized ratio (INR)</u> >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained CAB of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form</td></tr>
</table>

Liver Chemistry Stopping Criteria	
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline	**If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week) [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

11.7. Appendix 7: Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events Version 2.1, March 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

The table can be found at:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (accessed 6 April 2020)

The severity of injection site erythema/redness and swelling/induration will be graded based on surface area (and other symptoms) according to DAIDS.

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017]. Available from: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf

11.8. Appendix 8: Permissible Procedures during the COVID-19 Pandemic

The COVID-19 pandemic presents significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on an individual participant's ability to attend clinic visits. Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to allow flexibility to allow conduct of the study.

Permissible changes to procedures during the COVID-19 pandemic if deemed necessary by the investigator are outlined below. The investigator should discuss with the medical monitor the rationale if any of these changes are required for a participant. For further details refer to the Study Reference Manual (SRM).

- Participants previously deemed eligible during the screening period unable to attend within the allowable screening window due to COVID-19 may be rescreened.

- Oral CAB dosing Days 1 to 28. All doses except Day 1 and Day 14 may be administered at home if participants are unable to attend due to COVID-19.

- AE assessments during the oral lead in may be conducted by telephone at home if participants are unable to attend due to COVID-19.

- Duration of admission to the clinic may be extended if deemed necessary by the investigator due to the COVID-19 pandemic.

- Participants require two negative SARS-CoV-2 tests for inclusion in the study and prior to starting oral CAB in the OLI phase. Prior to Injection 1 and Injection 2:

    - **Where SARS-CoV-2 is circulating in the community**, participants should have one SARS-CoV-2 test approximately 1 week prior to admission to the clinic. A second test would be done upon admission; prior to the test result being known, participants should follow strict infection control procedures (PPE/social distancing) and should be isolated within an area of the unit to avoid exposure to COVID-19 negative participants until the test result is known. Once the test result is a confirmed negative, they can be released into the unit and follow infection control practices as per unit guidance. A further test will be done on Day 8 upon discharge from the clinic (or in Cohort 4h upon discharge from the clinic between Day 5 and Day 8).

    - **Where SARS-CoV-2 is NOT circulating in the community**, SARS-CoV-2 testing prior to dosing may be performed within 5 days of admission to the clinic, and if participants are not admitted, they will be advised to avoid exposure to COVID-19 and self-quarantine until entrance to the unit while awaiting final testing clearance. Sponsor approval is required for site(s) to adopt SARS-CoV-2 testing within 5 days of admission to the clinic if study participants do not remain and isolate within the unit until test results are known. A further test on Day 8 (or

in Cohort 4h between Day 5 and Day 8) upon discharge from the clinic is NOT required.

- Participants should follow local, regional, and national guidance on social distancing and/or self-isolation to decrease the probability of acquiring SARS-CoV-2 (outside of the clinical trial unit).

- The 7 to 14-day washout period after the oral lead in may be extended if deemed necessary by the investigator due to the COVID-19 pandemic.

- If a participant has suspected COVID-19, or tests positive for COVID-19, or has potential COVID19 exposure while enrolled in the study, the Investigator must assess the impact of this disease/situation on the benefit/risk for the participant(s) to continue in the study, as well as if the participant has met protocol withdrawal criteria. Any adverse events related to the COVID-19 infection should continue to be evaluated as to whether they meet SAE criteria as defined in Section 11.3.2., and if so, reported in line with the SAE reporting requirements (Section 11.3.4). Investigator(s) should utilise WHO Case Definitions to classify COVID-19 cases [World Health Organization, 2020]. The Sponsor recognises that COVID-19 case definitions may evolve during the study period, the most recent edition should be consulted for each case. For all AEs or SAEs related to COVID-19, details should also be entered into the specific COVID-19 eCRF. The study site should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation in the setting of clinically defined mild COVID-19 infection.

11.9. Appendix 9: Abbreviations and Trademarks

AC	Active control
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC0-t	Area under the concentration-time curve for each injected dose from time zero to last quantifiable time point
AUC(0-24)	Area under the concentration-time curve over 24 hours
AV	Atrioventricular
hCG	Human Chorionic Gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
C24	Concentration at 24 hours
CAB	Cabotegravir
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
Cτ	Last observed quantifiable concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling & Simulation
CRF	Case Report Form
CV	Coefficient of variance
DDI	Drug-drug interaction
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
ECG	Electrocardiogram
EDP	ENHANZE™ Drug Product
EW	Early withdrawal
FDA	Food and Drug Administration
FPFV	First participant First Visit
FRP	Females of reproductive potential
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Healthcare provider

HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HRT	Hormonal replacement therapy
HSR	Hypersensitivity Reactions
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
ISRs	Injection Site Reactions
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
λz	Terminal phase rate constant
L	Liter
LA	Long Acting
LAM	Lactational amenorrhoea method
LAP	Long acting parenteral
LFTs	Liver function tests
µg	Microgram
µL	Microliter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRHD	Maximum recommended oral human dose
MSDS	Material Safety Data Sheet
msec	Milliseconds
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOAEL	No-observed-adverse-effect level
NQ	Non-quantifiable
CCI	[redacted]
NTD	Neural tube defect
OLI	Oral Lead In
PCR	Polymerase chain reaction

PD	Pharmacodynamic
PGx	Pharmacogenetics
PI	Principal Investigator
CCI	
PK	Pharmacokinetic
PopPK	Population PK
POC	Proof of concept
PPE	Personal protective equipment
PrEP	Pre-exposure prophylaxis
PTT	Partial thromboplastin time
Q4W	Four-weekly
Q12W	Twelve-weekly
QC	Quality control
QD	Once daily
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RAMOS NG	Randomization and Medication Ordering System Next Generation
RBC	Red blood cells
rHuPH20	Recombinant Human Hyaluronidase PH20
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SRM	Study Reference Manual
STR	Study Team safety & PK Review
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
t½	Terminal phase half-life
τ	Dosing interval
tmax	Time of occurrence of Cmax
UGT	UDP glucuronosyltransferase
ULN	Upper limit of normal
VAPI	Vaccines' Perception of Injection
VSLC	ViiV Healthcare Safety and Labelling Committee
US	United States
WBC	White blood cells
WOCBP	Woman of Childbearing Potential

WPW syndrome	Wolff-Parkinson-White syndrome

Trademark Information

Trademarks of ViiV Healthcare
None

Trademarks not owned by the ViiV Healthcare
ENHANZE
HYLENEX
RANDALL NG
WinNonlin

11.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 5: 07-SEP-2021

Overall Rationale for the Amendment:

The primary reason for this amendment is to include a further cohort in Part 1 (Cohort 4b) which will evaluate subcutaneous abdominal injections 4 weeks apart with the use of a topical NSAID or topical steroid; relevant sections throughout the protocol were updated accordingly. Revisions were also made to clarify recording of injection site reaction adverse event data while information on collecting information on device efficiencies has been removed.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Objectives and Endpoints 3. Objectives and Endpoints, Primary	Update to PK primary endpoints	To reflect inclusion of Cohort 4b with this amendment Assessments of relative bioavailability are meaningful for pairwise comparison of cohorts, not for historical comparisons
1.1 Synopsis, Overall Design	New paragraph describing Cohort 4b added	To describe the design of Cohort 4b
1.1 Synopsis, Overall Design	A sentence describing timing of Injection 2 added	For clarification
1.1 Synopsis, Number of Participants	Overall participant numbers updated	24 more participants are to be enrolled in the study (Cohort 4b)
1.1 Synopsis, Intervention Groups and Duration 6.2.1. Dosage and Administration	Information on injections in Cohort 4b added and length of participants' stay in the clinic for different cohorts clarified	To specify injections, doses and route of administration in Cohort 4b and to update information on length of clinic stay following injections
1.2. Schema	Schema for Cohort 4b added	To describe the design of Cohort 4b
1.3. Schedule of Activities (SoA)	'12-Lead ECG' replaced by 'triplicate 12-Lead ECG' throughout	For clarification
1.3. Schedule of Activities (SoA) 6.1.2. Medical Devices 8.3. Adverse Events and Serious Adverse Events 8.3.1. Time Period and Frequency for Collecting AE and SAE Information 8.3.6. Medical Device Deficiencies 11.1.3. Informed Consent Process 11.7. Appendix 7: Device Deficiencies	New sections regarding reporting for medical device deficiencies had been added in protocol amendment 4; these have been removed again	It was previously thought that the FDA combination product reporting rule applied to Study 212482. The revised position is that the study is not in scope of post-marketing safety reporting for combination products since ViiV Healthcare/GSK do not supply devices (i.e. syringes and needles) with cabotegravir, and they are therefore not considered combination product devices.
1.3.3. CAB 400 mg/mL LA Injection Phase and Follow- up: Part 1 Cohort 4b	Cohort 4b schedule of activities added	To describe the timing of assessments in Cohort 4b

Section # and Name	Description of Change	Brief Rationale
2.2. Background	Summary of CAB clinical studies updated based on information from most recent CAB IB	To provide the most recent information
2.3.1. Risk Assessment, Injection Site Reactions (ISRs)	Mitigation strategies (use of topical NSAID or steroid) for Cohort 4b and further guidance on grading of erythema/redness and induration/swelling included	To reflect inclusion of Cohort 4b with this amendment
CCI [redacted]		
4.1. Overall Design 4.1.1. Part 1 4.1.5. Washout Period and Injection Phases	New information on Cohort 4b added	To describe the design of Cohort 4b
CCI [redacted]		
7.1. Discontinuation of Study Intervention	Footnote to ISR pausing criteria added	Where a cohort includes administration via different routes, the ISR data will be considered by each route of administration.
CCI [redacted]		
8.2.6. Assessment of Injection Site Reactions	Further guidance on grading of erythema/redness and induration/swelling and on recording grade changes in the CRF included	To further advise sites on recording ISR AE data
8.2.6.1. Diary Cards	Concomitant medications entered in diary cards to be recorded in the CRF	To remind sites to review diary entries and record concomitant medications in the CRF as required
CCI [redacted]		
8.4. Treatment of Overdose	Overdose definition updated and requirement to record overdoses in the CRF removed	To simplify definition of what constitutes an overdose updated and bring requirements or recording information in line with the CRF
10.2.1. Cohort 4b	Section on Cohort 4b sample size added	To provide rationale for Cohort 4b sample size
10.4.2. Primary Endpoints	Update to PK primary endpoints	To reflect inclusion of Cohort 4b with this amendment
10.5. Planned Analyses	An additional preliminary analysis has been added Formal Part 1 and Part 2 analyses following completion of the injection phases may be combined	To reflect inclusion of Cohort 4b with this amendment
11.7. Appendix 7	Guidance regarding the severity grading of injection site	To further advise sites on recording ISR AE data and ensure consistency across sites

Section # and Name	Description of Change	Brief Rationale
	erythema/redness and swelling/induration according to DAIDS added	
Throughout	Minor editorial and document formatting revisions	Minor and therefore have not been summarized

Amendment 4: (17-Feb-2021)

Overall Rationale for the Amendment:

Revisions were made to provide further details on the conduct and future dosing regimens following the review of preliminary PK and safety data from Cohorts 1, 2 and 3.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis / Rationale 1.1 Synopsis / Overall Design 1.3. Schedule of Activities (SoA)	Randomization in Part 2 will now occur on Day 1 of the injection phase	Randomization in Part 2 after the OLI phase mitigates the risk that a sentinel participant is withdrawn prior to the injection phase and less than 4 sentinel participants will receive their first injection
1.1 Synopsis / Objectives and Endpoints 3. OBJECTIVES AND ENDPOINTS	Objective and endpoints to describe the pharmacokinetic profile of oral CAB added	To align with final outputs described in the reporting and analysis plan
1.1 Synopsis / Overall Design 4.1.1. Part 1	Details on the conduct of Cohort 4, including doses agreed by the STR, added	To specify doses for Cohort 4 following an STR review of preliminary PK and safety data from Cohorts 1 and 2
1.1 Synopsis / Overall Design 1.3.3. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow- up: Part 2 Cohorts 5 and 6 2.3. Benefit/Risk Assessment 2.3.1. Risk Assessment 4.1.2. Part 2 4.1.5. Washout Period and Injection Phases	Details on the conduct of Cohort 5 added, including a reduced maximum dose (up to 1200 mg rather than up to 1400 mg of CAB 400 mg/mL formulation), Inclusion of four sentinel participants (instead of two) and a 10-day safety review, an additional review of Cohort 4 safety data prior to starting the injection phase of Cohort 5, and staggered recruitment of non-sentinel participants	To specify changes to the conduct of Cohort 5 triggered by the review of preliminary PK and safety data from Part 1
1.1 Synopsis / Intervention Groups and Duration 4.1.1. Part 1 4.1.2. Part 2 4.1.5. Washout Period and Injection Phases 6.2.1. Dosage and Administration	Dosing in Cohorts 2, 3, 4 and 5 has been updated	To specify changes to dosing during the injection phases of Cohorts 2, 3, 4 and 5 following VSLC and STR reviews of preliminary PK and safety data

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis / Intervention Groups and Duration 1.3.2. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow- up: Part 1 Cohorts 1-4 1.3.3. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow- up: Part 2 Cohorts 5 and 6	Participants will remain in the clinic for 7 days after each injection	To allow closer monitoring of participant safety during the first 7 days following each injection and aid recruitment
1.2 Schema	Schema and accompanying text provide updated information on the conduct of Cohorts 2, 3, 4 and 5, including dosing	To specify changes to dosing during the injection phases of Cohorts 2, 3, 4 and 5 following VSLC and STR reviews of preliminary PK and safety data
1.3. Schedule of Activities (SoA) 11.9. Appendix 9: Permissible Procedures during the COVID-19 Pandemic	Requirements for SARS-CoV-2 testing have been updated distinguishing between areas/countries where SARS-CoV-2 is circulating in the community and those where it is not	To provide further clarity on SARS-CoV-2 testing to avoid inclusion in the study of participants with COVID-19 and their admission to the clinic prior to dosing
1.3. Schedule of Activities (SoA) 8.2.6. Assessment of Injection Site Reactions	Further information on the assessment of injection site reactions, i.e. the measuring of injection site erythema and swelling, is provided	To collect information of the size of erythema and swelling (allowing grading) at every assessment in the CRF
1.3.3. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow- up: Part 2 Cohorts 5 and 6	Further safety assessments during the first 7 days after each injection, i.e. ECGs and clinical chemistry/haematology, are included	To monitor safety more closely following administration of higher CAB doses in Part 2
2.3.1. Risk Assessment	Risk mitigation strategies for Drug Induced Liver Injury and Injection Site reactions have been strengthened	To monitor safety more closely
2.3.1. Risk Assessment	A risk about the relationship between CAB plasma concentration and QTc was added and described where the median Cmax was 22.5 μg/mL and the maximum time-matched mean QTcF for CAB was 2.62 msec (1-sided 95% upper CI:5.26 msec). CAB did not prolong the QTc interval. PK and ECG mitigation strategies have been added	To describe the risk of any participant exceeding the Cmax criteria of 22.5 μg/mL in Cohorts 5 and 6 and to provide mitigation strategies.
4.2.3. Rationale Supporting Cmax criteria of 22.5 μg/mL in Part 2	New section added	To support using 22.5 μg/mL as a Cmax criteria for dose selection in Part 2
1.3. Schedule of Activities (SoA) 6.1.2. Medical Devices 8.3. Adverse Events and Serious Adverse Events 8.3.1. Time Period and Frequency for Collecting AE and SAE Information	New sections regarding reporting for medical device deficiencies added	

Section # and Name	Description of Change	Brief Rationale
8.3.6. Medical Device Deficiencies 11.1.3. Informed Consent Process 11.7. Appendix 7: Device Deficiencies		
6.3. Measures to Minimize Bias: Randomization and Blinding	To provide details on who is unblinded at what stage of the study and what data will be reviewed by the study team and STR	To clarify the blinding strategy for the study
6.5.1. Permitted Medications and Non-Drug Therapies	To provide more details on the use of analgesics following injection site reactions and the use of COVID-19 vaccines	To clarify what analgesics may be used following injection site reactions
7.1. Discontinuation of Study Intervention	Further pausing criteria related to liver biochemistry are added	To monitor safety more closely following administration of higher CAB doses in Part 2
10.4.4	Analysis of oral CAB PK secondary endpoints described and added	To align with final outputs described in the reporting and analysis plan
10.4.5. Bayesian Predictive Probability for Cohort 5 and 6 Dose Selection	New section added	To detail the Bayesian predicted probability that any participant's Cmax will exceed a criteria of 22.5 µg/mL following dose escalation will be used to support dose selection for Cohort 5 and 6
10.5. Planned Analyses	Three further preliminary analyses included Introduce some flexibility in terms of timings of these analyses	To allow for additional reviews of emerging PK and safety data from Cohorts 4 and 5
11.2. Appendix 2: Clinical Laboratory Tests	Further information on SARS-CoV-2 testing included	To clarify the types of tests that are acceptable for use in this study
Throughout	Minor editorial and document formatting revisions	Minor and therefore have not been summarized

Amendment 3: (29-Oct-2020)

Overall Rationale for the Amendment:

Revisions were made to study eligibility criteria, safety assessments and Appendix 8 for participant safety and to further mitigate the potential risks for study conduct during the COVID-19 pandemic and to rephrase sections that were ambiguous. Information on assessments required for sentinel participants in Cohorts 5 and 6 and the definition of what constitutes an overdose of oral cabotegravir have been updated.

Section # and Name	Description of Change	Brief Rationale
Title page	Global sponsor name and address (excluding US) added	Omitted in previous versions of the protocol
Title page	EudraCT number added	EudraCT number has been obtained since the last amendment

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis / Overall Design / Dosage and Administration 4.1 Overall Design 4.1.4 Oral Lead-in Phase 4.2.1 Oral dose 6.2.1. Dosage and Administration	The washout period starts on Day 29. The number of half-lives of CAB this period covers has been updated (~5-9).	For clarification
1.1 Synopsis / Overall Design 1.3.1. Screening Period and Oral Lead-in Phase: All Cohorts, footnote #11 4.1.5. Washout Period and Injection Phases 4.2.1. Oral Dose 7.1. Discontinuation of Study Intervention	The washout period may be extended if deemed necessary by the investigator and sponsor.	To add flexibility for starting the injection phase.
1.1 Synopsis / Overall Design 4.1 Overall Design 6.2.1. Dosage and Administration	If recruitment to or dosing of a cohort is paused, participants may be recruited or re-randomized (only prior to the injection phase) to subsequent cohorts if deemed appropriate by the investigator and sponsor.	To add flexibility and allow participants to continue in the study by entering a different cohort
1.1 Synopsis / Overall Design / Dosage and Administration 4.1.5 Washout Period and Injection Phases	The window for the second injection is ±3 days, rather than ±7 days.	To avoid that Day 22 and Day 28 visits merge in Part 1. For consistency, the same window will apply for the second injection in Part 2.

Section # and Name	Description of Change	Brief Rationale
6.2.1. Dosage and Administration		
1.1 Synopsis / Overall Design 4.1.2 Part 2	In Part 2, sentinel and other participants may be randomized at the same time but the latter may only proceed to the injection phase following the 72-hour review of safety data for sentinel participants	To clarify when sentinel and other participants may be randomized and dosed in Cohorts 5 and 6
1.3 Schedule of Activities (SoA)	Requirements for SARS-CoV-2 testing prior to the oral lead-in phase and prior the two injection phases of Part 1 and Part 2 revised: further guidance re self-isolation of participants inside the unit until test results are known	To mitigate further the risk to study conduct during the COVID-19 pandemic
1.3.1 Screening Period and Oral Lead-in Phase: All Cohorts	Separate requirement for urine dipstick at Screening removed since it is part of the urinalysis	For clarification
1.3.1 Screening Period and Oral Lead-in Phase: All Cohorts 8.5. Pharmacokinetics	Additional PK samples to be collected on Day 1 (at 8 h and 12 h post dose) during OLI phase for Cohorts 5 and 6	For accurate estimation of PK parameters through dense PK sampling
1.3.2. CAB 400 mg/mL or CAB 200 mg/mL LA Injection Phase and Follow- up: Part 1 Cohorts 1-4 1.3.3. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow-up: Part 2 Cohorts 5 and 6	Weight data to be collected during the follow-up phase	To study potential changes in weight during the study

Section # and Name	Description of Change	Brief Rationale
1.3.3. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow-up: Part 2 Cohorts 5 and 6	Haematology, clinical chemistry, and urinalysis assessments added for Week 4 and 8 following each injection	Omitted in previous versions of the protocol; to monitor safety labs between Day 22 and Week 12 following each injection
1.3.3. CAB 400 mg/mL or 200 mg/mL LA Injection Phase and Follow-up: Part 2 Cohorts 5 and 6	New footnote 11 included	To clarify what assessments are required for sentinel participants in Cohorts 5 and 6 who will be followed clinically for 72 hours after Injection 1
2.3.1. Risk Assessment / Potential effects in women exposed to dolutegravir during conception and early pregnancy	Summary of Data updated with information from final analysis of the Tsepamo study	To provide current data on estimated prevalence of NTDs with DTG exposure at conception
4.1.4. Oral Lead-in Phase	Participants complete 25 (not 26) days of oral CAB dosing at home.	For clarification
5.1. Inclusion Criteria – inclusion criterion #3	Updated inclusion criterion #3: for out-of-range clinical abnormalities or laboratory parameters, consultation with the medical monitor prior to enrolment is no longer required.	To streamline process
5.1. Inclusion Criteria – inclusion criterion #4 8.2.4 Clinical Safety Laboratory Assessments 11.2 Appendix 2: Clinical Laboratory Tests	Testing for SARS-CoV-2 may be based on molecular (PCR) as well as other validated tests	To allow for flexibility as new tests for SARS-CoV-2 are being established

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria – inclusion criterion #6	Male participants should refrain from donating sperm, and female participants agree not to donate eggs (ova, oocytes) for the purpose of reproduction during the study.	As per recommendation by Phase I unit
5.2. Exclusion Criteria	Exclusion criterion *A positive diagnostic HIV-1 antibody/ antigen test* removed; exclusion criterion #26 updated to specify that the HIV antibody/antigen test is for HIV-1 ± HIV-2	Exclusion already covered in exclusion criterion #26: *Positive human immunodeficiency virus (HIV) antibody/antigen test (HIV-1 ± HIV-2)*
7.1. Discontinuation of Study Intervention	Specified what reasons lead to discontinuation of study intervention Clarified follow-up requirements pre- and post-first injection Study reasons for pausing recruitment also apply to pausing dosing of a cohort following review of safety data or Study Team Review.	To provide more clarity with regards to participants discontinuing study intervention versus being withdrawn from the study To add flexibility re pausing recruitment and pausing dosing within a cohort
7.1.2. QTc Stopping Criteria 8.2.3. Electrocardiograms	Recording period to complete a full set of ECG triplicates set as less than 6 minutes.	For consistency
8.4. Treatment of Overdose	Definition of treatment overdose refined	A participant is required to take a CAB tablet at approximately the same time each day.
10.3. Populations for Analyses	Analysis populations redefined	To align with GSK/IDSL standards and the statistical analysis plan
10.5. Planned Analyses	Timepoints for preliminary analyses further defined and one further analysis (“when all participants in Cohort 5 complete Week 24”) added	For clarification

Section # and Name	Description of Change	Brief Rationale
11.8. Appendix 8: Permissible Procedures during the COVID-19 Pandemic	Requirement for participants to follow local, regional, and national guidance on social distancing and/or self-isolation added	To mitigate further the risk to study conduct during the COVID-19 pandemic
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 2: (26-Jun-2020)

Overall Rationale for the Amendment:

Revisions were made to the study eligibility criteria and safety assessments to further mitigate the potential risks for study conduct during the COVID-19 pandemic. Additional changes were made based on comments and recommendations for revisions of Protocol 212482 received from the FDA's Division of Antivirals as mentioned in the Division's 'Study May Proceed' letter dated 3 June 2020.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Rationale and Overall Design 1.3.1. Screening Period and Oral Lead-in Phase: All Cohorts	Randomization occurs on Day 1 of the Oral Lead-in Phase prior to dosing of oral CAB	For clarification
1.1 Synopsis, Intervention Groups and Duration 6.2.1. Dosage and Administration	Cohort 4 (optional cohort), first injection: participants receive CAB 400 mg/mL formulation (to a maximum of 1200 mg/3 mL if given IM or 600 mg/1.5 mL if given SC) **or matched volume of CAB 200 mg/mL formulation if SC, and matched dose if IM**. Dose determination by STR	Previously omitted information on comparator added for clarification
1.1 Synopsis, Overall Design 1.3 Schedule of Activities (SOA) (Part 1 and 2) 4.1.6. Follow-up/Withdrawal Visit	Participants will have PK monitoring up to and including Week 52 post their last CAB injection. Participants with undetectable CAB concentrations before Week 52 will be deemed to have completed follow up and return to the clinic for a last study visit at which activities specified for the Week 52/EW visit will be performed.	For clarification. Those participants with detectable drug level of CAB at the last follow up visit at Week 52 post last injection will not be monitored for safety and PK until the drug level is below the level of quantification every 12 weeks. Monitoring PK until Week 52 following the last injection or until the drug level of CAB is undetectable if this occurs at an earlier time point is consistent with the approach the sponsor has adopted across the CAB development programme.

Section # and Name	Description of Change	Brief Rationale
1.3.1. Screening Period and Oral Lead-in Phase: All Cohorts (footnote 7) 8.5. Pharmacokinetics	Oral Lead-in Day 2 PK sample taken between 20 h and 28 h post first oral dose; Day 29 PK sample taken between 20 h and 28 h post last dose on Day 28.	For clarification and as per comment from the FDA's Division of Antivirals re PK sampling window
1.3 Schedule of Activities (SOA)	SOA revised to include SARS-CoV-2 testing at Screening and before admission to the Phase I unit prior to the oral lead-in phase and before admission to the Phase I unit prior the two injection phases of Part 1 and Part 2	To mitigate risk to study conduct during the COVID-19 pandemic
1.3 Schedule of Activities (SOA)	Participants may be admitted to the clinic the day before Day 1 of each phase and have some assessments done on the day of admission.	To reflect practice at the Phase I units
2.3.1. Risk Assessment	Acquisition of HIV and theoretical risk of CAB resistance in the presence of waning CAB concentrations included as risk	For clarification
5.1 Inclusion Criteria	Participant age range revised so that no participants >50 years of age are included	To mitigate risk to study conduct during the COVID-19 pandemic
5.1 Inclusion Criteria	Included a new criterion for participants to have two consecutive negative tests for SARS-CoV-2 at Screening and within 5 days of admission	To mitigate risk to study conduct during the COVID-19 pandemic
5.2 Exclusion Criteria	Included two new criteria excluding participants having signs and symptoms suggestive of COVID-19 and participants who had contact with a known COVID-19 positive person/s	To mitigate risk to study conduct during the COVID-19 pandemic

Section # and Name	Description of Change	Brief Rationale
	within 14 days prior to admission	
5.2 Exclusion Criteria	Participants with a history of or on-going high-risk behaviours that may put the participant at increased risk for HIV acquisition are excluded	As per recommendation by the FDA's Division of Antivirals
6.3. Measures to Minimize Bias: Randomization and Blinding	Revised to improve clarity on use of RAMOS NG for study randomization	Implementation of use of RAMOS NG for randomization of participants
8.2.4. Clinical Safety Laboratory Assessments	Information on screening for SARS-Cov-2 included	To mitigate risk to study conduct during the COVID-19 pandemic
8.2.6.1. Diary Cards	Participants will be asked to collect their temperature daily for 14-days following each injection.	To address comment by the FDA's Division of Antivirals re collecting temperatures following CAB injections
11.2. Appendix 2: Clinical Laboratory Tests (Table 5)	SARS-CoV-2 test included as part of protocol-required safety laboratory assessments	To mitigate risk to study conduct during the COVID-19 pandemic
11.8. Appendix 8: Permissible Procedures during the COVID-19 Pandemic 11.11. Appendix 11: References	Investigator(s) should utilise WHO Case Definitions to classify COVID-19 cases [World Health Organisation, 2020]. WHO reference included.	To mitigate risk to study conduct during the COVID-19 pandemic
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Amendment 1: (22-Apr-2020)

Overall Rationale for the Amendment

The primary reason for this amendment is to reprioritise the cohorts: the order of Cohorts 2 and 3 has changed, i.e. the subcutaneous abdominal injection will now be evaluated in

Cohort 2 and the intramuscular lateral thigh injection in Cohort 3; participants will be enrolled sequentially into Cohorts 1, 2 and 3.

As the COVID-19 pandemic presents significant logistical challenges for many clinical sites, an appendix (Appendix 8 *Permissible Procedures during the COVID-19 Pandemic*) has been added.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 *Synopsis*	Rationale for development of long acting injectable versions of antiretrovirals added	To align with Section 2.1 Study Rationale
Section 1.1 *Synopsis* Section 3 *Objectives and Endpoints*	Details of comparisons of geometric mean ratios of trough concentrations (C_T) and Plasma AUC0-t between cohorts added	For clarification
Section 1.1 *Synopsis* Section 1.2 *Schema* Section 4.1.1 *Part 1* Section 6.2.1. *Dosage and Administration*	Change to the order of Cohorts 2 and 3, i.e. subcutaneous abdominal injection in Cohort 2 and the intramuscular lateral thigh injection in Cohort 3; participants will be enrolled sequentially into Cohorts 1, 2 and 3.	To prioritise evaluation of subcutaneous abdominal injection over intramuscular lateral thigh injection (following delays to study start due to COVID-19 pandemic)
Section 1.3. Schedule of Activities (SoA) Section 4.1.6. Follow-up/ Withdrawal Visit	Visit names updated	For clarification
Section 6.3 *Measures to Minimize Bias: Randomization and Blinding*	Explains and clarifies blinding of participant, investigator/site staff and sponsor	For clarification
10.4.2. *Primary Endpoints*	Explains and clarifies plans for statistical analyses	For clarification

Section # and Name	Description of Change	Brief Rationale
10.5. *Planned Analyses*		
Section 11.8 *Appendix 8: Permissible Procedures during the COVID-19 Pandemic*	New appendix added	The COVID-19 pandemic presents significant logistical challenges for many clinical sites and requires some flexibility in protocol procedures.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

11.11. Appendix 11: References

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