VH3810109 (N6LS)

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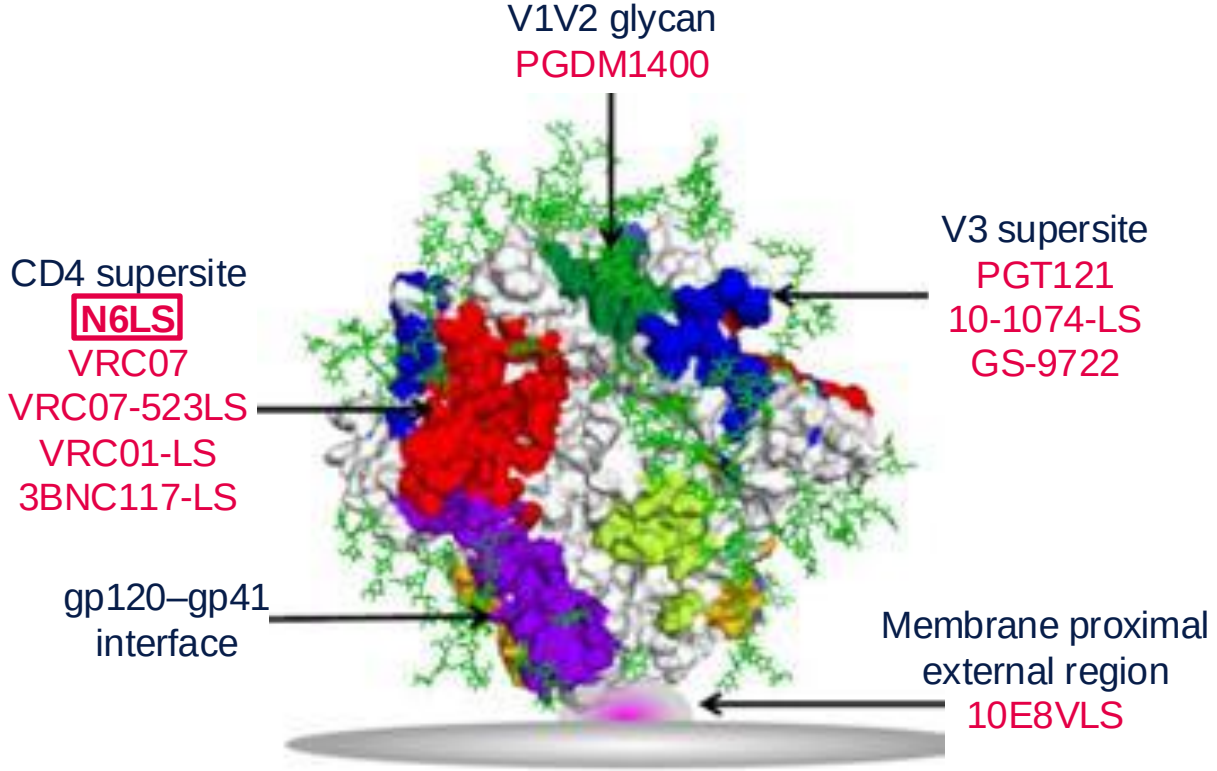
Introduction

- VH3810109 (N6LS) is a novel bNAb with broad and potent neutralization activity in vitro, which targets the CD4 binding site of the HIV-1 envelope protein
- N6LS has demonstrated robust antiviral effect in adults with HIV-1 in part 1 of the proof-of-concept phase 2a BANNER study[1]
  - N6LS led to virologic response in 13/14 participants, with a median decline in viremia of 1.72 log_{10} c/mL and maximum viral nadir from baseline of −2.60 log_{10} c/mL
- Overview POC of N6LS from BANNER part 1 and safety and tolerability of N6LS from parts 1 and 2 of BANNER when given IV or SC in ART-naive adults with HIV-1

bNAbs target 5 conserved regions on the envelope[2-10]



LS-containing bNAbs have been engineered to have long half-lives[11]

ART, antiretroviral therapy; bNAb, broadly neutralizing antibody; IV, intravenous; N6LS, VH3810109; SC, subcutaneous.

1. Leone et al. HIV Drug Therapy Glasgow 2022; Glasgow, Scotland. Slides O34. **2.** Bar et al. *N Engl J Med.* 2016;375:2037-2050. **3.** Kwon et al. *Retrovirology.* 2012;9(suppl 2):O34. **4.** Scheid et al. *Science.* 2011;333:1633-1637. **5.** Mouquet et al. *Proc Natl Acad Sci U S A.* 2012;109:E3268-E3277. **6.** Walker et al. *Nature.* 2011;477:466-470. **7.** Caskey. *Curr Opin HIV AIDS.* 2020;15:49-55. **8.** Doria-Rose et al. *J Virol.* 2015;90:76-91. **9.** Kwon et al. *J Virol.* 2016;90:5899-5914. **10.** Gaudinski et al. *Lancet HIV.* 2019;6:e667-e679. **11.** Huang et al. *Immunity.* 2016;45:1108-1121.

BANNER Study Design

Randomized, open-label, 2-part, multicenter study assessing safety, PK, and antiviral activity of N6LS in ART-naive adults

Single N6LS infusion

Inclusion criteria
- Age 18-65 years
- HIV-1 RNA ≥5000 c/mL
- CD4+ cell count ≥250 cells/mm^3
- ART-naive

Randomized 1:1

Part 1

- N6LS 40 mg/kg IV (n=8)
- N6LS 280 mg (~4 mg/kg[a]) IV (n=6)

Planned interim analysis[b]
- To determine whether to proceed to part 2 and to determine dose selection in part 2

Inclusion criteria
- Age 18-65 years
- HIV-1 RNA ≥5000 c/mL
- CD4+ cell count ≥250 cells/mm^3
- ART-naive

Randomized 1:1

Part 2

- N6LS 700 mg (~10 mg/kg[a]) IV (n=16)
- N6LS 70 mg (~1 mg/kg[a]) IV (n=16)
- N6LS 700 mg (~10 mg/kg[a]) SC (n=16)

Monotherapy endpoint criteria (Days 11-84)
- Virologic non-response (viral nadir decline <0.5 $\log_{10}$ c/mL at Day 11)
- Virologic rebound (VL rebound of ≥1.0 $\log_{10}$ c/mL increase from nadir or to <0.5 $\log_{10}$ c/mL from baseline)
- Missing/Delayed data from previous visits
- Reached Day 84

Participants receive INI-based SOC

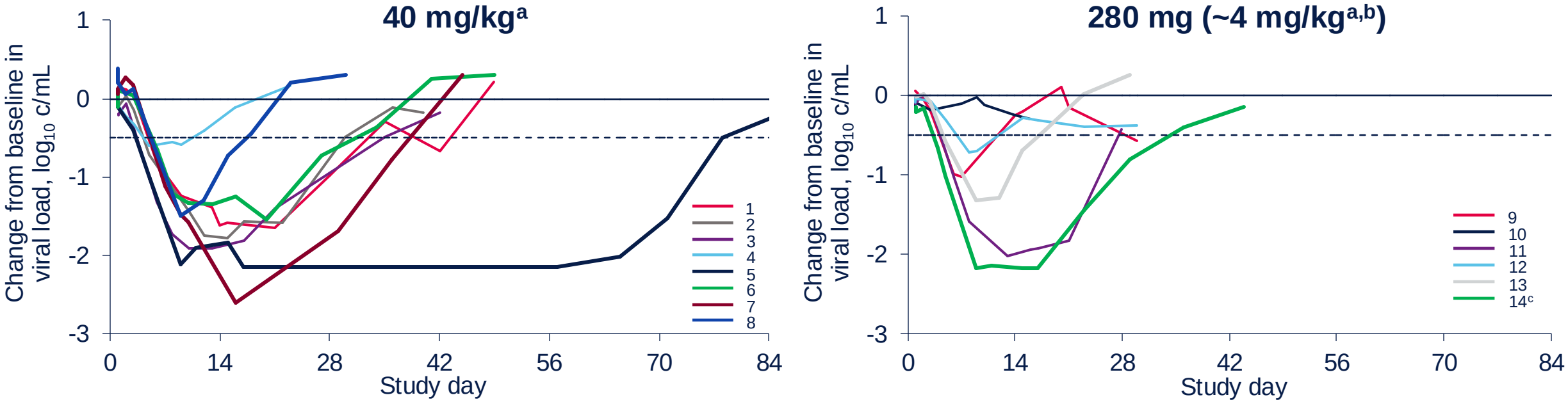
Day 1 | **Day 11** | **Monotherapy** | **Day 84** | **SOC[c] 48 weeks**

- Safety endpoints included incidence of adverse events and infusion/injection site reactions, vital signs, electrocardiograms, and clinical laboratory tests monitored through date of last participant completing the monotherapy phase

ART, antiretroviral therapy; INI, integrase inhibitor; IV, intravenous; N6LS, VH3810109; PK, pharmacokinetics; SC, subcutaneous; SOC, standard of care; VL, viral load.

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

N6LS Led to Virologic Response in 13/14 Participants

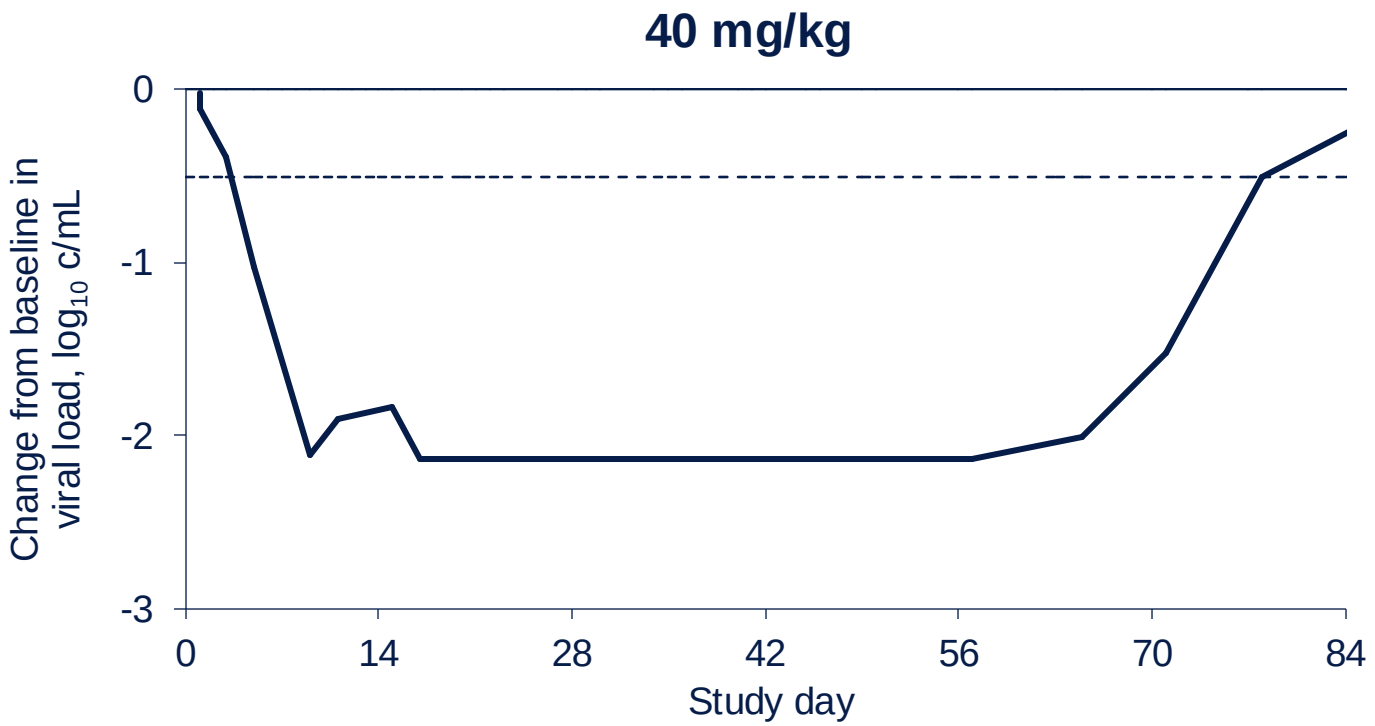


Viral dynamic measures	N6LS 40 mg/kg IV (n=8)	N6LS 280 mg IV (~4 mg/kg[b]; n=6)
Median (range) viral nadir from baseline, log_{10} c/mL	−1.72 (−0.60, −2.60)	−1.18 (−0.30, −2.18)
Median (range) time to viral nadir, days	16 (5-21)	9 (7-16)
Maximum viral nadir from baseline, log_{10} c/mL	−2.60	−2.18
Median (range) time to viral rebound among responders, days	35 (12-78) [n=8]	18 (14-29) [n=5]

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). IV, intravenous; N6LS, VH3810109.
[a]Each line represents an individual participant. [b]For a 70-kg individual. [c]Participant 14 is the only female participant in the study.
Leone et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Slides O34.

Leone et al. EACS 2023; Warsaw, Poland. Slides PS8.O5.

VH3810109 Virologic Response in Participant #5: Longest Suppression



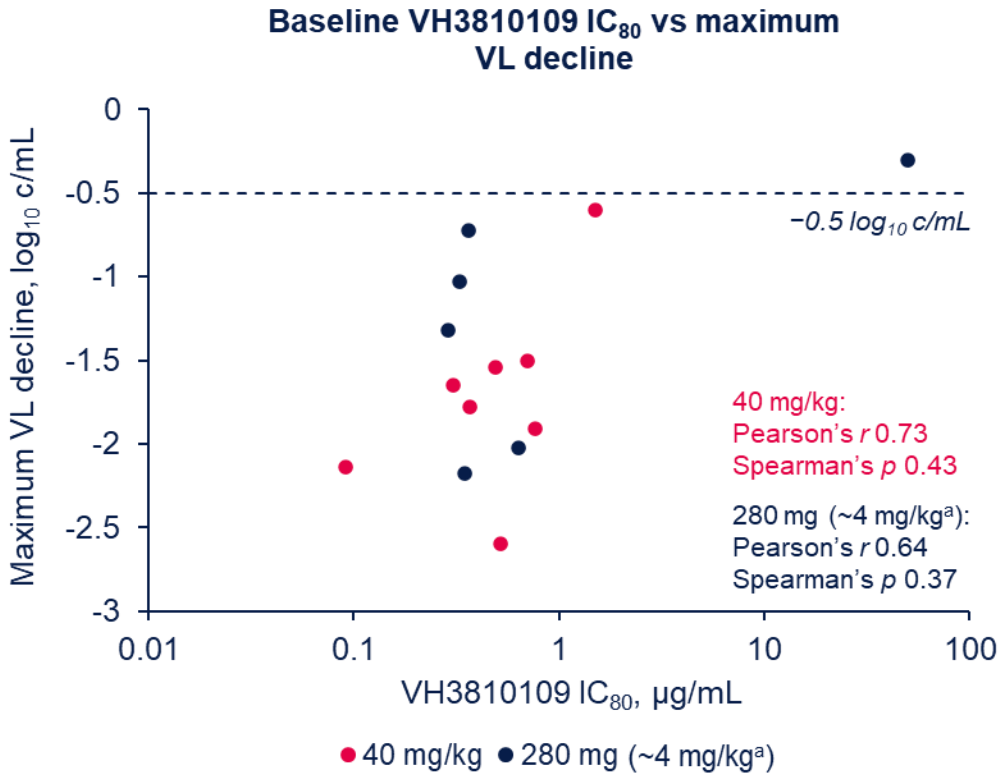
Viral dynamic measures	Participant #5
Baseline viral load, c/mL	5309
Baseline CD4+ cell count, cells/mm^3	700
Time to rebound, days[a]	78
Maximum viral load decline, log_{10} c/mL	−2.14
Time to maximum viral load decline, days	17
Baseline IC_{80}, µg/mL	0.09

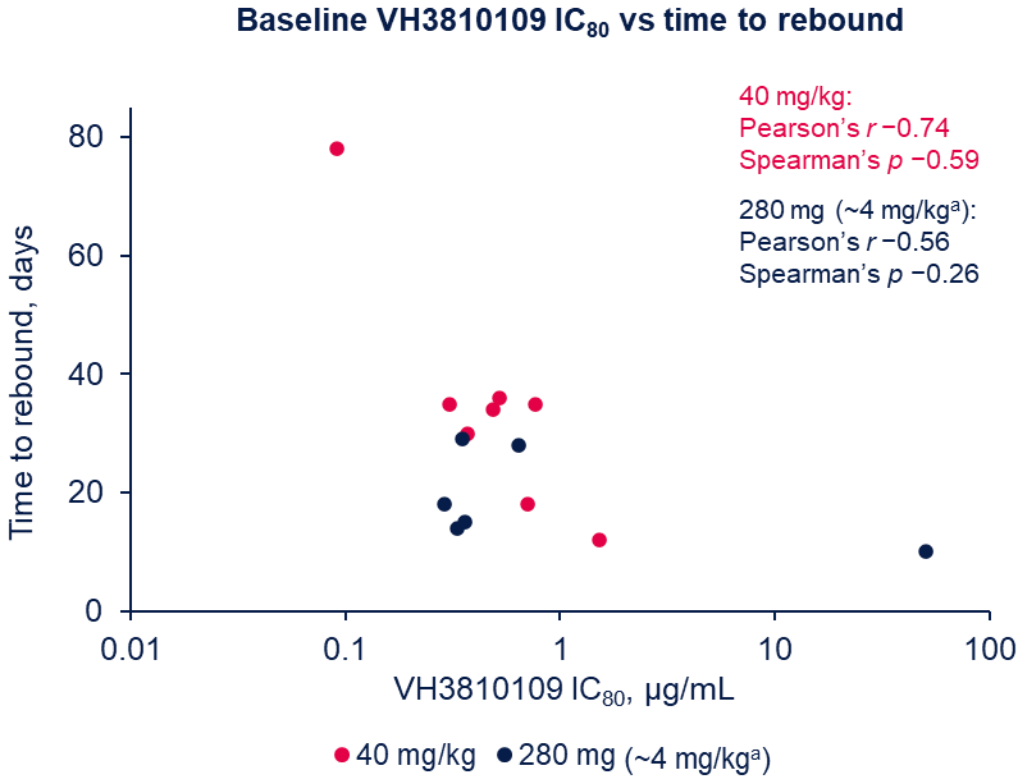
Solid line represents no change from baseline and dashed line represents virologic non-response (viral nadir decline <0.5 log_{10} c/mL at Day 11).
[a]Time to rebound is defined by time of VL ≥1.0 log_{10} c/mL increase from nadir or <0.5 log_{10} c/mL decrease from baseline.

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

Maximum VL Decline and Time to Rebound by Baseline VH3810109 IC_{80}

Baseline viral sensitivity moderately correlated with magnitude and duration of antiviral response





Each dot represents an individual participant. Horizontal dashed line represents virologic non-response (viral nadir decline <0.5 log_{10} c/mL at Day 11). [a]For a 70-kg individual.

BANNER Parts 1 and 2 Safety Summary: Monotherapy Phase

- N6LS was well tolerated, with few drug-related AEs and no serious AEs
  - Across dose groups, no noteworthy differences in overall AE incidences were observed
- Grade 3-4 AEs were reported in 10/62 (16%) participants; none were drug-related
  - Increased blood creatine phosphokinase and neutropenia were the only grade 3-4 AEs reported in >1 participant overall
- All drug-related adverse events were grade 1 or 2 in 13/62 (21%)
- No clinically significant safety trends in vital signs, electrocardiograms, or laboratory tests were observed across dose groups

	Part 1		Part 2			
Participants, n (%)	40 mg/kg IV (N=8)	280 mg IV (~4 mg/kg) (N=6)	700 mg IV (~10 mg/kg) (N=16)	70 mg IV (~1 mg/kg) (N=16)	700 mg SC (~10 mg/kg) (N=16)	Total (N=62)
Any AE	7 (88)	4 (67)	9 (56)	8 (50)	11 (69)	39 (63)
Drug-related	2 (25)	2 (33)	1 (6)	2 (13)	6 (38)	13 (21)
Grade 3-4 AEs	1 (13)	0	2 (13)	3 (19)	4 (25)	10 (16)
Drug-related	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0
Drug-related	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

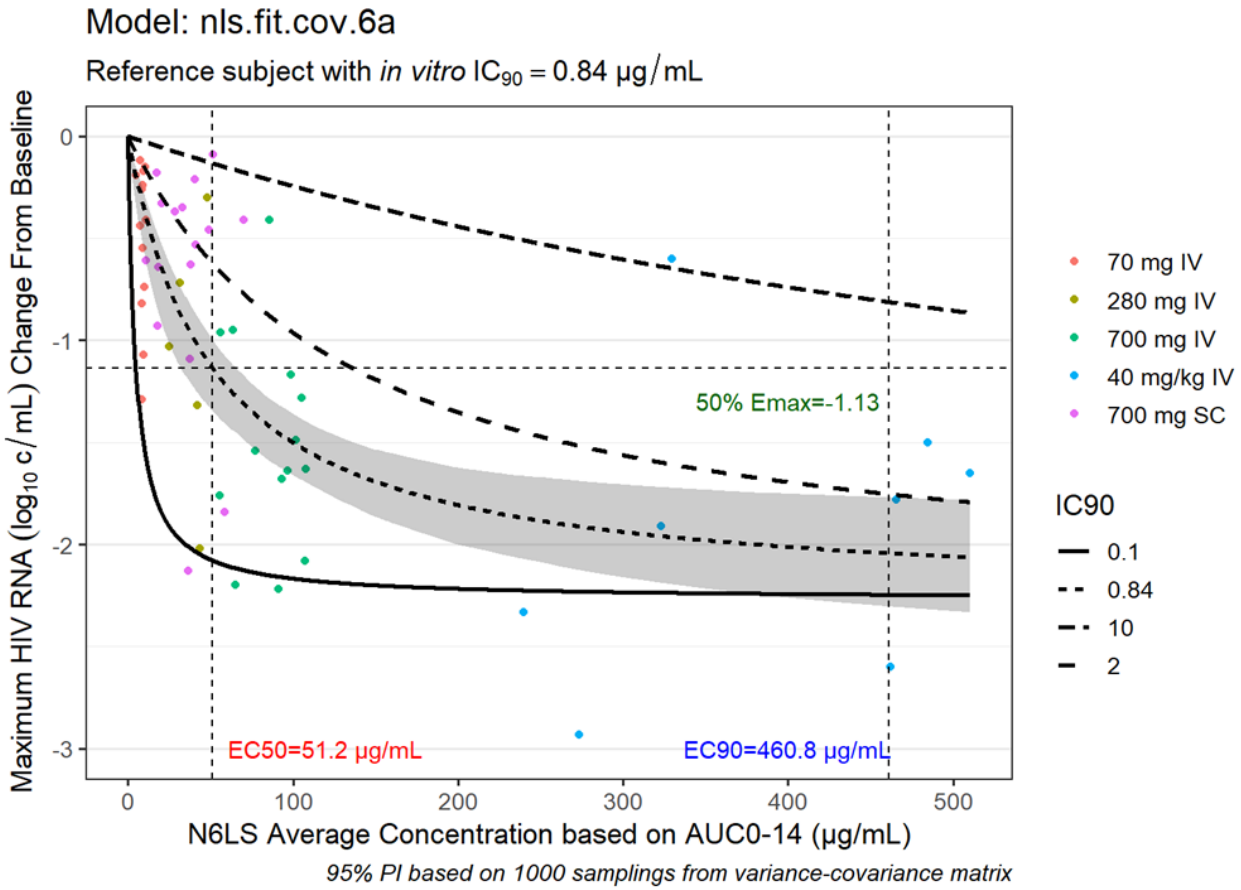
AE, adverse event; IV, intravenous; N6LS, VH3810109; SC, subcutaneous.

Leone et al. EACS 2023; Warsaw, Poland. Slides PS8.O5.

Average N6LS concentration (C_{avg} based on AUC_{0-14}) as the exposure predictor

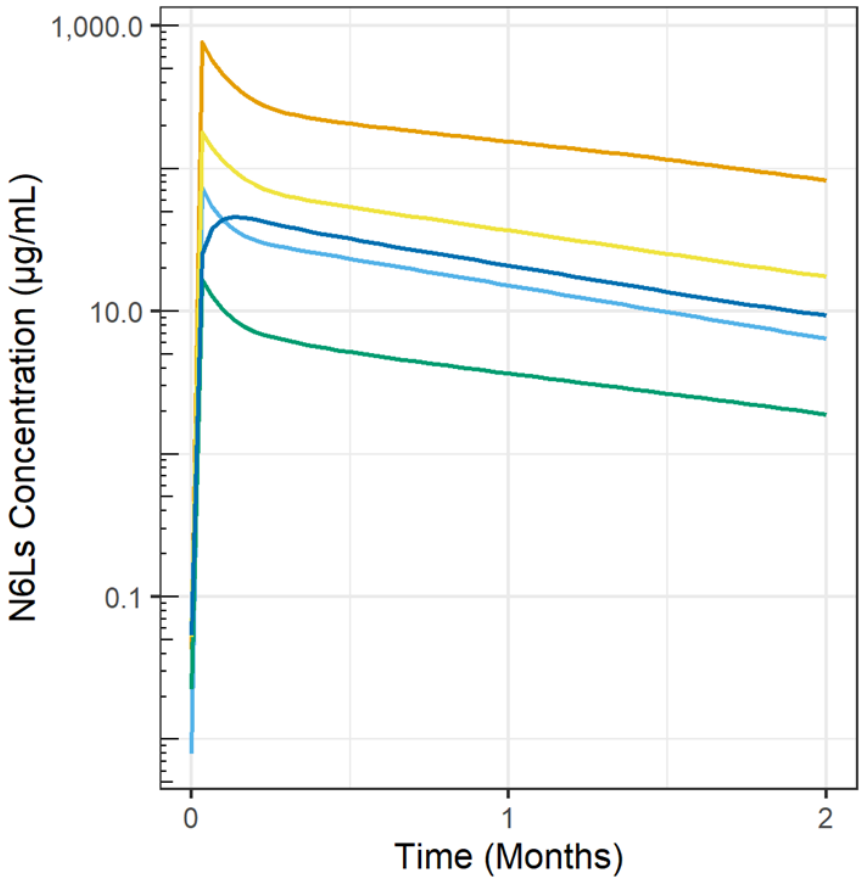
The final model were simulated 1000 times sampling from the variance-covariance matrix

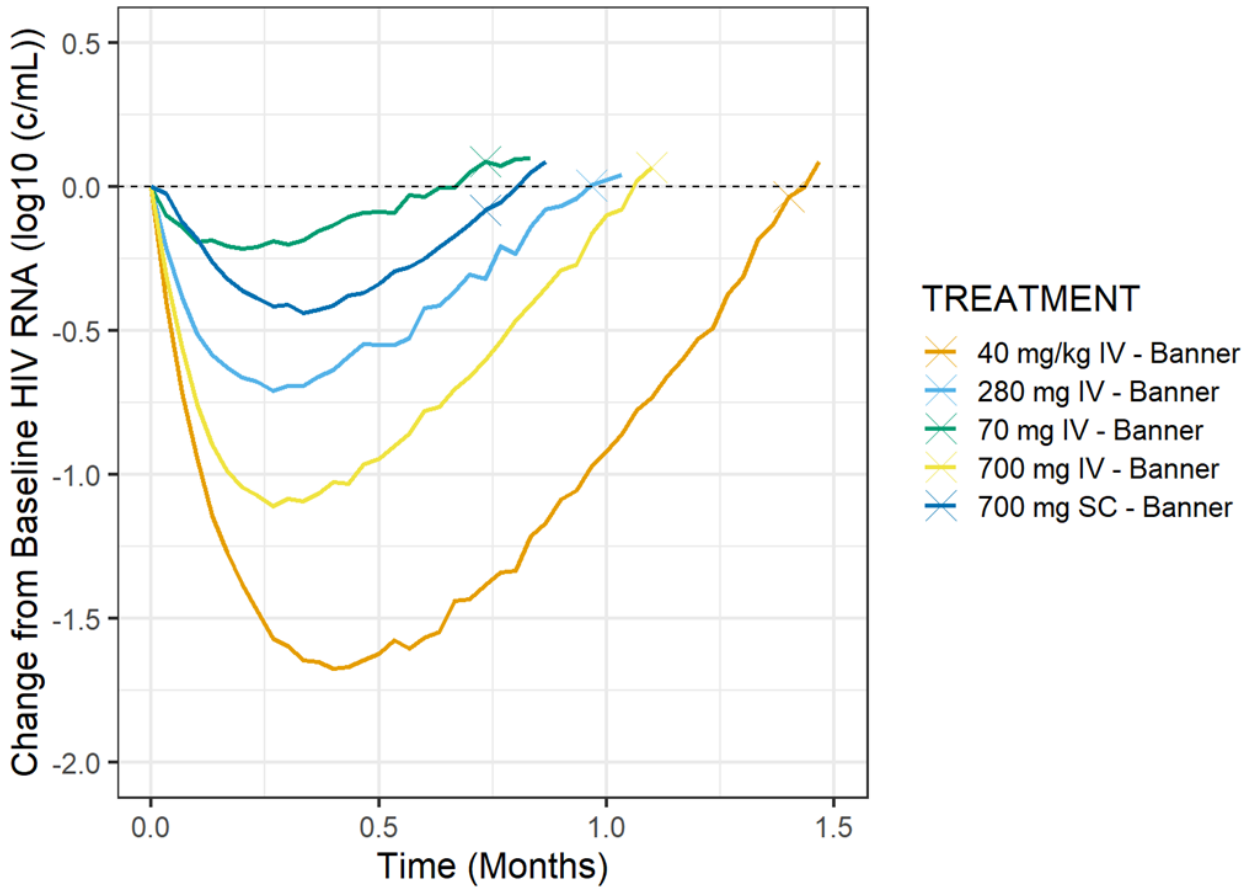
- Dashed line: Emax model fit; shaded region: 95% prediction interval (PI)
- Higher viral suppression was associated with higher N6LS exposure
- Participants with higher in vitro IC90 were likely to require higher N6LS exposure to achieve similar viral suppression compared to participants with lower in vitro IC90



PK/PD modeling

Simulated median PK and PD profile of Participants from BANNER



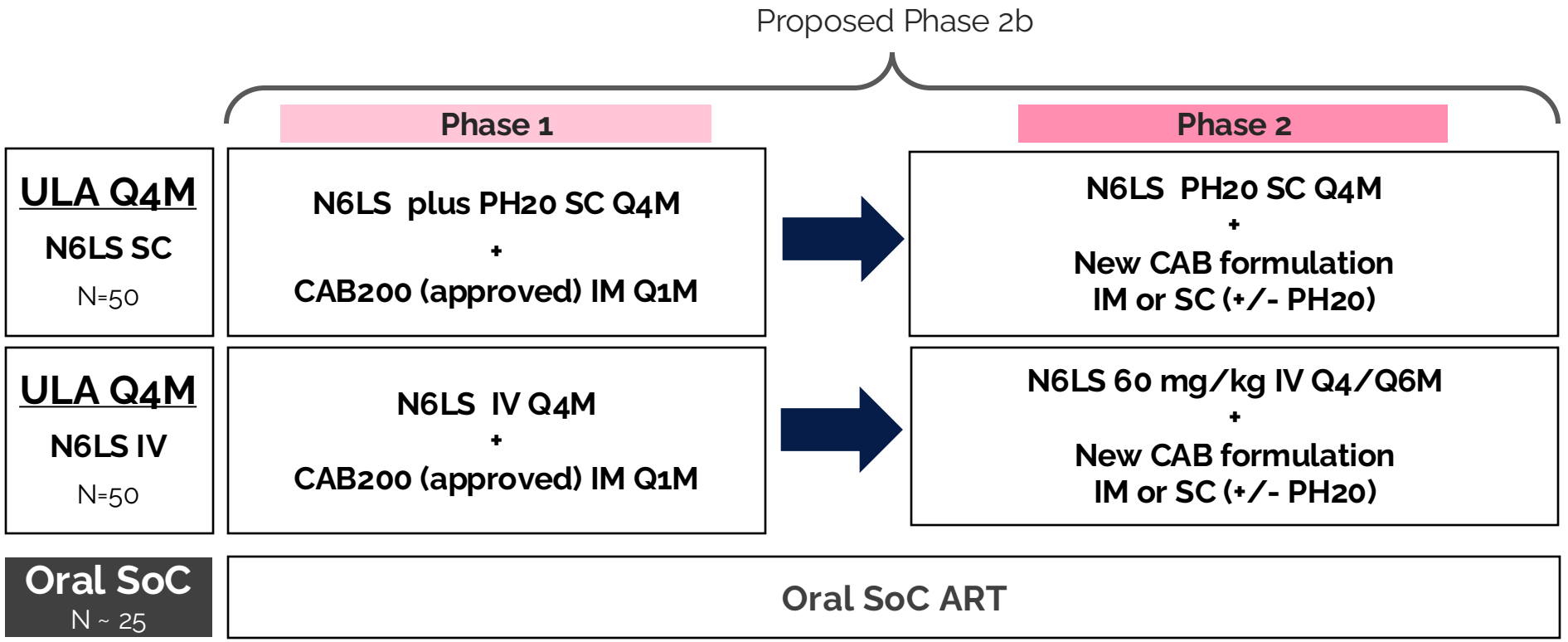


- *Model-predicted IC_{50} of 96.3 µg/mL are likely to be achieved at doses above 700 mg IV → consistent with the high response rate observed (>90%) in the 700 and 40 mg/kg IV group; PK/PD was consistent between SC and IV, but higher SC doses are needed to achieve comparable IV exposure.*
- *Viral rebound occurred quite rapidly after achieving nadir.*

Embrace Phase 2b Study Design: CAB + N6lS Q4M uLA

Key objectives: Determination of Efficacy (maintenance of virologic suppression, PK), Safety and tolerability to confirm Q4M dosing frequency and guide choice of Route of Administration in Phase 3.

Participants eligible with a viral phenotypic sensitivity to N6LS based on IC90 of ≤ 2 ug/ml and MPI >98% using the Monogram phenotypic assay at screening



Study Details | A Study to Investigate the Virologic Efficacy and Safety of VH3810109 + Cabotegravir Compared to Standard of Care (SOC) in Male and Female Adults Living With Human Immunodeficiency Virus (HIV) | ClinicalTrials.gov

Conclusions

- A single dose of N6LS was well tolerated, with few drug-related adverse events, including mild infusion/injection site reactions, and no serious adverse events during the monotherapy phase, at both high and low doses and with IV and SC administration
- In BANNER Part 1, baseline viral sensitivity to N6LS correlated with magnitude and duration of antiviral response
- POC and Safety data from parts 1 and 2 of BANNER support the ongoing development of N6LS into phase 2b for the treatment of HIV-1

Future Questions/Issues

- Can we define more clinically relevant cutoffs for viral phenotypic sensitivity?
- What is the relationship of viral sensitivity and vaccinal effect?
- Is a genotypic assay needed and possible?
- IVDR impact on studies in the EU and if adopted by the FDA?

References

- Edwards et al. EACS 2023; Warsaw, Poland. Poster eP.A.099
- Leone et al. HIV Drug Therapy Glasgow 2022; Glasgow Scotland, O34
- Leone et al. CROI 2023; Seattle, Washington 2023 P520
- Leone et al. EACS 2023; Warsaw, Poland PS8-05