0508

PHASE I DOSE-ESCALATION STUDY OF HUMAN MONOCLONAL ANTIBODY N6LS IN HEALTHY ADULTS

Alicia T. Widge[1], Katherine V. Houser[1], Martin R. Gaudinski[1], Cristina Carter[1], Somia P. Hickman[1], Jamie Saunders[1], Lasonji Holman[1], Ingelise Gordon[1], Sarah O'Connell[1], Edmund V. Capparelli[2], Mark Connors[3], Grace L. Chen[1], Richard A. Koup[1], John R. Mascola[1], and the VRC 609 Study Team
[1]Vaccine Research Center, NIAID, Bethesda, MD, USA, [2]University of California San Diego, La Jolla, CA, USA, [3]NIAID, Bethesda, MD, USA

BACKGROUND

Developing monoclonal antibodies that broadly neutralize HIV-1 (bnMAbs) through passive transfer is a key goal in the prevention and treatment of HIV-1 infection (1,2,3). N6LS is a bnMAb that was isolated from a patient who was HIV infected for 21 years and was not on antiretroviral treatment (4). N6LS targets the CD4-binding site (CD4bs) of the HIV-1 envelope glycoprotein and is a member of the VRC01 class of CD4bs antibodies (5). N6LS was produced as an IgG1 with two amino acid substitutions in the Fc region to create an LS mutation that enhances half-life by increasing binding affinity to the neonatal Fc receptor (6). VRC01LS was the first bnMAb with this enhanced durability to be tested in a Phase 1 trial (7). VRC07-523LS, the first bnMAb engineered for increased breadth and potency, has also proven safe in healthy adults (8).

N6LS is unique in that it mediates broad and potent neutralization of 98% of HIV-1 isolates in a comprehensive panel including Clade C and pseudoviruses that are resistant to VRC01 (4). N6LS achieves this enhanced neutralization in two ways: It is insensitive to mutations in the variable gp120 V5 loop and binds at an angle that avoids steric clashes between the light chain and the highly glycosylated V5 region of Env, which are major mechanisms of resistance for other bnMAbs in this class (4). The result is a bnMAb with the potential to neutralize a wide range of HIV-1 strains at a lower concentration than other CD4bs antibodies.

This phase 1, first-in-human, study aimed to assess the safety, tolerability, and pharmacokinetics of N6LS in healthy adults.

METHODS AND SUBJECTS

- We conducted a first-in-human dose-escalation open-label phase 1 clinical trial of N6LS in healthy HIV-1 negative adults to determine its safety, tolerability, and pharmacokinetic (PK) profile.
- 23 participants enrolled between June 18, 2018 and February 12, 2019.
- Eligible volunteers were healthy adults, between 18 and 50 years of age.
- There were 9 (39%) males and 14 (61%) females.
- Three groups received a single intravenous (IV) dose of 5, 20, or 40 mg/kg, and one group received a single subcutaneous (SC) dose of 5 mg/kg. Two multi-dose groups received three doses of either 5 mg/kg SC or 20 mg/kg IV at 12-week intervals.
- 22 participants received all N6LS administrations for a total of 42 product administrations. One participant withdrew after enrolling, but before receiving product. All other participants completed every study visit.

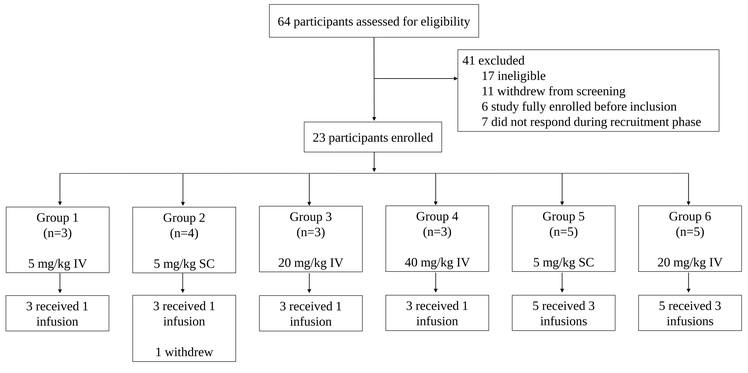

Figure 1. CONSORT diagram of N6LS clinical trial

RESULTS: Safety and Reactogenicity

- N6LS was safe and well tolerated at all doses and routes.
- All reported reactogenicity was mild to moderate in severity, with the most common being mild pain/tenderness at the injection site in SC groups (n=6, 75%).
- IV infusions were administered over a range of 15-45 minutes with an average infusion time of 26 minutes.
- SC infusions were administered via slow push.
- No infusion reactions occurred.
- Six adverse event (AEs) were assessed as related to N6LS administration: diarrhea ranging from grade 1-grade 3 occurring from 1 to 6 days after administration (n=3), grade 2 injection site reaction 7 days after product administration (n=1), grade 2 neutropenia 23 days after product administration (n=1), and asymptomatic grade 1 ALT elevation 3 days after administration (n=1). All AEs self resolved without sequalae.

RESULTS: Pharmacokinetics

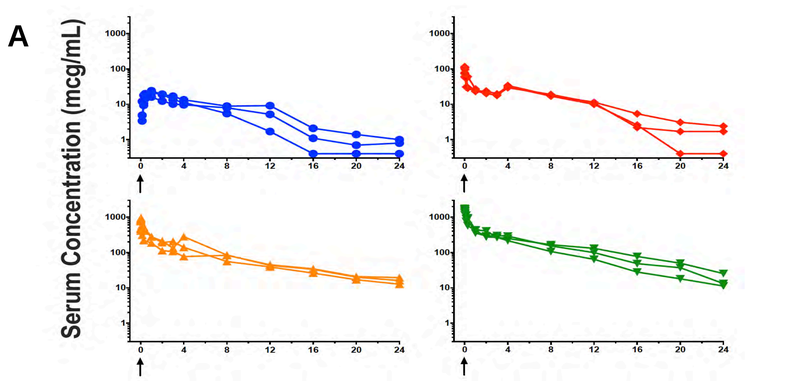

Figure 2. N6LS serum concentrations. (A) Serum concentrations (mcg/mL) by individual participants, (B) group geometric mean serum concentrations (mcg/mL) with error bars indicating the SD for 24 weeks after a single administration of N6LS. The upward pointing arrows indicate the time at which a dose of N6LS was administered. SC=subcutaneous. IV=intravenous.

- Overall compartmental half-life ($t_{1/2\beta}$) of N6LS is currently estimated to be 44±6 days for IV administrations and 40±4 days for SC administrations
- No evidence of anti-drug antibody

Group and Dose	Maximum serum conc. C_{MAX} [mcg/mL]	T_{MAX} [days]	4 week serum conc. C_{28D} [mcg/mL]	12 week serum conc. C_{84D} [mcg/mL]	AUC[a] [mcg*d/mL]	Clearance CL [mL/day][b]	Serum half-life $t_{1/2\beta}$ [days]
Mean (SD)							
5 mg/kg SC (n=8)	27 (9.8)	6.4 (3.6)	15 (5.8)	6.3 (2.7)	1,101 (386)	338 (81)	40 (4.0)
5 mg/kg IV (n=3)	101 (23)	0.04 (0.02)	32 (2.3)	11 (0.8)	1,874 (125)	178 (44)	43 (1.5)
20 mg/kg IV (n=8)	601 (215)	0.1 (0.07)	95 (22)	38 (7.5)	8,805 (2,813)	143 (20)	46 (6.8)
40 mg/kg IV (n=3)	1,717 (50)	0.1 (0.07)	254 (38)	99 (34)	20,659 (2,990)	104 (21)	38 (5.3)

Table 1. N6LS pharmacokinetic parameters by group after administration of N6LS
IV= intravenous, SC= subcutaneous
PK parameters shown for all participants who received at least one administration of N6LS and represent the first dose only PK except for $t_{1/2\beta}$ and CL (calculated from all doses).
[a] $AUC_{0\text{-}84D}$ shown for all dose groups.
[b] Value following SC administration represents CL/F.

RESULTS: Pharmacokinetics

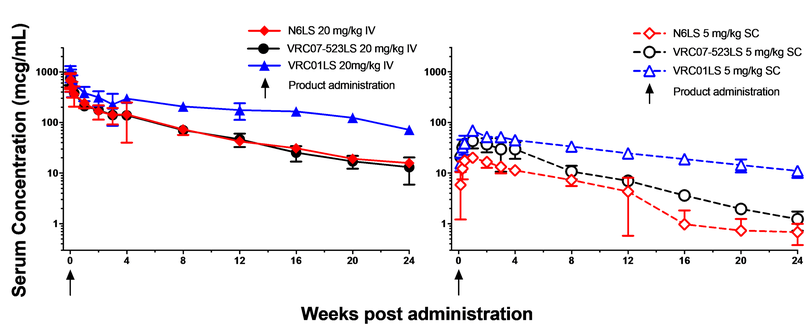

Figure 3. Comparison of participant serum concentrations (mcg/mL) following a single administration of N6LS, VRC07-523LS, or VRC01LS. Group geometric mean serum concentrations (mcg/mL) with error bars indicating the standard deviation for up to 24 weeks after receipt of either a single 20 mg/kg IV (solid lines) or 5 mg/kg SC (dotted lines) dose of either N6LS, VRC07-523LS, or VRC01LS. Upward pointing arrows indicate antibody administration. Each group includes 3 participants.

CONCLUSIONS

- N6LS was safe and well tolerated via both IV and SC routes in 22 participants in this Phase 1 Trial.
- Local and systemic reactogenicity was mild to moderate when reported. No serious adverse events, dose-limiting toxicities, or infusion reactions were observed.
- N6LS demonstrated equivalent to enhanced half-life and neutralization in sera when compared to other CD4bs bnMAbs (analysis ongoing).
- Additional assessment of N6LS in combination with Halozyme's rHuPH20 to allow for higher dose SC administration will begin enrolling this Spring.
- The favorable durability and breadth of N6LS make this antibody a leading candidate for inclusion in HIV-1 prevention and therapeutic strategies.
- N6LS has been licensed for advanced development by GSK/ViiV.

REFERENCES

1. Pegu A, Hessell AJ, Mascola JR, Haigwood NL. Use of broadly neutralizing antibodies for HIV-1 prevention. Immunol Rev. 2017;275(1):296-312.
2. McCoy LE, Burton DR. Identification and specificity of broadly neutralizing antibodies against HIV. Immunol Rev. 2017;275(1):11-20.
3. Caskey M, Klein F, Nussenzweig MC. Broadly Neutralizing Antibodies for HIV-1 Prevention or Immunotherapy. N Engl J Med. 2016;375(21):2019-21.
4. Huang J, Kang BH, Ishida E, Zhou T, Griesman T, Sheng Z, et al. Identification of a CD4-Binding-Site Antibody to HIV that Evolved Near-Pan Neutralization Breadth. Immunity. 2016;45(5):1108-21.
5. Ledgerwood JE, Coates EE, Yamshchikov G, Saunders JG, Holman L, Enama ME, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. Clin Exp Immunol. 2015;182(3):289-301.
6. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, et al. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. Nature. 2014;514(7524):642-5.
7. Gaudinski MR, Coates EE, Houser KV, Chen GL, Yamshchikov G, Saunders JG, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: A Phase 1 open-label clinical trial in healthy adults. PLoS Med. 2018;15(1):e1002493.
8. Gaudinski MR, Houser KV, Doria-Rose NA, Chen GL, Rothwell RSS, Berkowitz N, et al. Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial. Lancet HIV. 2019;6(10):e667-e79.