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INVESTIGATOR'S MEETING

August 2nd, 2023

Atlanta, GA

WELCOME & INTRODUCTIONS

Jan Losos

Medicine Development Lead

Central Study Team	
Peter Leone	Project Physician Lead
Rulan Griesel	Medical Monitor
Chelsea Macfarlane	Clinical Science Lead
Paul Wannamaker	Clinical Science Lead
Viviana Wilches	Study Delivery Lead
Anshika Tripathi	Data Manager Lead
Margaret Gartland	Virologist
Elizabeth Wonderlich	Clinical and Translational Immunology Lead
Cassidy Gutner	Implementation Science Lead
Christina Donatti	Global Health Outcomes Director
Amy Cutrell	Statistician
Morgan Gapara	Lab Study Manager
Jane Fricker	Asset Lead
Jan Losos	Medicine Development Lead
Lisa Petty	ViiV Clinical Operations Lead

LOC Study Team	
Christine Nase	Local Delivery Lead
Dawn Hall	Project Lead
Nicole Washco	Study Start-up Lead
Monitoring Team	
Jasmine Leos	Dr. Manne-Goehler; Dr. Slim; Dr. Frank; Dr. Kumar; Dr. Sobieszczyk
Jodi Lawrence	Dr. Kinder; Dr. Ramgopal; Dr. Bolivar
Justin Bonie Racine	Dr. Zashir; Dr. Evans; Dr. Bettacchi
Karyms Luna Miller	Dr. Morales-Ramirez; Dr. Santiago-Colon
Naneika McLendon	Dr. Schreibman; Dr. Dreiter; Dr. Rolle; Dr. Pierone; Dr. Whitehead
Shelly Caruso-Vonwerder	Dr. Stein; Dr. Aberg; Dr. Fichtenbaum; Dr. Drelichman; Dr. McGowan
Tina Schaffner	Dr. Towner; Dr. Felizarta; Dr. Brinson; Dr. Alozie
Tracey Helm	Dr. Dandachi; Dr. VanDam; Dr. Berthaud; Dr. Wohl; Dr. Cook

AGENDA – DAY 1

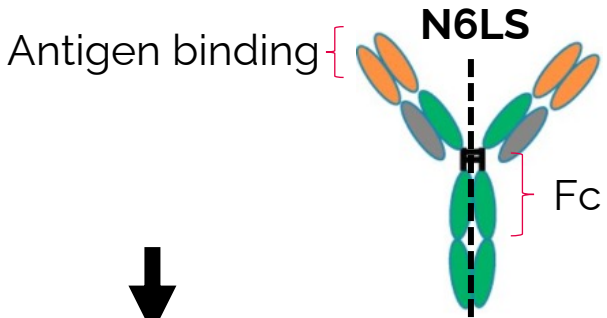
Topic	Presenter	Time
Welcome	Jan Losos	1:00 – 1:15
BNAB Landscape	Peter Leone	1:15 – 1:35
Compound Safety Overview	Rulan Griesel	1:35 – 2:00
Looking to the Future	Paul Wannamaker	2:00 – 2:15
Virology	Margaret Gartland	2:15 – 2:45
Protocol Overview / Snapshot Algorithm	Chelsea Macfarlane / Amy Cutrell	2:45 – 3:15
Break	All	3:15 – 3:30
Open Discussion Breakout	All	3:30 – 4:00
Dinner Reception	All	6:00 – 8:00

MEETING REMINDERS

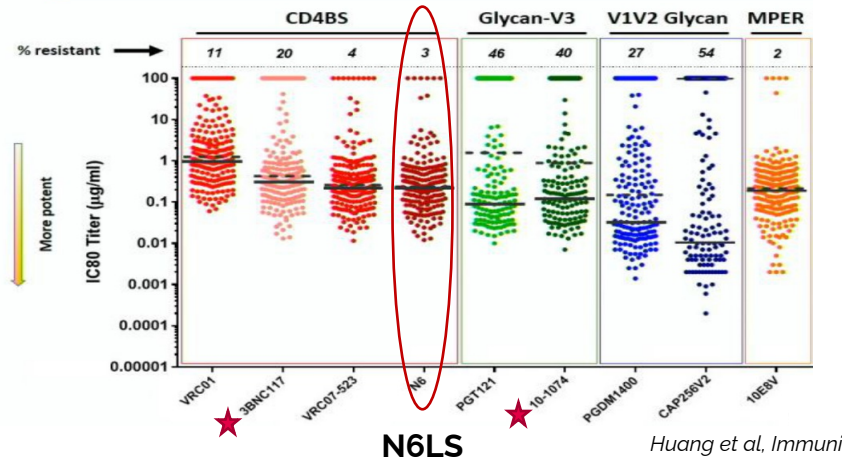
Please stay engaged and respond to interactive questions during the meeting

- Make sure phones, computers are switched off or to silent
- Ask Questions during Q&A slots!
- Please remember your attendance will be tracked and serves as training certification
- Return promptly from breaks

BNABS POSE "DUAL THREAT" TO HIV



Neutralization
(Direct acting antiviral)



N6LS

Huang et al, Immunity 2016

Best in class *in vitro* potency and 97% coverage

Enhanced Host Immune Response

Multiple modes of action

- B and T cell activation
- Clearance of infected cells (ADCC/ADCP)
- Reservoir reduction
- Anti-inflammatory

→ Differentiation from all small-molecule competitor therapeutics

Need to demonstrate meaningful clinical benefit…

★ Gilead's Phase 2b bNAbs

CABNAB Q4M ULA TMP for Treatment Switch Patients

Q4M

Primary Q4M TPP
ULA HCP Administered

SC N6LS + PH20*

IM or SC new CAB formulation

Timing of injections:
Under 30 minutes for both injections

*PH20= SC delivery enhancement agent

or

Best in Class Q6M

Alternative Q6M TPP
ULA HCP Administered

IV N6LS

IM or SC new CAB formulation

Timing of injections:
Under 45 minutes for both injections

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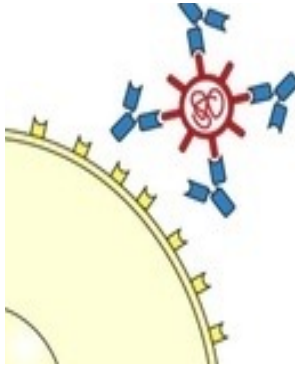
BNAB LANDSCAPE

Peter Leone

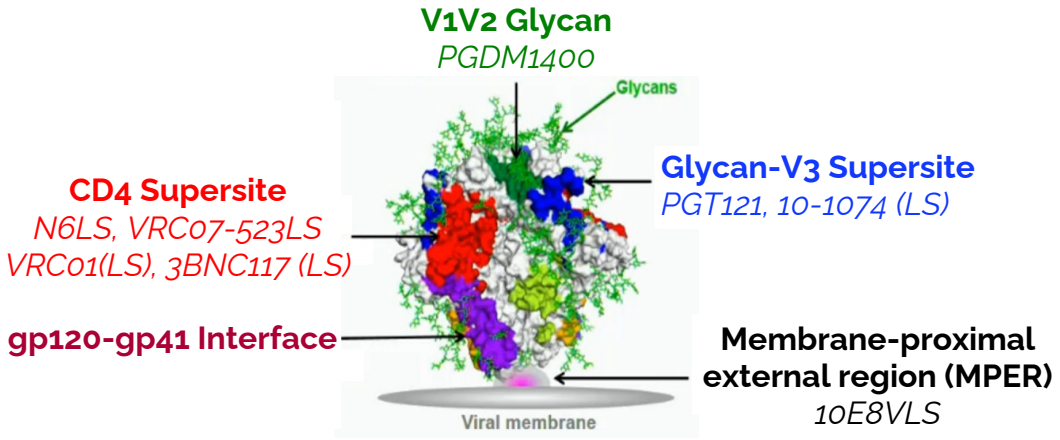
Project Physician Lead

Broadly Neutralizing Antibodies (bNAbs):
Long acting Regimens for HIV Treatment



A New Class of HIV Entry Inhibitors

- bNAbs: Bind to surface proteins/ glycans on HIV and prevent virus entry into target cells (neutralization)
- Develop in a small fraction (~1%) of HIV+ individuals after years of infection
- Currently in development for treatment, prevention, and cure

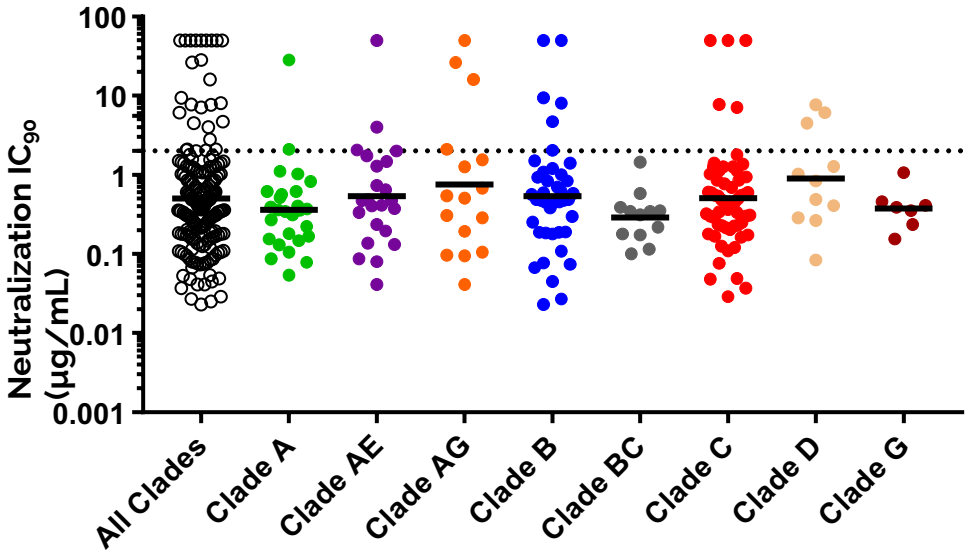


Directed to 5 conserved regions on HIV envelope

SUPERIOR ANTIVIRAL POTENCY AND CROSS CLADE COVERAGE

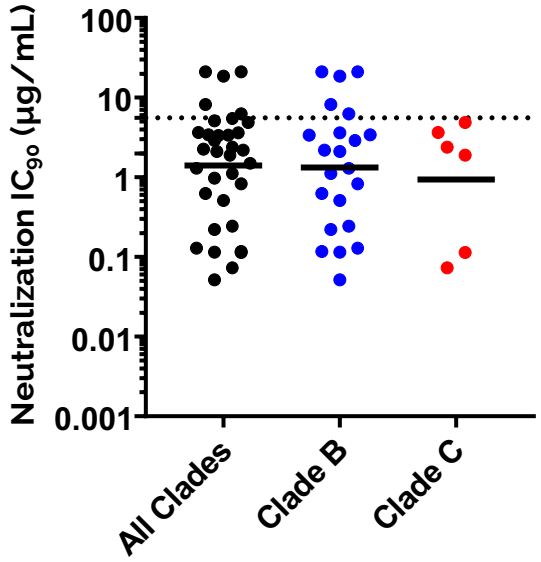
NEUTRALIZES 97% OF HIV ENVELOPES

N6 Cross-Clade Neutralization of HIV-Pseudoviruses (n=208)



Geometric Mean IC_{90} for all viruses is 0.5 µg/mL
$4xIC_{90}$ = 2 µg/mL

N6 Neutralization of HIV Clinical Isolates (n=36)



Geometric Mean IC_{90} for all viruses is 1.4 µg/mL
$4xIC_{90}$ = 5.6 µg/mL

N6LS C_{trough} >6 µg/mL

Advantages

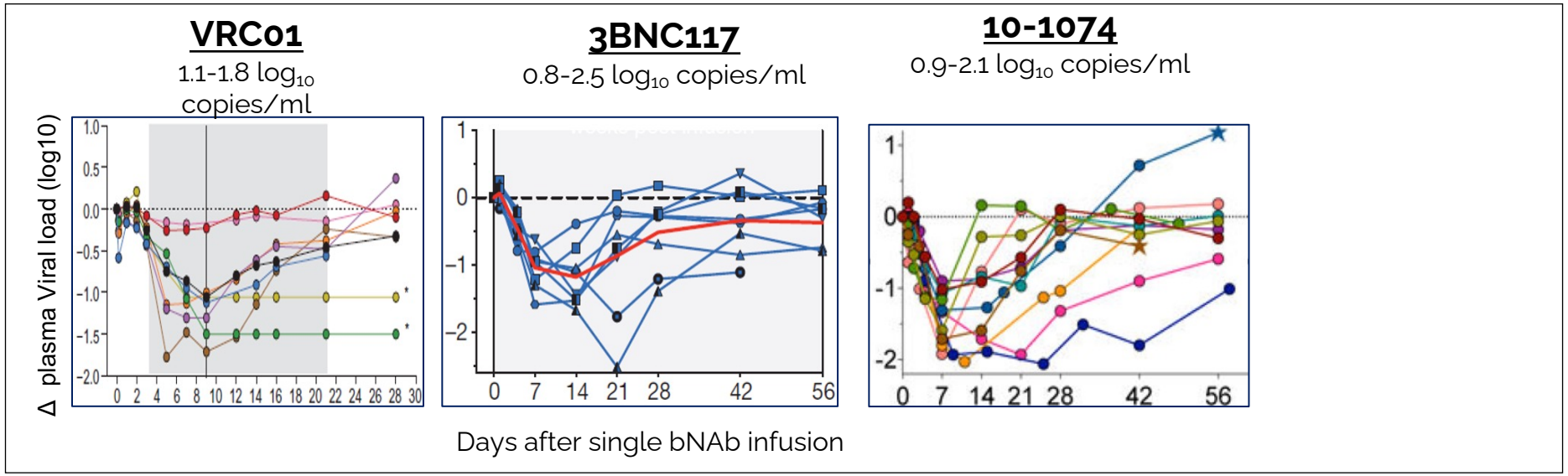
- Low toxicity
- Lack of DDI
- Improved pharmacokinetics
- Fc-mediated immune effector function
- Possible triple application: prevention, treatment, cure

Disadvantages

- Prescreening for decreased sensitivity
- Low barrier to resistance
- Different studies showed suboptimal efficacy in cell-to-cell viral transmission
- Unclear effects on the cell-associated HIV-1

BNABS HAVE DEMONSTRATED POC CLINICAL EFFICACY

All were well tolerated with NO severe adverse reactions



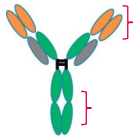
>1.0 log_{10} mean reduction in viral load following single dose monotherapy in people living with HIV (treatment naive)

Caskey 2015 Nature, Lynch 2015 SciTransMed, Caskey 2017 Nat Med

N6LS – BROADLY NEUTRALIZING ANTIBODY (BNAB)

- Exclusive license was executed with the NIH on Nov 13 2019
- Mechanism of action

N6LS has been engineered to have a long half-life and also has the potential to pose a dual threat to HIV



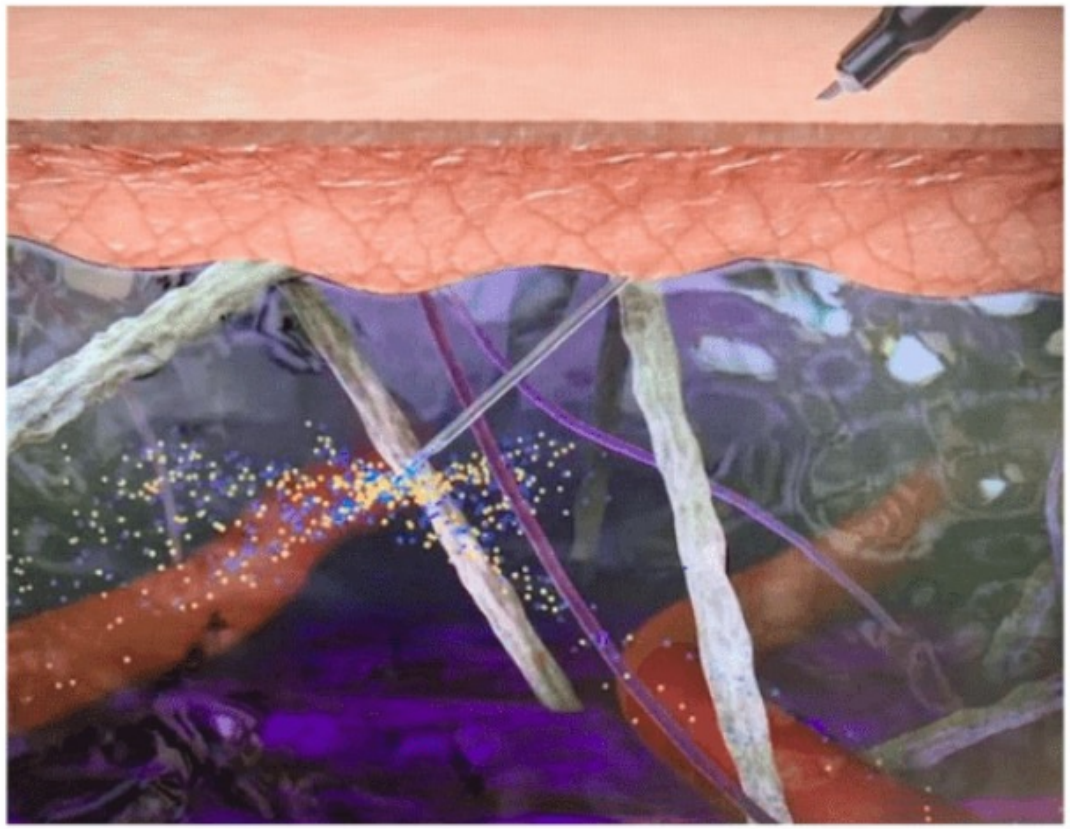
Enhanced antiviral immune response

Neutralization of viral entry (97% coverage)

- FTIH complete and safety profile was well-tolerated and consistent with the CD4 binding class)
- FTIH N6LS PK profile supports multiple LA regimens (IV or SC Q4M)
- 2DR combination : CAB400 + N6LS (CABNAB)
- MoA Video

MECHANISM OF ACTION - VIDEO

ENHANZE®: Patented, De-risked, Commercial Platform Technology Enabling Rapid, High Volume Subcutaneous Delivery of IV Drugs



What it does: ENHANZE® creates temporary space for SC fluid dispersion which returns to normal; reduces backpressure

ENHANZE®

Uniquely enables rapid SC delivery
- 5-15mL over 2-5 minutes
- 300-600mL at 5 mL/min

Decreased injection site swelling and induration

Aids absorption leading to increased bioavailability versus subcutaneous without ENHANZE®[1]

Potential for decreased systemic infusion related reactions

[1] Morcos International Journal of Clinical Pharmacology and Therapeutics, Vol. 51 – No. 7/2013 (537-548)

VH3810109 (N6LS) DEVELOPMENT STRATEGY

FTI - Human Experience VRC609

- Safety, Tolerability, PK, ADA of 5 doses of VH3810109 5 mg/kg IV & SC (SD/RD), 20mg/kg IV & SC (SD/RD), 40mg/kg IV (SD)

SPAN Ph1:

- Safety, Tolerability, PK, ADA
  - **Parts 1 and 3:** 20 mg/kg and 3000mg **SC + PH20 SC** for q4 month dosing
  - **Part 2:** 60 mg/kg **IV** for q4-6 month dosing

BANNER Ph2a:

- Virologic activity, Safety, Tolerability, PK, ADA
  - Dose response/ dose finding: 40 mg/kg IV, 280mg mg IV [Part 1],
  - 700mg and 70 mg IV & 700 mg SC [Part 2]

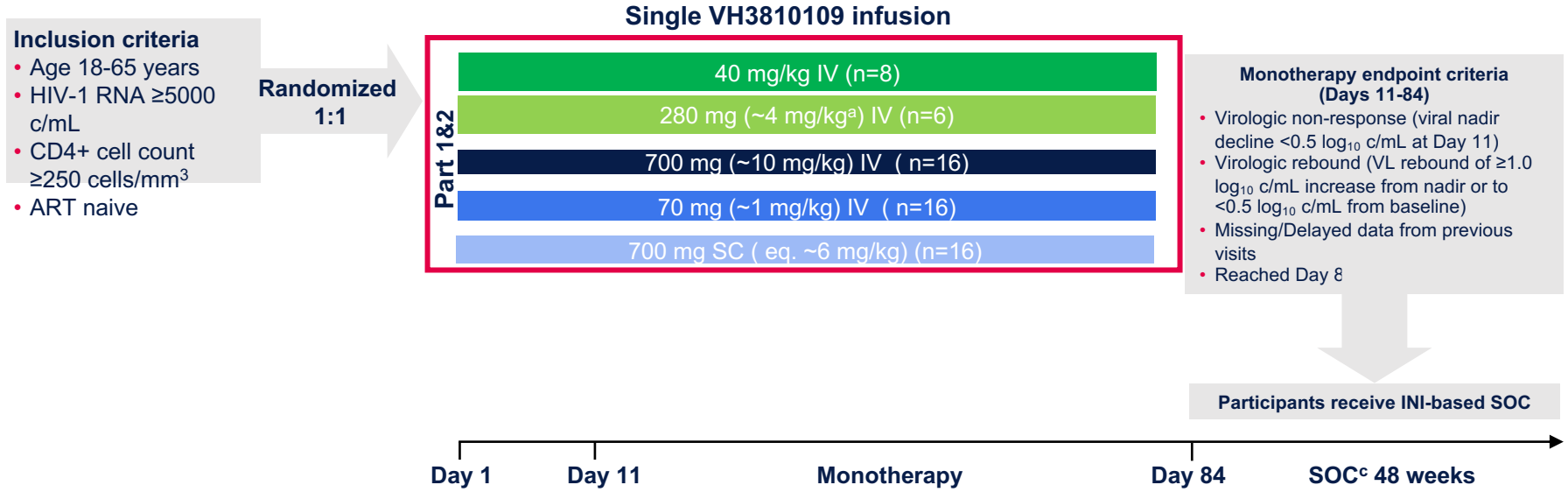
EMBRACE Ph2b (VH3810109 + CAB maintenance dosing):

- Maintenance of virologic suppression, Safety/Tol, Virology, PK, ADA, HO
  - Selected **IV q 4m** and **SC+PH20 q 4m** + CAB; control continuation of oral standard of care

Ph3: (VH3810109 + CAB maintenance dosing)

- HIV-1 RNA, Safety/Tol, Virology, PK, ADA, Acceptability, etc
  - **IV q 4m or SC+PH20 q 4m** + CAB q 4m with control arm of Cabenuva maintenance dosing

PHASE 2A POC: BANNER
RANDOMIZED, OPEN-LABEL, 2-PART, MULTICENTER, SINGLE-DOSE, ADAPTIVE STUDY IN ART-NAIVE ADULTS

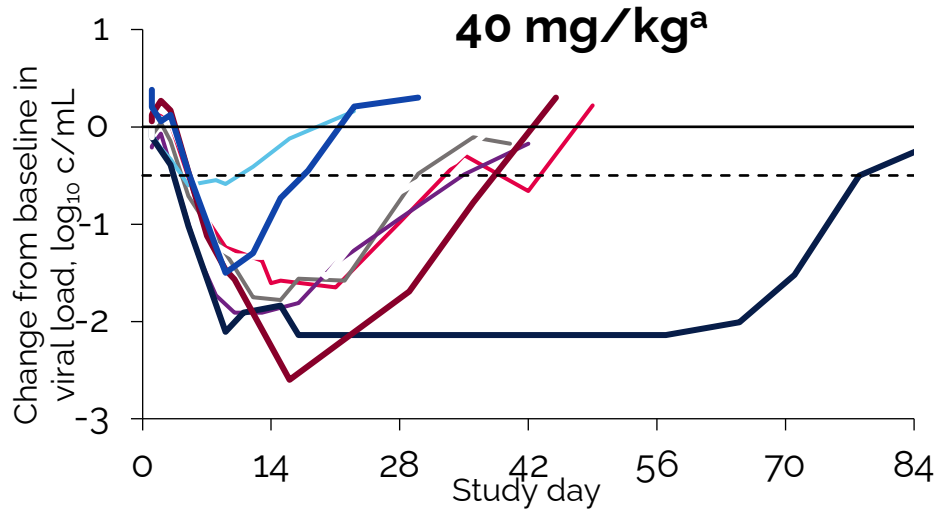


- Primary endpoints were plasma HIV-1 RNA maximum change from baseline during monotherapy and safety parameters
- Secondary endpoints included VH3810109 PK parameters and incidence and titer of anti-VH3810109 antibodies
  - Antibody susceptibility was determined retrospectively using the PhenoSense monoclonal antibody assay

Leone et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Slides O34.

[a]For a 70-kg individual. [b]A planned interim analysis was performed to evaluate virologic response, safety, and PK from the monotherapy and ongoing SOC periods in part 1. [c]An SOC integrase inhibitor–based regimen (DTG/3TC) was provided at the end of the monotherapy periods in parts 1 and 2.

BANNER INDIVIDUAL VIRAL LOAD PROFILES 40 MG/KG IV RESPONSE IN 8/8



Viral dynamic measures	VH3810109 40 mg/kg IV (n=8)
Median (range) viral nadir from baseline, log_{10} c/mL	−1.72 (−0.60, −2.60)
Median (range) time to viral nadir, days	16 (5-21)
Maximum viral nadir from baseline, log_{10} c/mL	−2.60
Median (range) time to viral rebound among responders, days	35 (12-78) [n=8]

Leone et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Slides O34.

Solid line represents no change from baseline and dashed line represents virologic non-response (viral nadir decline <0.5 log_{10} c/mL at Day 11).
[a]Each line represents an individual participant. [b]For a 70-kg individual.

EFFICACY CONCLUSIONS

- BANNER established antiviral activity of N6LS in naïve patients with no pre-screening using both IV and SC dosing. A single IV infusion or SC administration of N6LS showed antiviral efficacy from 40 mg/kg to 1 mg/kg
- Mode of delivery (SC or IV) is not a factor when controlling for Cmax
- Baseline screening sensitivity is correlated with magnitude and duration of VL response.
- SPAN and BANNER established the safety and tolerability of N6LS in both IV and SC

1. Caskey et al. *Nature*. 2015;522:487-491.

Leone et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Slides O34.

DOSE JUSTIFICATION AND SELECTION

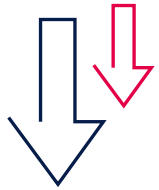
- Baseline sensitivity cutoff of IC90 of ~2.0 ug/ml and MPI > 98% is estimated to cover ~85% of individuals

- Phase 2b N6LS target concentration of 11 µg/mL was derived from in vitro data of 330 clinical isolates from three studies (SAILING, BRIGHTE, BANNER). The target concentration of 11 µg/mL is ~12x median IC90 of BANNER.

- Dosing recommendations were made to achieve the target concentration within < 24 hrs and to maintain serum concentrations above 11 µg/mL in 95% of subjects.

ADDITIONAL STUDY QUESTIONS

Evaluate patient and staff experiences with subcutaneous and intravenous administration of N6LS and understand what type of support may be needed to make implementation easier in routine care



Acceptability: Does N6LS meet your/your patients' approval? Is it appealing?

Feasibility: Does N6LS fit in your clinical setting/in your patients lives? Is it suitable for use?

Process: What are the steps involved in administering N6LS? Are there any challenges?

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COMPOUND SAFETY OVERVIEW

Rulan Griesel

Medical Monitor

SAFETY RISK MANAGEMENT: OVERVIEW

- **Important Identified Risks:** local reactogenicity (injection/infusion site reactions), systemic reactogenicity, gastrointestinal disorders (diarrhea, abdominal pain, dyspepsia)

- **Important Potential risks:** serious/severe immune reactions, neutropenia, immunogenicity

N6LS SAFETY - FTIH (HEALTHY VOLUNTEER) PHASE 1 TRIALS

	VRC 609 (VRC Clinical Trials Program)
Study arms	• **3 groups** single IV dose 5, 20, or 40 mg/kg (n=9) • **1 group** single SC 5 mg/kg (n=3) • **2 groups** for 3 doses q12w: 20 mg/kg IV or 5 mg/kg SC (n=10) • ***2 groups*** *single SC dose 5 mg/kg and 20 mg/kg with rHuPH20 (n=10)*
Safety summary *(06-26-22)*	
AE summary	16 (72.7%) at least one AE: G1 (n=5), G2 (n=10), **G3** diarrhoea (n=1) (study drug related - **SDR**) **SDR** AEs: 6 all resolved without sequelae (3 x diarrhoea [**G1-3**], 1 x ISR [**G2**], 1 x neutropenia [**G2**], 1 x elevated ALT [**G1**]). No withdrawals due to AEs
SAE and deaths summary	No SAEs or deaths
Laboratory parameters	**G1-2** elevations (n=4), no trends; **G1** increased ALT (n=1) (**SDR**), all resolved
Local reactogenicity/ISRs by *3-day diary card*	In SC groups: pain/tenderness (n=6), swelling (n=2), redness (n=2), pruritis (n=2) (**all G1-2**)

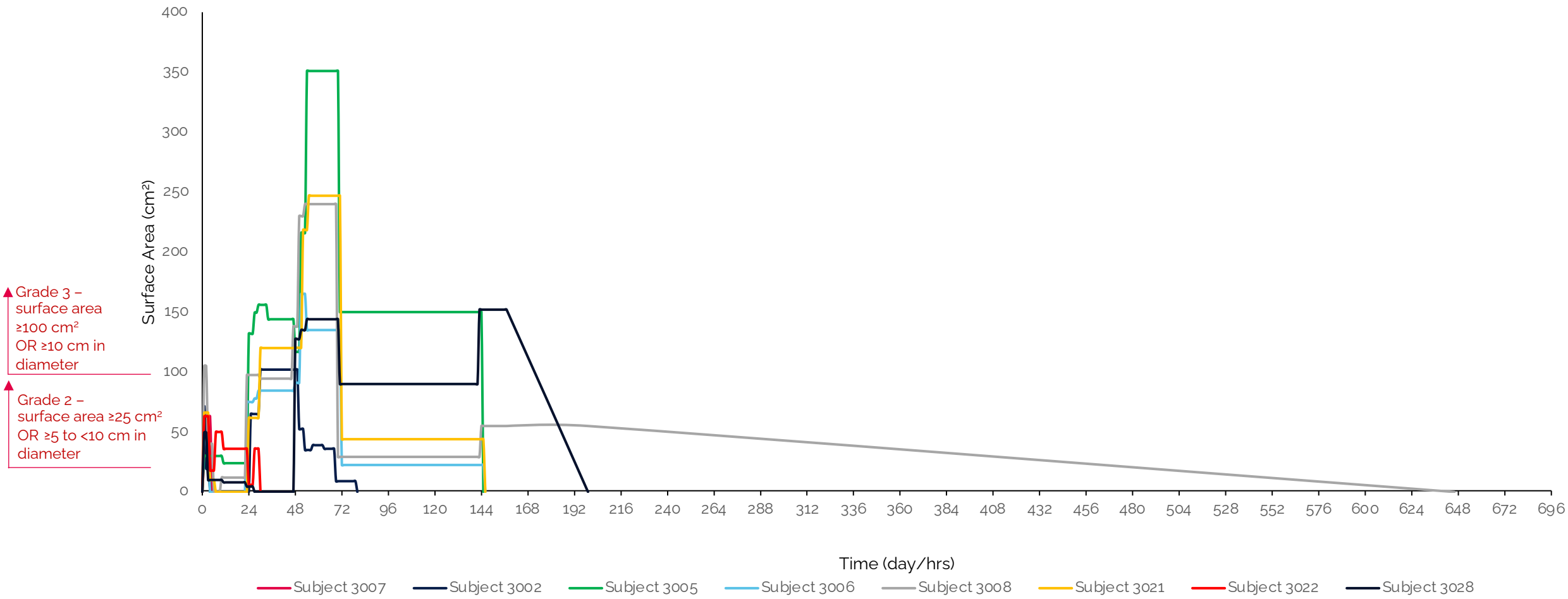
N6LS SAFETY - FTIH (HEALTHY VOLUNTEER) PHASE 1 TRIALS

	SPAN (ViiV Healthcare)
Study arms	• **Part 1**: 20 mg/kg SC with rHuPH20 (n=8) • **Part 2**: 60 mg/kg IV (n=8) • **Part 3**: 3000 mg SC with rHuPH20 (n=8)
Safety summary	
AE summary	**Part 1**: 8 (100%) at least 1 AE; **≥G2** injection site erythema (n=7) (**SDR**), **G2** headache (n=1), **G2** site pruritis (n=1) (**SDR**), **G1** (n=1) site pain (**SDR**) **Part 2**: **G1** medical device site dermatitis (n=1) and **G1** muscle tightness (n=1), **none SDR** **Part 3**: 8 (100%) at least 1 AE; **G3** injection site erythema (n=8) (**SDR**), **G1** injection site bruise (n=2) (**SDR**), **G1** injection site pain (**SDR**) (n=2), **G1** injection site induration (n=1) (**SDR**), **G1** injection site warmth (n=1) (**SDR**), **G1** COVID-19/URTI (n=4), **G1** ear pain (n=1), **G1** flatulence/dyspepsia (n=1) (**SDR**) No withdrawals due to AEs
SAE and deaths summary	No SAEs or deaths
Laboratory parameters	No clinically relevant changes from baseline (no neutropenia)

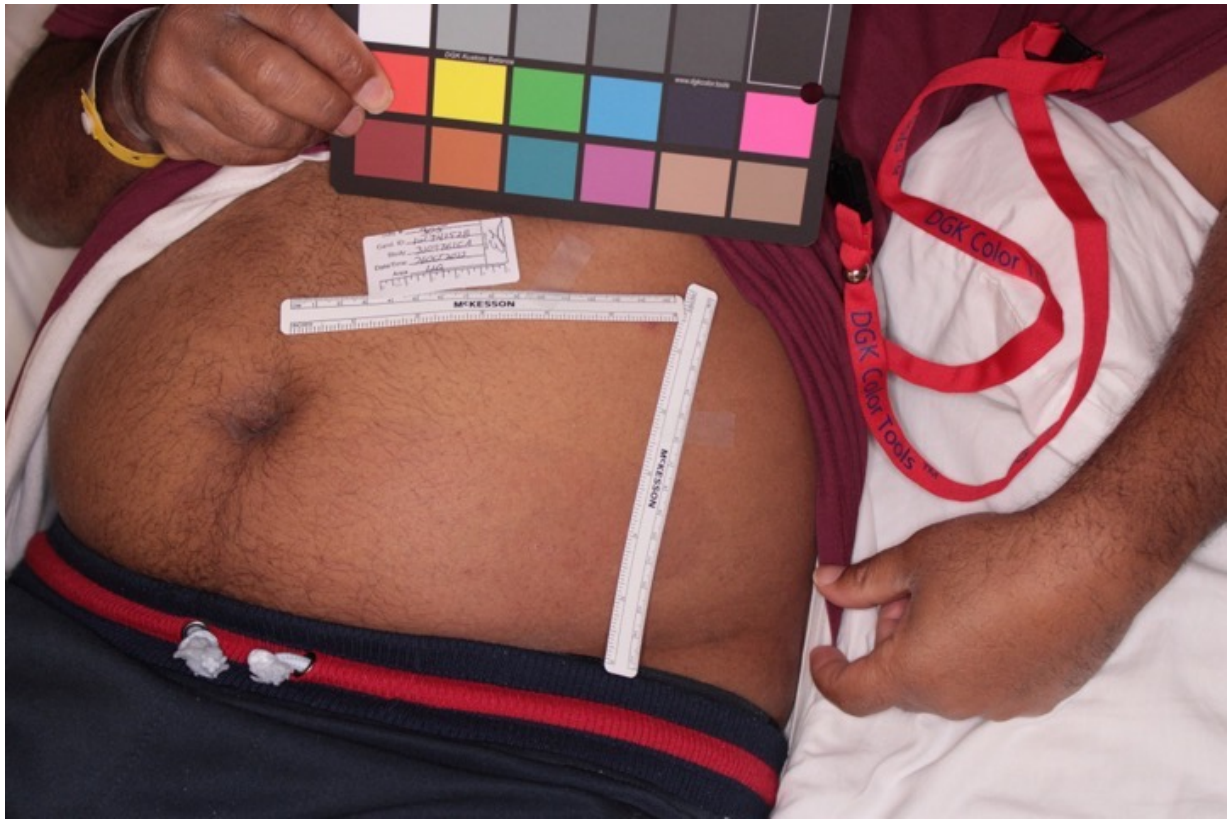
SPAN: Injection Site Reaction Summary

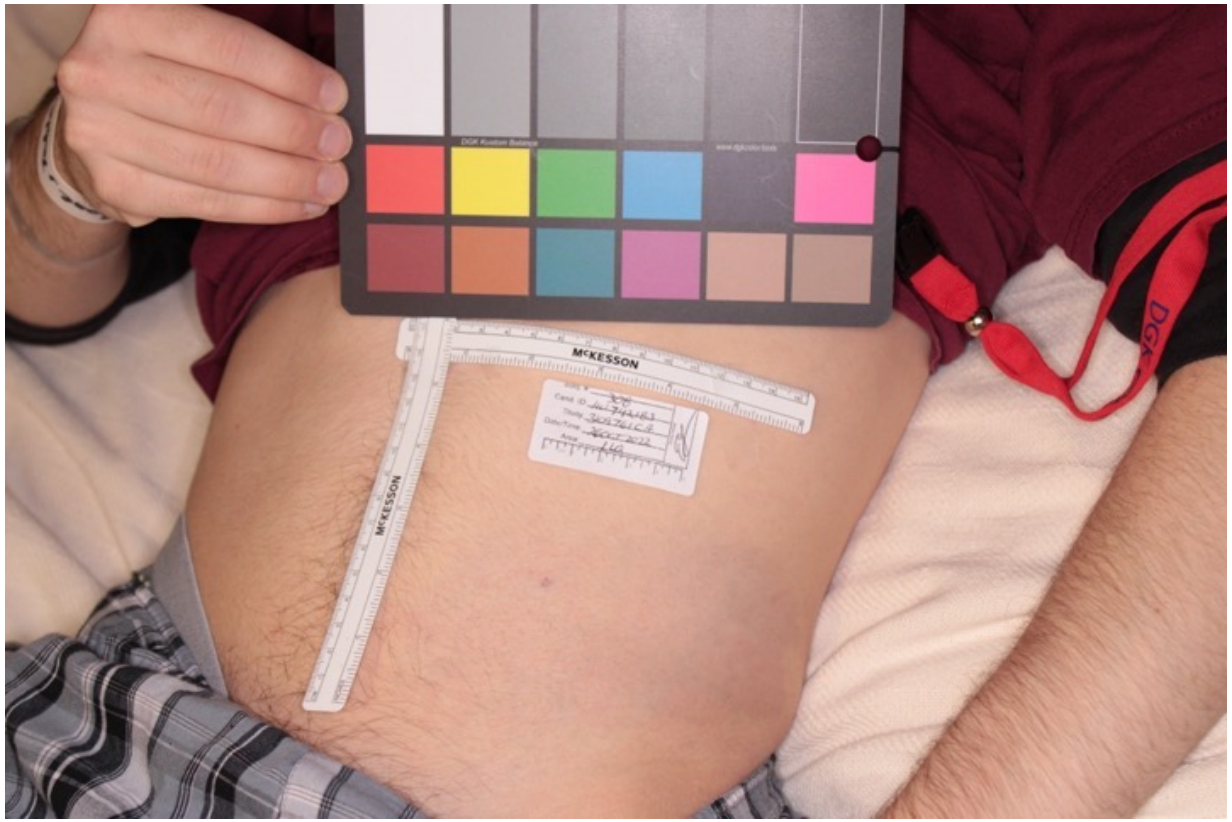
- SC administration with rHuPH20 led to **G3** injection site erythema in participants in Part 1 (6/8 [88%]) and Part 3 (8/8 [100%]) **NOTE** – no nodules seen
- Duration of **G3** injection site erythema ranged from <1 day to 7 days with majority resolved within 3 days and a maximum duration of 27 days (only 1 participant)
- Biphasic/intermittent injection site erythema noted in **Part 1** participants (2/8 [25%]) and **Part 3** participants (4/8 [50%])
- **Numerical Rating Scale** and **Perception of Injection** assessments: majority participants local reactions and pain were 'totally acceptable'
- PI stated that all ISRs including Grade 3 injection site erythema **were well tolerated amongst participants without complications** and did **not have any impact on usual social or functional activities**

SPAN Part 3: Injection Site Erythema (Surface Area over Time)

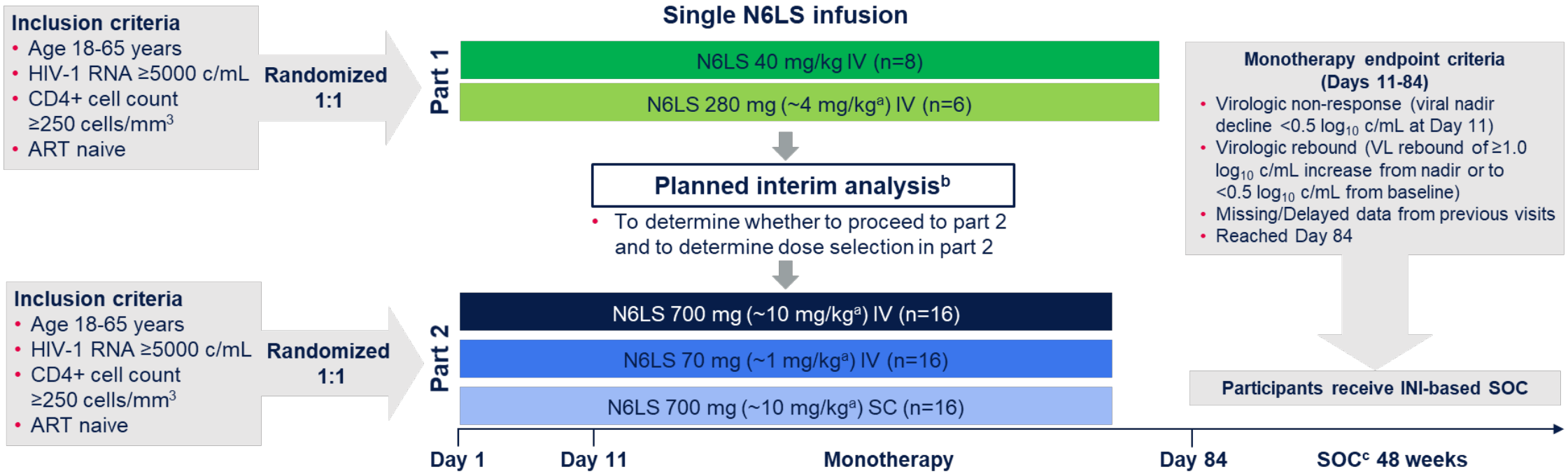


SPAN: ISR G3 erythema





N6LS SAFETY - PHASE 2A POC (BANNER)



- **Safety summary:**
  - Across dose groups no noteworthy differences in overall AE incidences observed
  - No clinically significant safety trends in vital signs, electrocardiograms, or laboratory tests observed across dose groups

N6LS SAFETY - PHASE 2A POC (BANNER): AES

Preferred Term	40mg/kg IV (n=8)	280mg IV (~4mg/kg) (n=6)	700mg IV (~10mg/kg) (n=16)	70mg IV (~1mg/kg) (n=16)	700mg SC (~10mg/kg) (n=16)	Total (N=62)
Any AE	*8 (100%)*	5 (83%)	10 (63%)	11 (69%)	14 (88%)	48 (77%)
AEs SDR	2 (25%)	2 (33%)	1 (6%)	2 (13%)	6 (38%)	13 (21%)
Any grade 2-4 AE	5 (63%)	2 (33%)	4 (25%)	7 (44%)	11 (69%)	29 (47%)
AEs leading to permanent discontinuation of study treatment	0	0	0	0	0	0
Any SAE	*1 (13%)*	*0*	*0*	*0*	*0*	*1 (2%)*
SAEs related to study treatment	0	0	0	0	0	0
Fatal SAEs	0	0	0	0	0	0
Fatal SAEs related to treatment	0	0	0	0	0	0

N6LS SAFETY - PHASE 2A POC (BANNER): ≥G3 AES

Dose Group	Preferred Term (event level)	Grade	Relatedness	Seriousness
40mg/kg IV (N=8)	Hypertriglyceridemia Suicide attempt	Grade 3 Grade 4	No No	No Yes
280mg IV (~4mg/kg) (N=6)	-	-	-	-
700mg IV (~10mg/kg) (N=16)	Aspartate aminotransferase increase* Blood creatine phosphokinase increase* Dysuria# Pollakiuria#	Grade 3 Grade 4 Grade 3 Grade 3	No No No No	No No No No
70mg IV (~1 mg/kg) (N=16)	Anal abscess Neutropenia Blood creatine phosphokinase increase	Grade 3 Grade 4 Grade 4	No No No	No No No
700mg SC (~10mg/kg) (N=16)	Blood creatine phosphokinase increased Blood creatine phosphokinase increased Neutropenia Neutropenia	Grade 3 Grade 4 Grade 4 Grade 4	No No No No	No No No No

*Events in same participant
#Events in same participant

N6LS SAFETY - PHASE 2A (BANNER): ISR SUMMARY

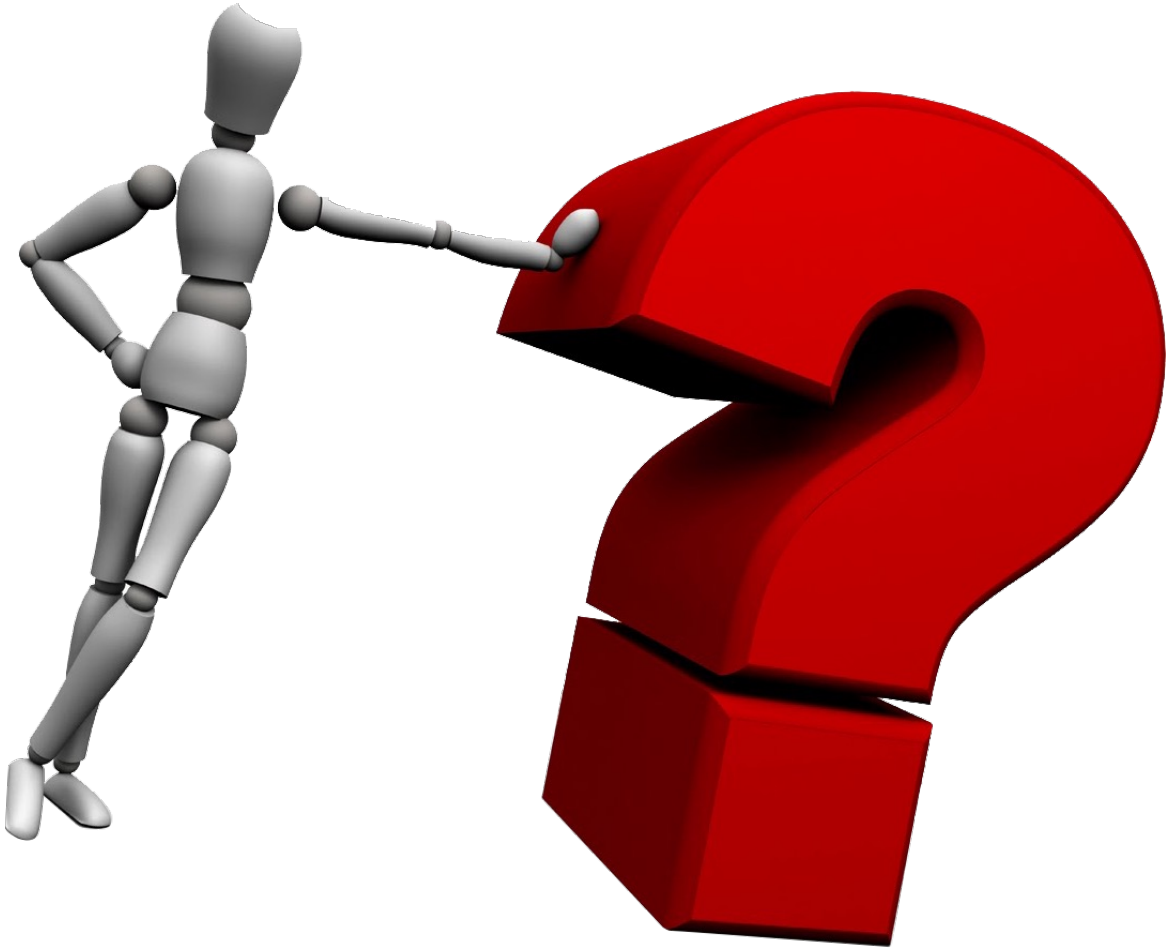
- 7/62 (11%) participants experienced 9 injection/infusion site reactions. All ISRs **G1 (SDR)** and a maximum duration of **10 days**
- **Part 1**
  - **40 mg/kg IV:** n=1 infusion site erythema, n=1 infusion site pain
- **Part 2**
  - **700 mg IV:** n=1 infusion site pain
  - **70 mg IV:** n=2 infusion site bruising (same participant)
  - **700 mg SC (3 x 233 mg injections):** n=1 injection site bruising and n=1 injection site discoloration (same participant), n=1 injection site pain, n=1 injection site pruritus

NOTE – no nodules seen

N6LS SAFETY - SUMMARY

- **SPAN**
  - IV arm (**60 mg/kg largest IV dose**) (**very well tolerated with no SDR AEs**)
  - SC arms (**3000 mg largest SC dose with rHuPH20**)
    - Injection site reaction erythema (**max G3 – due only to erythema surface area**)
    - Gastrointestinal (dyspepsia/flatulence) (**G1**)
- **BANNER**
  - IV arms
    - Systemic reactogenicity (**G1-2**)
    - Gastrointestinal disorders (**G1**)
  - SC arm (**700 mg largest SC dose without rHuPH20**)
    - Injection site erythema (**G1**)
    - Systemic reactogenicity (**G1-2**)
    - Gastrointestinal disorders (**G1**)

Questions?



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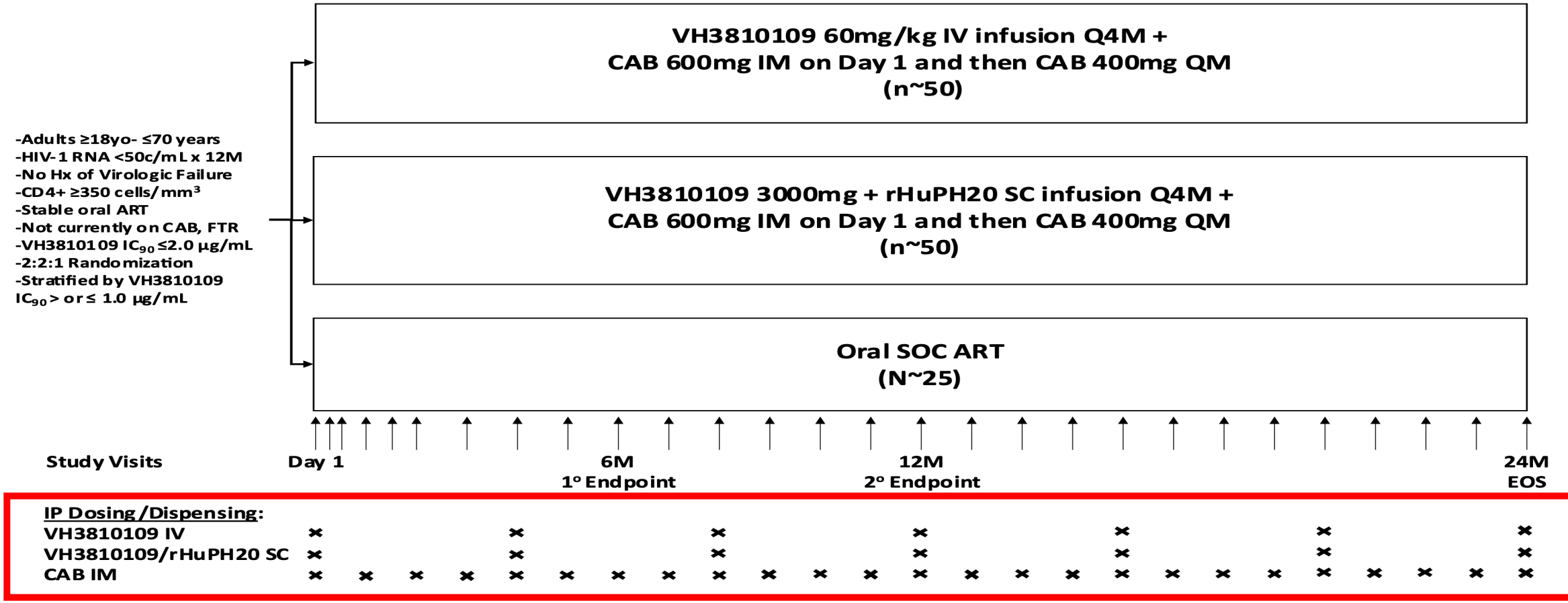
Looking to the ***Future***

Dosing 2-3x/year

Paul Wannamaker
Clinical Science Lead, N6LS

WHERE ARE WE NOW?



WHERE ARE WE NOW?

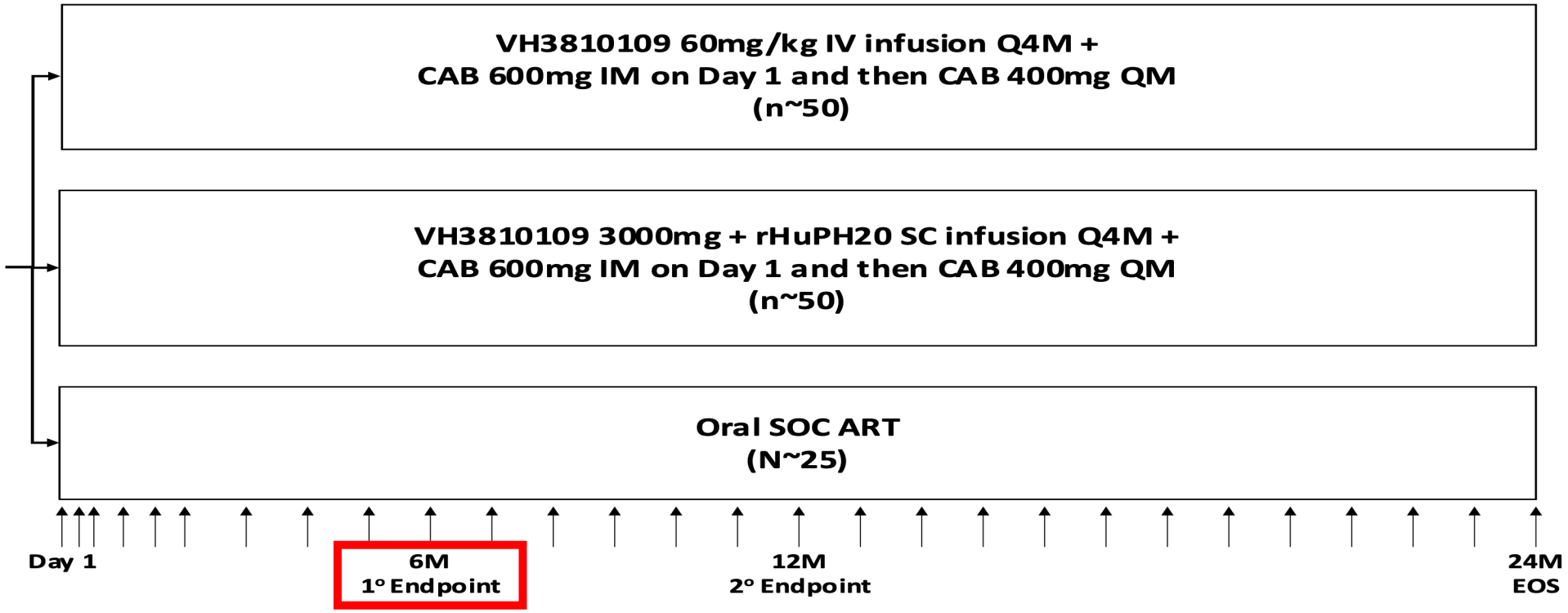
CABENUVA

cabotegravir 200 mg/mL; rilpivirine 300 mg/mL
extended-release injectable suspensions

INITIATION			CONTINUATION			
						
MONTH 1	MONTH 2	MONTH 3	MONTH 4	MONTH 5	MONTHS 6, 8, AND BEYOND	
Administer the first CABENUVA injections (1 LA cabotegravir 600 mg/3 mL and 1 LA rilpivirine 900 mg/3 mL). Administer the second set of initiation injections 1 month later.			For duration of treatment, administer CABENUVA injections (1 LA cabotegravir 600 mg/3 mL and 1 LA rilpivirine 900 mg/3 mL) every 2 months.			

WHERE ARE WE NOW?

-Adults ≥18yo- ≤70 years
-HIV-1 RNA <50c/mL x 12M
-No Hx of Virologic Failure
-CD4+ ≥350 cells/mm^3
-Stable oral ART
-Not currently on CAB, FTR
-VH3810109 IC_{90} ≤2.0 µg/mL
-2:2:1 Randomization
-Stratified by VH3810109 IC_{90} > or ≤ 1.0 µg/mL



IP Dosing/Dispensing:																							
VH3810109 IV	×			×			×			×			×			×			×				
VH3810109/rHuPH20 SC	×			×			×			×			×			×			×				
CAB IM	×	×		×		×		×		×		×		×		×		×		×		×	

WHERE ARE WE GOING?

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VIROLOGY

Margaret Gartland

Study Virologist

VIROLOGY TOPICS

1. Virology Inclusion/Exclusion Criteria Protocol Section 5.1 and 5.2
   - Inclusion Criteria: Phenotypic Sensitivity to VH381010
     - Access to Monogram v-link Results Portal
   - Exclusion Criteria: Presence of any Major Cabotegravir RAMs

2. Handling of Viral Load Blips

3. Suspected Virologic Failure

4. Confirmed Virologic Failure

5. Resistance Testing in the Event of CVF

IN-VITRO PHENOTYPIC CUT-OFF FOR VIRAL SENSITIVITY IS ALIGNED WITH CUT-OFF USED FOR OTHER BNABS IN CLINICAL DEVELOPMENT

- **N6LS phenotypic sensitivity cut-off value for enrollment into EMRACE = IC90 ≤2 µg/mL and MPI >98%**

- Aligns with sensitivity threshold for VRC07-523LS in the ACTG5357 study of IC50 ≤0.25 µg/mL and MPI >98% (selected from the 85th percentile of VRC07 IC50 values from analysis of Week 48 on-ART PBMC samples) [NCT03739996]

- Aligns with sensitivity threshold used for 3BNC117-LS and 10-1074-LS of IC90 ≤2 µg/mL in the LEN plus 2 bnAb phase 1b and phase 2 studies [NCT04811040; NCT05729568]

SENSITIVITY TO VH3810109 IS ASSESSED USING THE MONOGRAM BIOSCIENCES PHENOSENSE MAB DNA ASSAY

- Whole blood samples in EDTA collected at Screening are shipped (~5 days) to Central Lab Q2 for PBMC processing and 2x 1mL vials (total 20M) PBMCs are shipped from Q2 to Monogram (~10 days)
- Phenotypic sensitivity of proviral DNA to VH3810109 is assessed using the PhenoSense mAb DNA Assay (~30 days). Results are posted to the Monogram v-link portal
- **Based on Inclusion Criteria 9, VH3810109 IC90 ≤ 2µg/mL and Maximum Percent Inhibition (MPI) >98%, this individual is eligible for enrollment in EMBRACE.**

PhenoSense mAb
MONOCLONAL ANTIBODY ASSAY DNA

GSK
5 Moore Drive
Research Triangle Park, NC 27709
USA

Study

Client:

Project:

Monogram BIOSCIENCES
LabCorp Specialty Testing Group

Weidong Huang, MD, Medical Director
345 Oyster Point Blvd
South San Francisco, CA 94080 - Tel: (800) 777-0177

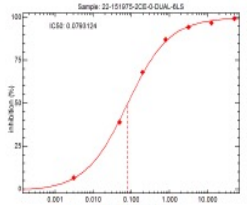
Patient Initials:	DOB	Patient ID/Medical Record #	Gender U	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode W	Report Status **FINAL**
Investigator			Specimen ID	
Comments:				

Drug Susceptibility

Drug Name/ Brand Name	IC50	IC80	IC90	IC95	Ref IC50	Units	MPI	Ref ID
GSK-3810109A/ N6LS	0.07931	0.45535	1.27228	3.29323	0.10816	µg/mL	99	JRCSF

Drug Susceptibility Curves

GSK-3810109A



IC50: 0.07931

Please download and print out a copy of the PhenoSense mAb DNA results and file with source documents

POLLING QUESTION:

Based on results of the PhenoSense mAb DNA Assay, which of the following would meet phenotypic inclusion criteria for enrollment into EMBRACE?

A. VH3810109 IC90 value = 0.15532 µg/mL and MPI value = 100

B. VH3810109 IC90 value = >50 µg/mL and MPI value = 86

C. VH3810109 IC90 value = 2.26327 µg/mL and MPI value = 99

D. VH3810109 IC90 value = 1.90536 µg/mL and MPI value = 98

Stratification to ensure even distribution of phenotypic sensitivity between treatment arms, based on VH3810109 phenotypic sensitivity (IC90 >1 or ≤1µg/mL, as per protocol Section 4.1, will be done using the RAMOS system.

ACCESS TO THE MONOGRAM V-LINK PORTAL

- List of all site and study team personnel requiring access to the v-link portal has been shared with Monogram
- Individuals should receive an email:

  "Welcome to Monogram Biosciences vLink"

Thank you for registering for vLink.
Your username: _____
The [temporary] password will follow in a second email.

Follow the link below to access the web site:
https://urldefense.com/v3/__https://vlink.monogrambio.com__;!!AoaiBx6H!yWXSEQ3bfUkEPZXV_anHr2XbFk96jKICdw5x24EV3SEPLLZADS3_q1F6FovE2fDqI7g4VEVABaWcQ6oD8szlvfMN$

When a report is final and posted to vLink, a notification will be sent to the email address you provided.

Please reach out to the study team for any questions or help with v-link access

EXCLUSION CRITERIA 30: PRESENCE OF ANY MAJOR CABOTEGRAVIR RAMS

Participants are excluded from the study if there is any evidence of viral resistance based on the presence of any major cabotegravir resistance-associated mutation [IAS-USA, 2022] in any historic resistance test result.

CABOTEGRAVIR RAMs [IAS 2022]
G**118R**
G**140R**
Q148H/K/R
N**155H**
R**263K**
BOLD denotes major resistance associated mutations

HANDLING OF VIRAL LOAD BLIPS PROTOCOL SECTION 7.4.1.4

- Transient increase in HIV-1 RNA ≥50 but <200 copies/mL
- Any questions please contact the Medical Monitor

Visit	Screen	Day 1 Baseline	Week 1	Week 2	Month 1	Month 1 plus 2 Weeks	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8
HIV-1 RNA c/mL	<50	<50	<50	<50	<50	<50	**≥50 <200**	<50	<50	<50	**≥50 <200**	<50	<50

Repeat HIV-1 RNA is required, within 2 to 4 weeks
Unscheduled visit
or
Next scheduled visit

intercurrent illness?	**Perform repeat HIV-1 RNA 2 to 4 weeks after resolution**
recent immunization?	**Perform HIV-1 RNA 4 weeks post immunization**
interruption of oral therapy (SOC arm)?	**Perform repeat HIV-1 at least 2 weeks after restarting oral therapy**

Month 6 and Month 12
FDA Snapshot visit window is +/- 6 weeks

Month 6 (Primary Endpoint)
Month 12 (Secondary endpoint)

Repeat HIV-1 RNA no later than 2-4 weeks
after the date of the Month 6 or Month 12 visit
such that the result falls
within the Snapshot analysis window.

VIROLOGIC FAILURE PROTOCOL SECTION 7.4.1.1

Definition of Virologic Failure (applies only during the Intervention Period of the study)

Section 7.4.1.2

SVF Suspected Virologic Failure: A single HIV-1 RNA value ≥200 c/mL with second plasma HIV-1 RNA performed at least two weeks but not more than 4 weeks apart from the date of the original sample

Visit	Screen	Day 1 Baseline	Week 1	Week 2	Month 1	Month 1 plus 2 Weeks	Month 2	Month X	Second HIV-1 RNA performed 2 to 4 weeks after date of the SVF sample
HIV-1 RNA c/mL	<50	<50	<50	<50	<50	<50	<50	≥200	<200

Suspected VF not confirmed

Repeat HIV-1 RNA is required, within 2 to 4 weeks
Unscheduled visit
or
Next scheduled visit

- **intercurrent illness?** → **Perform repeat HIV-1 RNA 2 to 4 weeks after resolution**
- **recent immunization?** → **Perform HIV-1 RNA 4 weeks post immunization**
- **interruption of oral therapy (SOC arm)?** → **Perform repeat HIV-1 at least 2 weeks after resumption of oral therapy**

Please discuss any treatment interruptions for participants receiving VH3810109 + CAB with the Medical Monitor

VIROLOGIC FAILURE PROTOCOL SECTION 7.4.1.1

Definition of Virologic Failure (applies only during the Intervention Period of the study)

Section 7.4.1.3

CVF Confirmed Virologic Failure: Virologic rebound as indicated by two consecutive plasma HIV-1 RNA values ≥200 c/mL.

Visit	Screen	Day 1 Baseline	Week 1	Week 2	Month 1	Month 1 plus 2 Weeks	Month 2	Month X	Second HIV-1 RNA performed 2 to 4 weeks after date of the SVF sample
HIV-1 RNA c/mL	<50	<50	<50	<50	<50	<50	<50	≥200	≥200

Repeat HIV-1 RNA is required, within 2 to 4 weeks
Unscheduled visit
or
Next scheduled visit

- **intercurrent illness?** → **Perform repeat HIV-1 RNA 2 to 4 weeks after resolution**
- **recent immunization?** → **Perform HIV-1 RNA 4 weeks post immunization**
- **interruption of oral therapy (SOC arm)?** → **Perform repeat HIV-1 at least 2 weeks after resumption of oral therapy**

Confirmed Virologic Failure

Participants must discontinue Investigational Product and switch immediately to a standard of care ART regimen.
An initial regimen including either DTG 50mg twice daily or a boosted PI is recommended until results of a viral genotype are available.
Please discuss selection of an alternative ART regimen with the Medical Monitor.

RESISTANCE TESTING TO BE PERFORMED IN THE EVENT OF VIROLOGIC FAILURE

- Once a participant has been determined as meeting confirmed virologic failure, reverse transcriptase, protease and integrase genotypic and phenotypic HIV-1 resistance testing will be performed using plasma samples from the suspected virologic failure time point (Monogram Biosciences PSGT+IN assay)

- Results will be made known to the study investigator when available, to inform on a new ARV-regimen.

- Baseline genotypic testing of proviral DNA will be performed using whole blood samples collected at Day 1 (Monogram Biosciences GenoSure Archive)

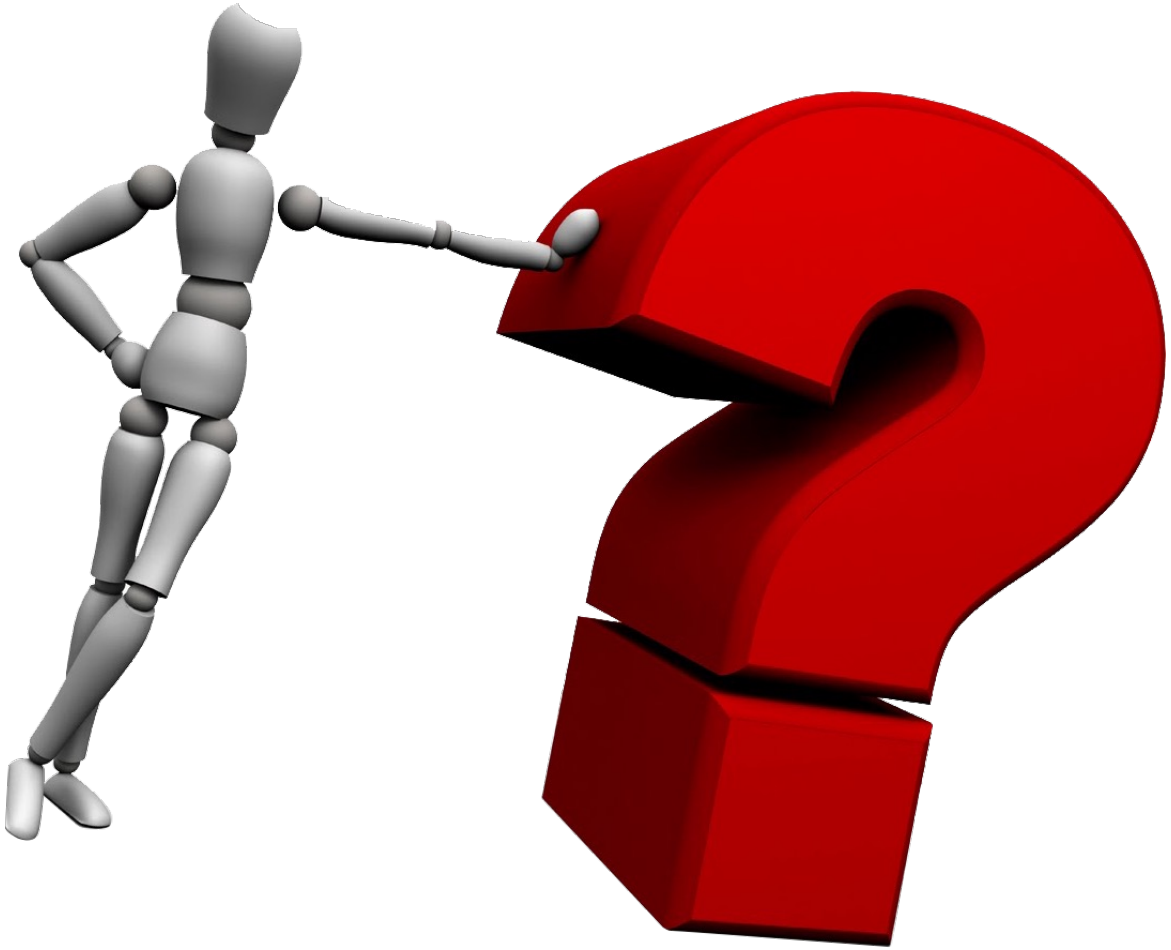
- HIV envelope genotyping and phenotyping for VH3810109 sensitivity will be assessed using a plasma sample collected at the time of suspected virologic failure.

SUMMARY

- **Proviral phenotypic sensitivity to N6LS at screening is required for inclusion in EMBRACE**
  - VH3810109 IC90 ≤ 2µg/mL and Maximum Percent Inhibition (MPI) >98% in the PhenoSense mAb assay

- **Frequent viral load monitoring schedule and immediate switch to oral ART following confirmed virological failure is anticipated to result in rapid re-suppression of HIV-1 RNA and minimize the risk of emergent resistance**

Questions?



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PROTOCOL OVERVIEW

Chelsea Macfarlane

Clinical Science Lead

STUDY DESIGN OVERVIEW

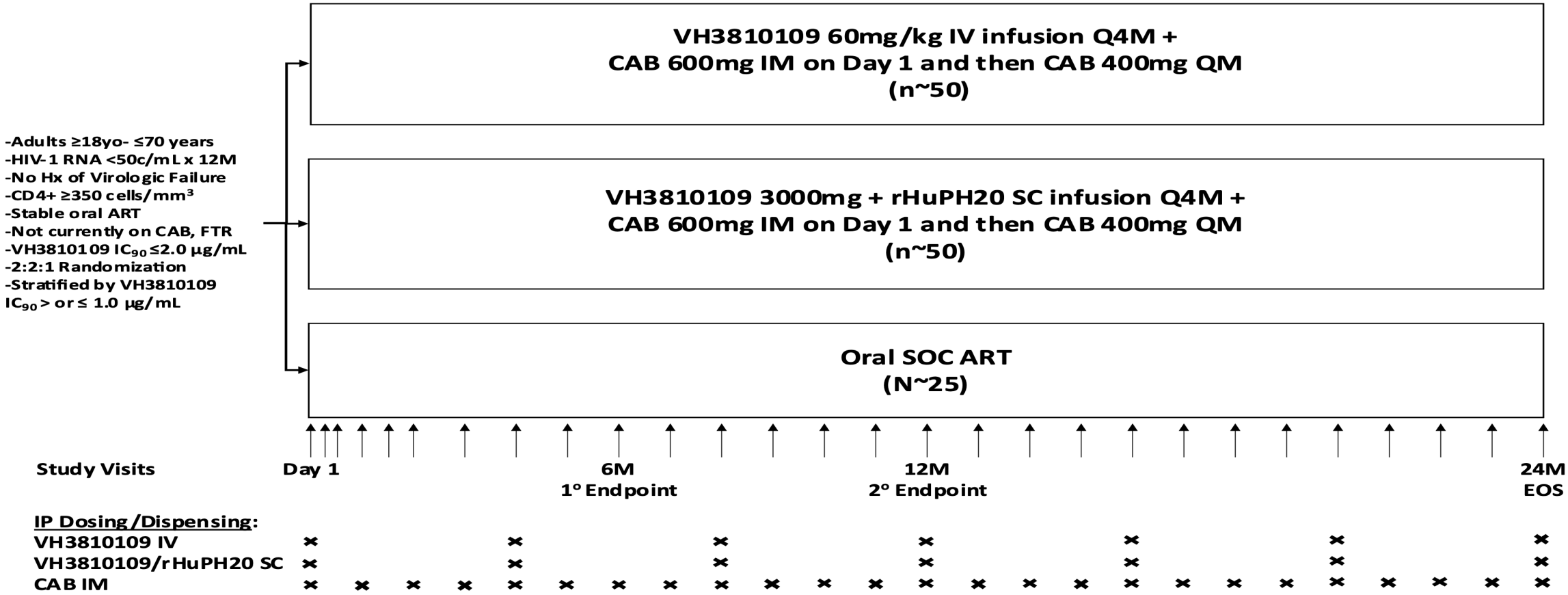
Study Phase 2B

Location: Continental USA and Puerto Rico

Design: Open Label, Multicenter, Randomised, 3-Arm study (Two investigational Arms and 1 SOC Arm)

Purpose: To assess the efficacy of VH3810109 (N6LS), dosed q4 mos. either IV infusion or SC infusion with rhuPH20 (Halozyme®) - both in combination with CAB IM dosed every 1 mo.) in virologically suppressed, ART-experienced adults living with HIV

EMBRACE STUDY SCHEMA



Study Objectives

STUDY OBJECTIVES

Primary Objective

- To evaluate the efficacy of VH3810109, dosed every 4 months as either IV infusion or SC infusion with rHuPH20, in combination with CAB IM dosed every 1 month in virologically suppressed, ART-experienced adults living with HIV

- * This objective is being evaluated using the study endpoint of: ***Plasma HIV-RNA greater than or equal to 50 copies/mL as per Food and Drug Administration (FDA) Snapshot algorithm at Month 6. The FDA Snapshot algorithm will be described further later in the presentation.***

STUDY OBJECTIVES

Secondary

- To evaluate the safety/tolerability of VH3810109 dosed every 4 months (+/-rHuPH20) + CAB IM every 1 month compared to oral Standard of Care in virologically suppressed, ART-experienced adults living with HIV
- To evaluate the efficacy of VH3810109, dosed every 4 months as either IV infusion or SC infusion with rHuPH20, in combination with CAB IM dosed every 1 month in virologically suppressed, ART-experienced adults living with HIV (looking at changes in HIV RNA levels and disease progression).
- To characterize VH3810109 and CAB pharmacokinetics
- To evaluate the impact of VH3810109 + CAB administration on immunologic parameters
- To evaluate the immunogenicity of VH3810109
- To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure

STUDY OBJECTIVES

Exploratory

- To evaluate the impact of VH3810109 on the HIV-1 envelope and potential decreased sensitivity to VH3810109
- To determine the impact of VH3810109 dosed every 4 months (+/-rHuPH20) + CAB IM dosed every 1month compared to standard of care on immune responses
- To evaluate the impact of VH3810109 on HIV-1 reservoirs
- To evaluate the acceptability, tolerability and feasibility of administering VH3810109 and any impact on health-related quality of life and treatment satisfaction

PLANNED ANALYSIS AND EOS

1) **Interim Analysis** for Internal Safety Review Committee (once 50% of participants have reached the Month 6 visit endpoint)
2) **Primary Analysis** for Primary Endpoint (when all randomized participants have completed their Month 6 visit)
3) **Secondary Analysis** (when the last participant has reached their Month 12 visit)
4) **End of Study Analysis** (when the last participant has completed their Month 24 visit)

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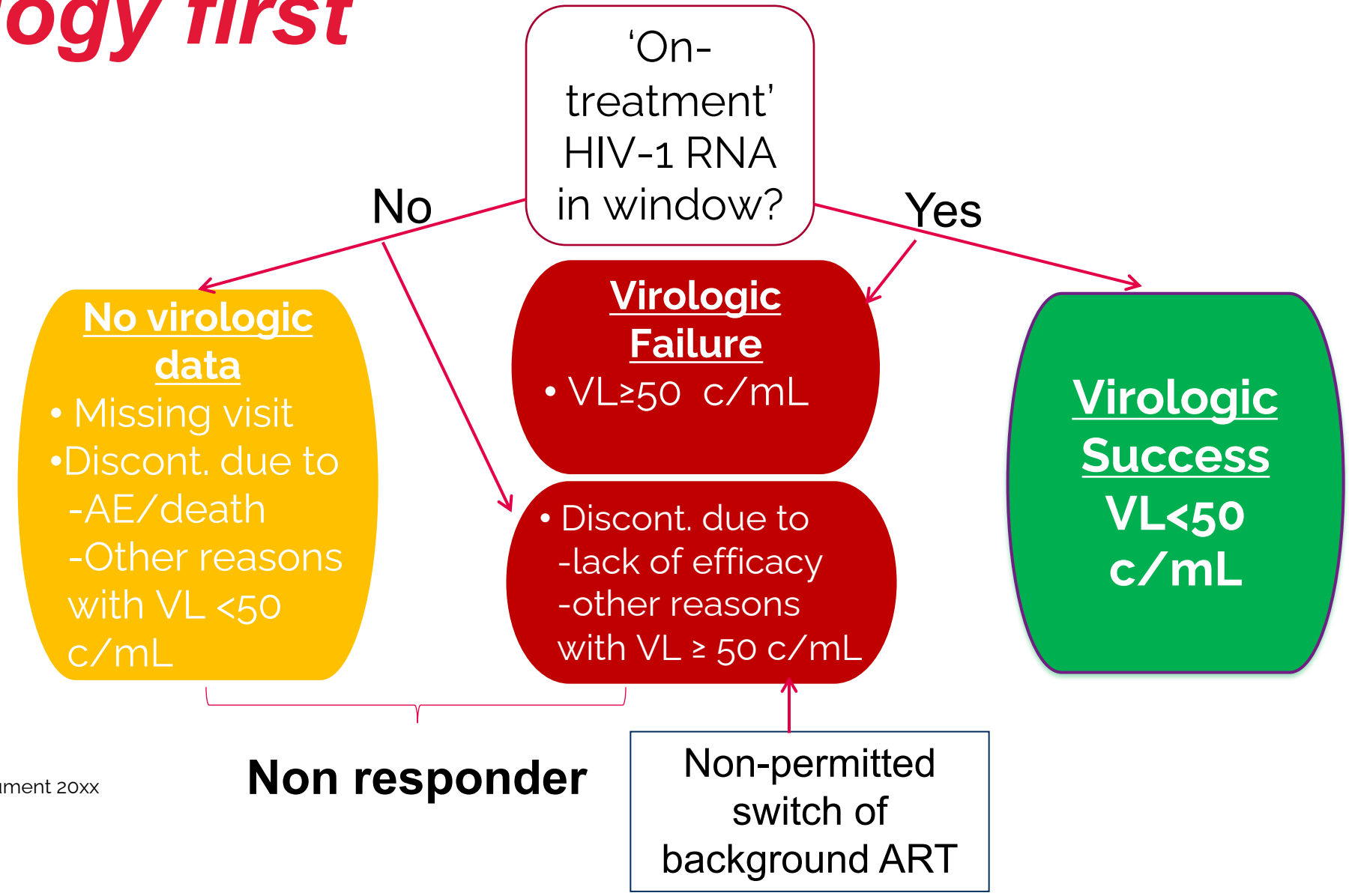
Analysis of Objectives/Endpoints

QUICK GUIDE TO FDA'S SNAPSHOT ALGORITHM FOR ANALYZING HIV RNA RESULTS

Amy Cutrell
ViiV Clinical Statistics, Durham

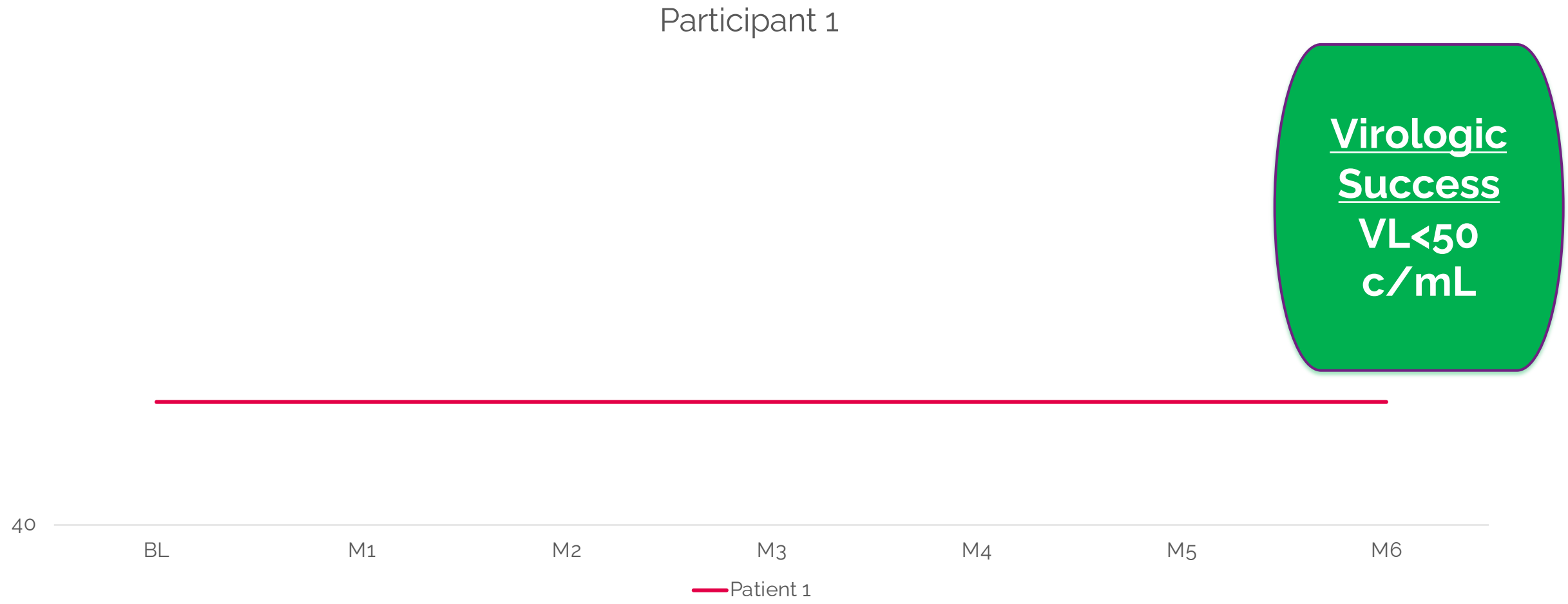
October 2016

Snapshot Algorithm: hierarchy of *virology first*



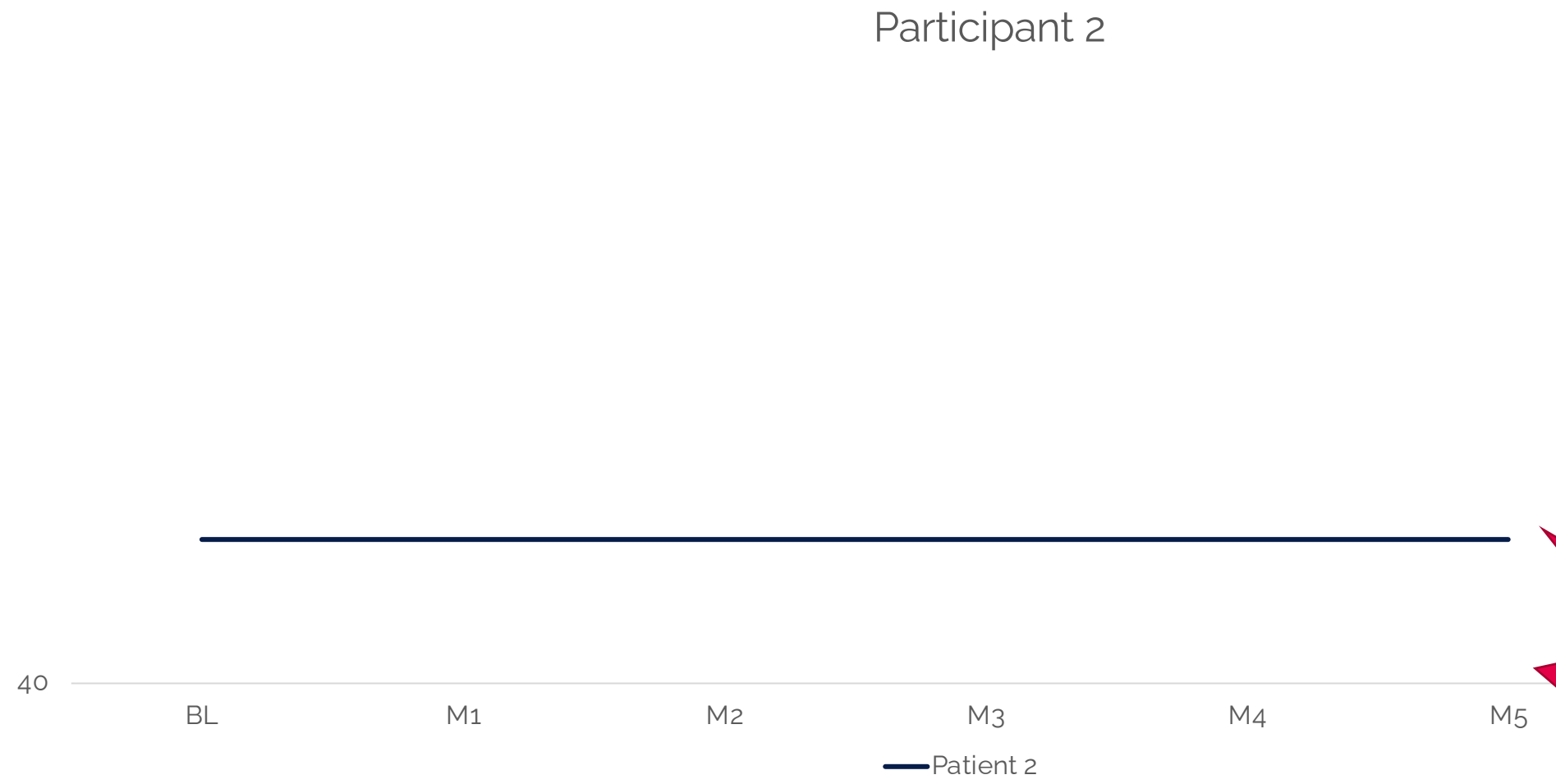
FDA Guidance Document 20xx

Hypothetical individual RNA profiles



NOTE: Assume suppressed viral load = 50 c/mL

Hypothetical individual RNA profiles



No virologic data

- Missing visit
- D/c due to
  - -AE/death
  - -Other reasons with VL <50 c/mL

?

Take care to avoid missing data, esp for 1˚ endpoint

NOTE: Assume suppressed viral load = 50 c/mL

Blips and Low-Level Viremia

Viral ‘blips’ are routinely observed (even on IM dosing with directly observed therapy)

HIV-1 RNA “blips” are not usually associated with subsequent virologic failure [DHHS, 2015].

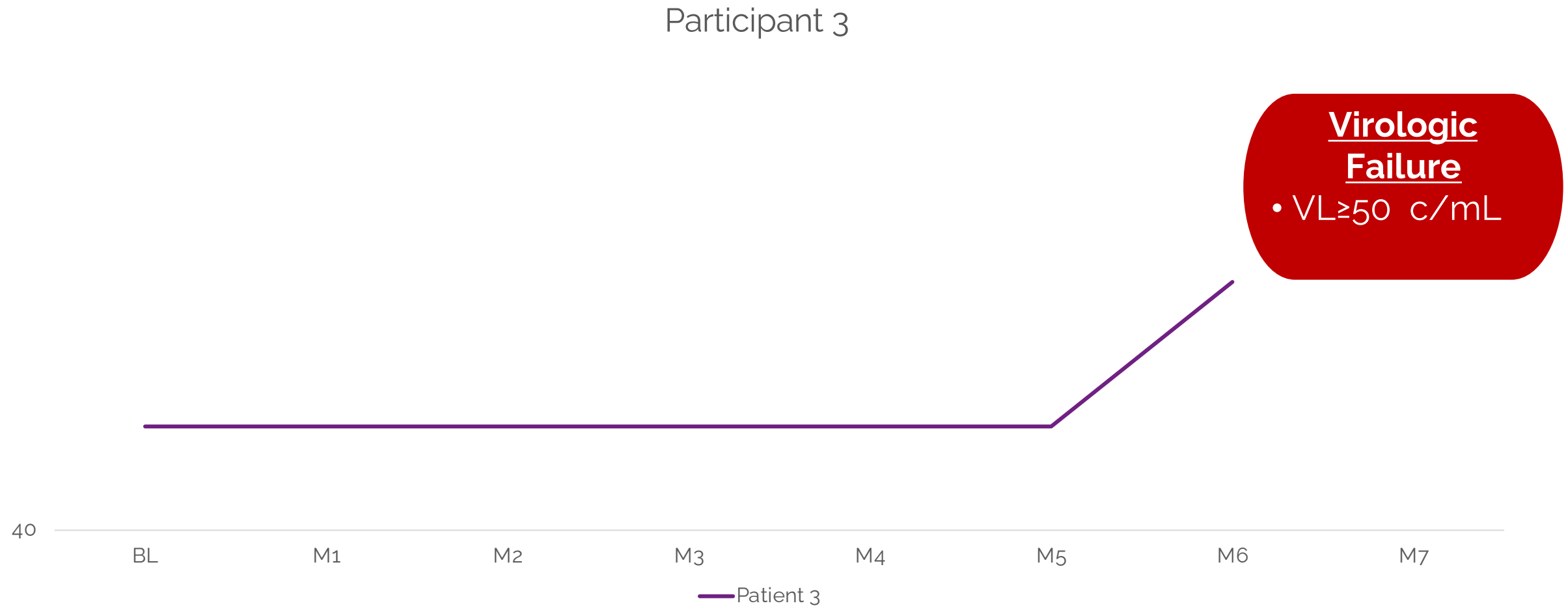
Participants with transient increases in HIV-1 RNA (‘blips’ HIV-1 RNA <200 c/mL) are not considered suspected virologic failures and do not require a change in therapy.

- could simply be a function of the variability of the assay

Participants who have a HIV-1 RNA ≥ 50 c/mL and <200 c/mL at key analysis timepoints (Month 6, Month 12, Month 24) must return to the clinic as soon as possible (but no more than 4 weeks from the key visit) for a repeat HIV-1 RNA test, such that the result falls within the same analysis window.

Hypothetical individual RNA profiles

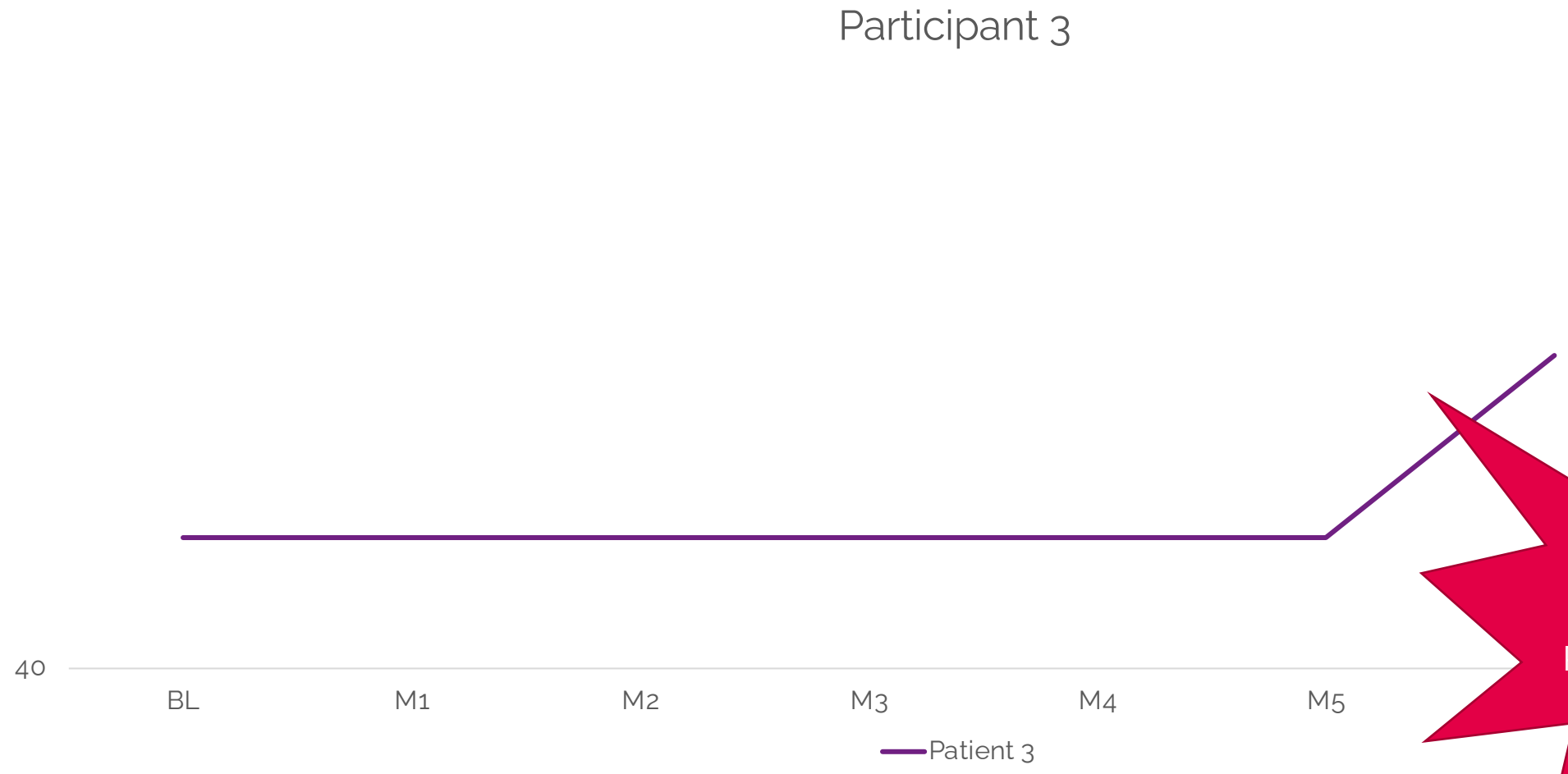
Retesting at Key Timepoints



NOTE: Assume suppressed viral load = 50 c/mL

Hypothetical individual RNA profiles

Retesting at Key Timepoints

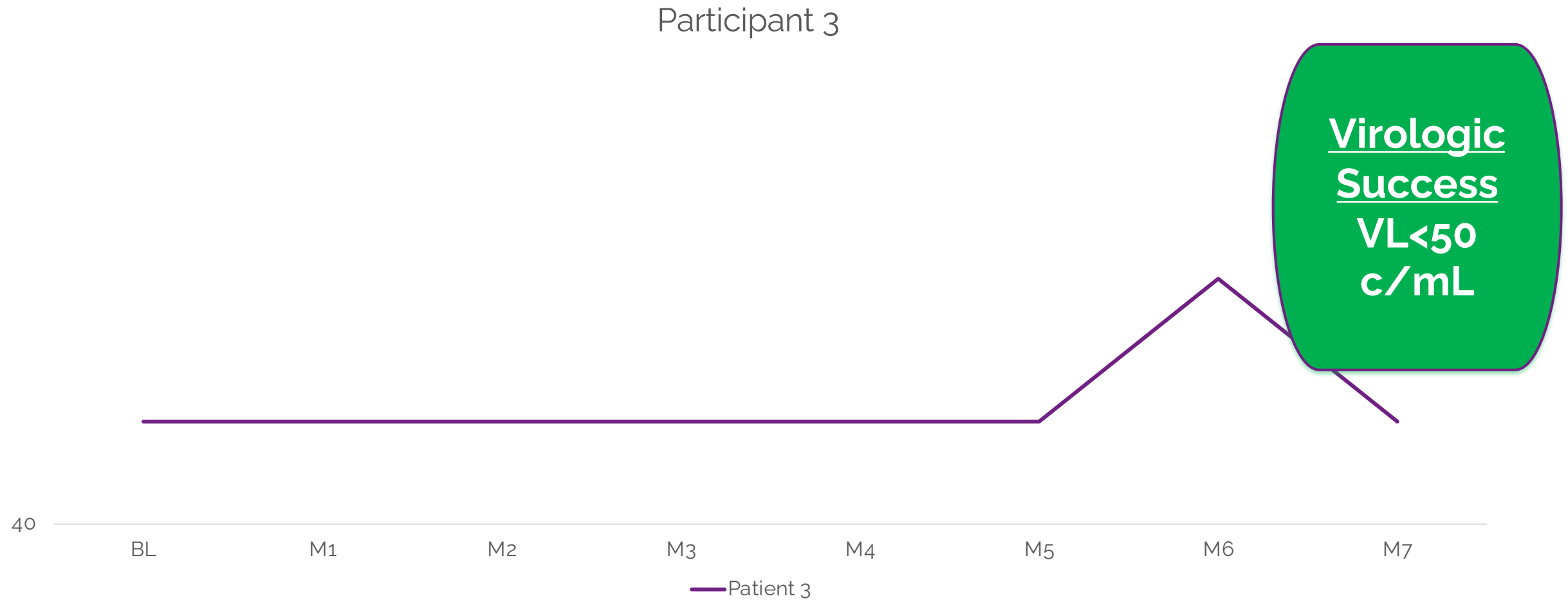


Protocol instructs to bring patients back for a repeat RNA test within 2-4 weeks

NOTE: Assume suppressed viral load = 50 c/mL

Hypothetical individual RNA profiles

Retesting at Key Timepoints



NOTE: Assume suppressed viral load = 50 c/mL

BREAKOUT SESSIONS

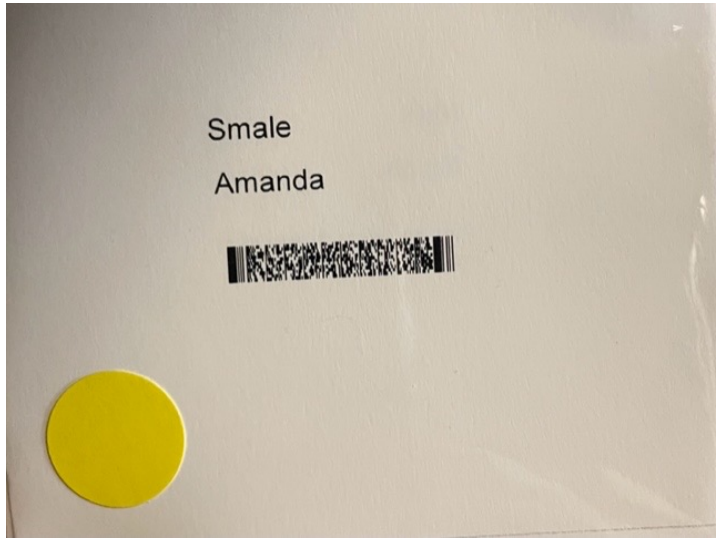
- Site staff attendees have been divided across 4 breakout sessions
- The colored sticker on your name tag outlines the breakout room you will be in
- Please head to that breakout room after the break

Heritage A/B (General Session Room)

Heritage C

Marietta

Augusta



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BREAK