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INVESTIGATOR BREAKOUT SESSION

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Safety and Risk management

Rulan Griesel

Medical Monitor

OVERVIEW – TOPICS FOR REVIEW AND DISCUSSION

1. Safety Assessments
2. C-SSRS
3. ISR Assessment
4. Study Pausing Rules
5. AE and SAE Reporting
6. **Toxicity Management***
7. **Treatment of Overdose***
8. **Risk Management – Mitigation Strategies***

1. SAFETY ASSESSMENTS

- **SoA for timing of safety assessments (Section 1.3)**
  - Physical examination (**Section 8.2.1** and **8.2.7**)
  - Vital signs (**Section 8.2.2**)
  - EKGs (**Section 8.2.3**)
  - Clinical safety laboratory tests (central laboratory, see **Sections 8.2.4** and **10.2**)
  - Pregnancy testing for POCBP (**Section 8.2.5**)
  - SARS-CoV-2 (Exclusion criterion, **Sections 10.12**)
  - Suicidal ideation and behaviour risk monitoring (C-SSRS, see **Section 8.2.6**)
  - Assessment of ISRs (**Section 8.2.8**)

2. C-SSRS

- **C-SSRS**: Columbia Suicidality Severity Rating Scale
  - Validated and standardized questionnaire
  - Definitions based on the Columbia Suicide History Form (Posner et al, 2007)
  - Prospective assessment instrument to detect **early signs of suicidal ideation** & **behaviour** and allow time for appropriate action
  - Gather history of suicidal ideation & behaviour at Day 1 (**lifetime experiences** and current experiences – **last 2 months**) and at each clinic visit (in **relation to last assessment**)
  - Investigator initiated and completed with participant on computer/tablet

2. C-SSRS

- Time for completion is usually **<5 minutes**, can be up to 20 minutes
- A positive alert for suicidal ideation or behaviour should be managed as in clinical practice
- Clinical judgment to determine if **mental health consultation** or referral is necessary
- Positive alerts to be discussed with the ViiV Medical Monitor (MM)

Training resource for investigators:

Training for Researchers - The Columbia Lighthouse Project

2. C-SSRS

- **PSRAE** (Possible Suicidality-Related AE) **eCRF**: an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide

  NOTE: This could be any event, with or without a positive C-SSRS alert

- Information is collected and reported using the PSRAE eCRF form, within **1 week** of awareness
- A PSRAE is also an AE/SAE, so the events needs to be entered as an **AE/SAE** too

3. ISR ASSESSMENTS

- **Injection Site Reaction** – pain, pruritis, warmth, infections, rash, erythema, swelling (or induration), and nodules (granulomas or cysts)
- Injection site erythema or swelling/induration graded using the greatest measured surface area and impact on usual social and functional activities as per **DAIDS**
- The **greatest width** and **length** should be recorded in the eCRF at each assessment
- Injection site **nodules** – the largest diameter recorded at each assessment
- If the grade of an ISR changes over time, **each change to be recorded**

3. ISR ASSESSMENTS

- Criteria for ISRs of interest (**Section 8.2.9**)

  - Any Grade 4 injection site reaction;
  - An ISR of at least Grade 3 in severity where the ISR AE includes any of the following:
    - Ulceration
    - Secondary infection
    - Phlebitis
    - Sterile abscess
    - Drainage
  - ISRs that are Grade 3 based upon the size of erythema or induration alone or based upon pain or symptoms causing inability to perform usual social & functional activities will not be included for the purpose of the ISR monitoring/pausing criteria but will be reviewed and considered when reviewing the ISR data.
  - Any ISR associated with IV or SC administration of VH3810109 should be followed to resolution.

- Discuss with MM and study drug **paused** for participant

3. ISR ASSESSMENTS

- **Digital photographs** documented, where possible, for ISR with visible observations which are **serious/≥Grade 3/persist >2 weeks**

- **Dermatology** consulted for ISRs considered **serious**, or include all of the following: **≥Grade 3, clinically significant or persistent beyond 30 days** (exclude Grade 3 ISRs that include only erythema and/or pain)

4. STUDY STOPPING RULES

Participants must be discontinued from the study for any of the following:

- **Virologic** withdrawal criteria are met (**Section 7.4**)
- **Liver toxicity** stopping criteria are met (**Section 7.1**)
- **Rash** criteria are met (**Section 10.6.2**)
- **Renal toxicity** are met (**Section 10.6.3**)
- **Grade 4** clinical AE considered **causally related** to study drug
- **Pregnancy** (intrauterine), regardless of termination status of pregnancy
- New diagnosis of **Hepatitis B or C** viral infection
- Moderate to severe **COVID-19** infection
- New onset **suicidal ideation**
- Any clinically relevant **Grade 4 laboratory abnormalities** in the absence of a compelling alternate cause (exception of an asymptomatic grade 4 cholesterol, triglycerides or CPK)
- A triplicate set of on-treatment ECGs show the average **QTcF** >550 msec or increase from baseline QTcF >60 msec (**Section 7.3**)
- **ISR** stopping criteria are met (**Section 8.2.9**)

4. STUDY STOPPING RULES

- Participant safety will be monitored by the MM and **safety review team** (SRT) throughout the study
- **Internal safety review committee** (iSRC) review of accumulated data once 50% of participants reach 24-week timepoint
- Ad hoc iSRC review if/when 3 participants experience **confirmed virological failure** (CVF)
- Recommendations of the iSRC may be to continue, pause or stop as a whole or a specific arm of the study

4. STUDY STOPPING RULES

- **ISR Monitoring/Discussion Criteria (Section 8.2.9** and **10.6.2)**
  - ISRs which meet any of the below criteria will be discussed by the SRT:
    - Grade 4 ISR
    - An ISR of at least Grade 3 in severity where the ISR AE includes any of the following (but not limited to): ulcertation, secondary infection, phlebitis, sterile abscess, drainage.
    - Where the PI and study team have concerns regarding an ISR (not listed above) or the ISR profile, this would prompt SRT review and VSLC update with further discussion with VSLC as apprpriate.
  - **≥2 cases** would automatically initiate ViiV safety and labelling committee (**VSLC**) discussion and may cause (i) stopping further dosing in the participant, (ii) pausing recruitment or dosing of a cohort, or (iii) stopping the study

4. STUDY STOPPING RULES

- **Liver chemistry stopping criteria for Phases IIB-IV studies**

- Study treatment must stop immediately when participant meets criteria described in **Table 7**
- A list of Required Actions, Monitoring and Follow up Laboratory Assessments following Liver Stopping Event in **Appendix 10.7**
- Refer to **Section 10.8** for details on study drug restart following transient resolving liver events not related to IP

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If baseline ALT ≤ 1.5x ULN	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If baseline ALT >1.5x ULN	
ALT-absolute	ALT ≥5x baseline OR >500 U/L (whichever occurs first)
ALT Increase	ALT ≥3x baseline but <5x baseline persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3x baseline OR >300 U/L (whichever occurs first) **and** bilirubin ≥2xULN
Cannot Monitor	ALT ≥3x baseline but <5x baseline and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3x baseline and symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

4. STUDY STOPPING RULES

- **QTc Stopping criteria**
  - **QTc** interval >550 msec considered **causally related** to study drug
  - The QTc should be based on averaged QTc values of **triplicate** EKGs obtained over a brief recording period (5 min)
  - QTcF (**Fridericia**) correction formula must be used to determine eligibility and discontinuation
  - QTc stopping criteria met – participant remains in the study and evaluated for all follow-up as per SoA

Severity Grade 1	460 msec or greater but less than 480msec
Severity Grade 2	480 msec or greater but less than 500 msec
Severity Grade 3	500 msec or greater OR 60 msec or greater than baseline AND 480 msec or greater
Severity Grade 4	Life-threatening consequences (e.g., Torsades de Pointes, other serious ventricular dysrhythmias)

Section 10.3

Any untoward medical occurrence temporally associated with the use of a medicinal product, whether or not considered related to the product.
Any unfavourable and unintended sign (including a clinically significant abnormal lab finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

5. AE AND SAE REPORTING

a. Results in death
b. Is life-threatening
c. Requires hospitalisation or prolongation of existing hospitalisation
d. Results in disability/incapacity
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical events that may not immediately result in death or hospitalisation, but may jeopardise the subject, or • Medical events that may require medical/surgical intervention to prevent one of the other outcomes listed in the above definition (i.e., invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias,or convulsions)
g. Is associated with liver injury + impaired liver function: • ALT ≥ 3xULN + total bilirubin ≥ 2xULN (>35% direct), or • ALT ≥ 3xULN + INR > 1.5.

5. AE AND SAE REPORTING

- Investigator is responsible for detecting, documenting, and recording AEs, and FU
- Methods for recording, evaluating, and assessing causality (**Section 10.3**)
- Report all study drug related SAEs from signing the **ICF till final FU** and all **AEs** from **start of study drug till final FU**
- **AEs of special interest:**
  - **VH3810109:** injection site reactions, infusion related reactions, serious/severe immune reactions and neutropenia
  - **Cabotegravir:** seizures

5. AE AND SAE REPORTING

Event	Time Frame for Initial Report	Documents
AEs	1 week	AE eCRF
AESIs	24 hours	AE eCRF
SAEs	24 hours	SAE eCRF
CV event	1 week	CV eCRF
Death	24 hours	Death eCRF
Pregnancy	24 hours	Pregnancy notification form
Liver Event	24 hours	Liver event eCRF
Possible suicidality related AE	1 week	PSRAE eCRF + AE/SAE eCRF

5. AE AND SAE REPORTING

- **Contact information** for reporting SAEs, AESIs, pregnancies and study stopping criteria events

Study contact for questions regarding SAEs, AESIs and pregnancies: Contact GSK's local and/or medical contacts (medical monitor).	**Study contact for reporting of study stopping rules:** If a stopping rule is met, the investigator must immediately inform the GSKs Local and/or Medical contacts (medical monitor).
Contacts for reporting SAEs, AESIs and pregnancies: Available 24/24 hours and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com	**Backup study contact for escalation of stopping rules:** Medical Monitor: Rulan Griesel rulan.x.griesel@viivhealthcare.com +44 7442 775996

5. AE AND SAE REPORTING

- **Pregnancy**
  - No further doses of study drug but may continue other study procedures at the discretion of investigator
  - Collect follow-up information on the participant and the neonate (**consent required**)
  - Details of all pregnancies can be collected after the start of study intervention until **12 months after the last dose (long-term FU period)**
  - **Details of pregnancies in partners of participants do not need to be collected**
  - Pregnancy complication/**abnormal outcome*** or elective termination for medical reasons reported as an AE/**SAE***

5. AE AND SAE REPORTING

- **CV and Death events** – specific CV and Death eCRF section completion guidance (**Section 8.3.9**)
- **Disease-related events/outcomes not qualifying as AEs/SAEs** – events or outcomes listed in CDC Classification System for HIV-1 infections are reported as HIV-associated conditions and not as AEs/SAEs (except exclusions, see **Section 8.3.10**)

  - The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (Section 8.3), or
  - The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or
  - Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
  - Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

6. TOXICITY MANAGEMENT

- **DAIDS** table provides a grading (severity) scale for each AE term; graded 1-5
  - Applies to clinical signs, symptoms and lab analytes
  - All deaths related to an AE are to be classified as grade 5

Grade	Symptoms causing….
Grade 1 (Mild)	No or minimal interference with usual social & functional activities
Grade 2 (Moderate)	Greater than minimal interference with usual social & functional activities
Grade 3 (Severe)	Inability to perform usual social & functional activities
Grade 4 (Potentially-Life Threatening)	Inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability

6. TOXICITY MANAGEMENT

- See **Appendix 6 (Section 10.6)**
- ≥1 ART medication is held due to toxicity/AE, all ART medications should be held to **reduce the risk of resistance**
- **No** toxicity-related **dose reductions** of study drug allowed
- Participants who develop a **Grade 1** or **Grade 2 AEs/toxicity** may continue study treatment at discretion of investigator

6. TOXICITY MANAGEMENT

- **Grade 3 AE/toxicity**:
  - Compelling evidence not related to study treatment – **dosing may continue** (discuss with MM)
  - Related/possibly related to the study drug – should have **study treatment withheld**, rechecked each week until the AE returns to **Grade 2** (once AE is Grade ≤2, **study treatment may be restarted**)
  - Should Grade 3 AE **recur** within **28 days** in the same participant, study treatment should be **permanently discontinued**
  - Participants with Grade 3 AEs requiring permanent discontinuation of study treatment **followed weekly until resolution** of the AE
  - Initiate treatment with **cART** and enter the **long-term FU**

6. TOXICITY MANAGEMENT

- **Grade 4 AE/toxicity:**
  - Study treatment should be **discontinued**
  - If compelling evidence that **not causally related** to study drug, dosing may continue (discuss with MM)
  - Recheck each week until returns to **Grade 2**
  - If permanent discontinuation – start **cART** and follow-up weekly until resolution of AE during **long term follow-up**

- **Rash (Section 10.6.2)**
- **Decline in Renal Function (Section 10.6.3)**
- **CPK elevation (Section 10.6.5)**

MEDICAL MONITOR CONTACTS

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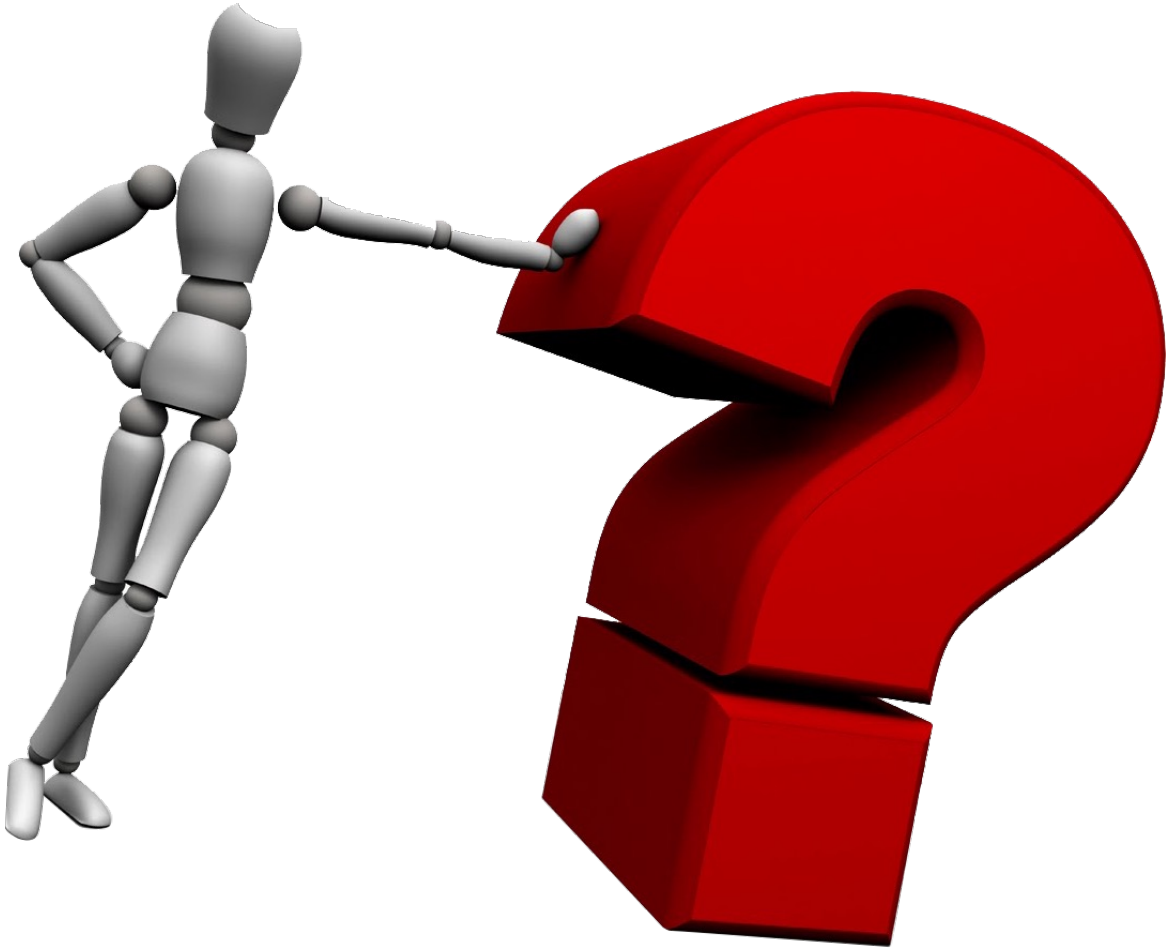
Questions?



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INVESTIGATIONAL PRODUCT

Peter Leone

Project Physician Lead

VH3810109A for Injection, 440mg/vial

GSK3810109A for Injection, 440mg/vial is presented as a sterile, white to yellow, uniform lyophilized powder in a 25 mL clear glass, stoppered vial. The recommended storage condition is store at 2-8°C (36-46°F), protected from light.

Recombinant Human Hyaluronidase 1mg/mL

Each vial of Recombinant Human Hyaluronidase 1mg/mL contains 0.5 mL of rHuPH20 formulated at a concentration of 1 mg/mL (~110 000 U/mL rHuPH20) and is supplied in 2 mL glass vials as a sterile, single-dose, injectable liquid. The recommended storage condition is store at 2-8°C (36-46°F), protected from light

N6LS FOR IV ADMINISTRATION

N6LS 440 mg/vial should be reconstituted with **sterile Water for Injection** (WFI) and then diluted in IV bag containing compendial 5% dextrose.

- The concentration of reconstituted GSK3810109A drug product (DP) is 80 mg/mL.
- The extractable volume/vial for GSK3810109A DP is 5.5 mL (440 mg).
- The reconstituted DP is diluted to 250 mL using 5% dextrose.
- The concentration of N6LS for IV dosing can range from 3.2 mg/mL to 30 mg/mL.

N6LS dosing solutions may be stored at room temperature for up to **4 hours**.

IV DOSING CALCULATIONS

N6LS IV dosing is a weight based dose of **60 mg/kg**.
Dosing is based on **body weight on the day of dosing**.

Determine the dose in milligrams required by the subject (**weight to be rounded to one decimal point**)

Calculated dose (mg) = subject weight (kg) x 60 mg/kg

Calculate the required volume of reconstituted N6LS (80 mg/mL) :

Required volume of reconstituted DP (mL) = Calculated dose (mg) ÷ 80mg/mL (concentration of IP)

Calculate the required number of lyophilized N6LS vials needed to prepare the dosing solutions :

Required # of lyophilized vials (round to whole number) =
Required volume of reconstituted DP (mL) ÷ 5.5.ml of extractable volume

Calculate the concentration of prepared IV dose:

Concentration of IV dosing solution (mL) = Dose (mg) ÷ 250 mL (volume of 5% dextrose injection)

N6LS RECONSTITUTION

- Remove the required number of vials from 2˚ to 8˚C storage based upon the calculated dose.

Allow the vial(s) to equilibrate to ambient room temperature, protected from light, for **~ 30 minutes**.

- Remove the seal. Wipe the top of the vial(s) with disinfecting tissue of isopropyl alcohol 70% or similar and allow the alcohol to dry.

- Reconstitute the vials by adding 5.2 mL of WFI to each vial (use 10 mL syringe/ 18G needle combination). Direct the stream directly onto the center of the lyophilized powder.

- **Gently swirl the vial for 10 seconds with circular motion at 15-second intervals, until cake is fully dissolved**, and the product is uniform in appearance. A small amount of foaming may be transiently observed during reconstitution. Allow foam to subside before withdrawing contents from vial.

- **After reconstitution, visually inspect the DP vials** The reconstituted DP solution should appear as a **clear to opalescent; colorless to yellow or brownish yellow liquid; essentially free from visible particulates**.

- **If visible particles, unusual discoloration** is observed, then the **product should not be used**.

PREPARATION OF N6LS IV DOSING SOLUTION

- Reconstituted N6LS must be **further diluted to 250 mL using an IV bag containing 5% dextrose**.
- From a **250 mL IV bag** containing **5% dextrose** injection, **remove the required volume of the diluent to accommodate the volume of reconstituted N6LS to be added**. Add the calculated volume of the reconstituted N6LS as described in the dose calculations section. Alternatively, use an empty infusion bag and prepare the dose by adding the calculated volume of 5% dextrose injection followed by the calculated volume of reconstituted VH3810109 DP.
- **Gently invert the container 5 to 10 times** to ensure complete mixing. **Avoid shaking** or excessive agitation.
- Prior to administration, visually inspect the N6L IV dosing solution for visible particles or unusual discoloration**. If unexpected visible particles, unusual discoloration**, the **product should not be used**.

PREPARATION OF SC DOSE OF N6LS

- SC dose of N6LS is 3000 mg containing approximately 1600 U/mL of rHuPH20 (60,000 u)

- The SC dosing volume calculation :
  - Dose Volume of N6LS = 3000 mg dosage volume + 4.5 mL Overfill Volume
  - Total (U) rHuPH20 = Total Volume (VH3810109) * 1600 U/mL
  - Total Volume RHUPH20 (mL) = Total (U) rHuPH20 / (110,000 U/mL)

PREPARATION OF N6LS + PH20 FOR SC ADMINISTRATION

- Remove the 8 vials of N6LS drug product from 2˚ to 8˚C storage.
- Allow the vials to equilibrate to ambient room temperature, protected from light, for ~ 30 minutes.
- Remove the seal. Wipe the top of the vial(s) with disinfecting tissue of isopropyl alcohol 70% or similar and allow the alcohol to dry.
- Reconstitute the lyophilized vials (see dose calculation section) by adding 5.2 mL of WFI to each vial (use 10 mL syringe/ 18G needle combination). Direct the stream directly onto the center of the lyophilized powder.
- **Gently swirl** the vial for **10 seconds** with **circular motion at 15-second intervals**, until cake is fully dissolved, and the product is uniform in appearance. A small amount of foaming may be transiently observed during reconstitution. Allow foam to subside before withdrawing contents from vial.
- Remove **2 vials of PH20** solution, 110,000 U/mL, from 2˚C to 8˚C storage temperature.
- Allow the vials of PH20 to sit for **15 minutes to come to room temperature.**.

N6LS +PH20 FOR SC ADMINISTRATION (CONTINUED)

- **Visually inspect the reconstituted DP and PH20 DP vials** prior to SC dose solution preparation. The reconstituted N6LS solution should appear as a clear to opalescent; colorless to yellow or brownish yellow liquid; essentially free from visible particulates. The PH20 DP should appear as a clear and colorless solution. **If visible particles, unusual discoloration** , then the products should **not** be used.
- Reconstituted N6LS (**42 mL**) must be **co-mixed** with **0.6 mL of PH20** (~ 1600 U/mL)

Mixing steps are described below:

- 50mL syringe/18 G needle combination to draw a total volume of 42 mL of the reconstituted DP from 8 vials.
- Transfer 42mL of VH3810109 DP from the 50mL syringe into a single 50 or 100mL stoppered and sealed sterile glass vial. Gently swirl the solution to ensure homogeneity.
- Draw a total volume of 0.6 mL ofPH20 from 2 vials (0.3mL from each vial) using a 1mL syringe/27G needle . Transfer 0.6 mL rHuPH20 into the 50 or 100mL vial containing 42 mL GSK3910109 DP.
  Gently mix the solution to ensure homogeneity.
- Take a 50 mL syringe/18G needle combination and draw the admixture of GSK3810109 and rHuPH20 prepared in the previous step. Discard the needle and cover the end of the syringe with a cap.
- Place the 50 mL syringe in the syringe pump connect the extension set Program the pump for SC infusion of 38.1mL volume at a rate of 3mL/min.

VIDEO https://vimeo.com/850628116/9a9a476f9f?share=copy

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