N6LS WITH RHUPH20 ENABLES SAFE HIGH DOSE MONOCLONAL ANTIBODY SUBCUTANEOUS DELIVERY

499

Richard L Wu[1], Katherine V Houser[1], Myra Happe[1], Martin R Gaudinski[1], Seemal F Awan[1], Alicia T Widge[1], Lasonji A Holman[1], Jamie Saunders[1], Christian Buettner[1], Bob C Lin[1], Mike Castro[1], Edmund V Capparelli[2], Robert A Seder[1], Richard A Koup[1], Lesia K Dropulic[1] and the VRC 609 Study Team

[1]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA
[2]School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, San Diego, CA, USA

Background

- Passive immunization with a broadly neutralizing monoclonal antibody (bnMAb) is a potential strategy for the prevention and treatment of HIV-1 infection.
- N6 is a human bnMAb that was derived from a patient who had HIV infection for 21 years without antiretroviral treatment. An LS mutation, M428L/N434S, was included in the C-terminus of the heavy chain constant region to extend serum half-life.
- N6LS is a member of the VRC01 class of antibodies that targets the CD4-binding site of the HIV-1envelope glycoprotein. Its neutralizing abilities are broader and more potent than VRC01, neutralizing up to 98% of viral strains on a 181 pseudovirus panel.

Methods

- In this first-in-human phase 1 clinical trial (NCT03538626), we assessed the safety and pharmacokinetics (PK) of N6LS administered to healthy adults 18-50 years of age either by intravenous (IV) or subcutaneous (SC) routes.
- Additional participants received SC administrations with recombinant human hyaluronidase PH20 (rHuPH20). Hyaluronidase acts by degrading hyaluronic acid in connective tissue, allowing for rapid high dose/volume subcutaneous drug delivery.

Trial Schema

Group	Subjects	Study Products		Dosing Schedule		
		N6LS Dose & Route	rHuPH20 Dose	Day 0	Week 12	Week 24
1	3	5 mg/kg IV	-	X		
2	**4***	**5 mg/kg SC**	**-**	**X**		
3	3	20 mg/kg IV	-	X		
4	3	40 mg/kg IV	-	X		
5	5	5 mg/kg SC	-	X	X	X
6	5	20 mg/kg IV	-	X	X	X
7	**5**	**5 mg/kg SC**	**2000 U/mL**	**X**		
8	**5**	**20 mg/kg SC**	**2000 U/mL**	**X**		
Total	33					

- N6LS was previously demonstrated to be safe and well tolerated when administered by IV or SC routes (5, 20, or 40 mg/kg IV or 5 mg/kg SC) to 22 participants with a serum half-life of over 40 days.
- Ten additional participants were enrolled and received N6LS at 5 or 20 mg/kg SC co-administered with 2000 U/mL of rHuPH20.

Safety Results

- Infusion site erythema was reported in all 10 participants who received N6LS with rHuPH20.
- 5 mg/kg SC + rHuPH20 erythema severity: 1 mild, 3 moderate, and 1 severe.

  20 mg/kg SC + rHuPH20 erythema severity: 1 moderate and 4 severe.
- Participants tolerated the post-infusion period well, without concomitant systemic reactions or complications.
- The erythema was self-limiting with all cases resolving between 1-30 days post product administration.
- Solicited systemic reactogenicity was mild.
- No serious adverse events, dose-limiting toxicities, or infusion reactions occurred.

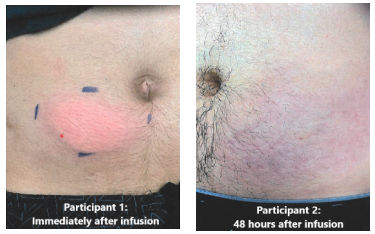

Figure 1. Infusion site erythema. Typical observations following SC administration of N6LS with rHuPH20 immediately after infusion (left) and 48 hours after infusion (right).

Administration of **N6LS** with **rHuPH20** allows for the *safe subcutaneous* delivery of *higher doses* and larger volumes of monoclonal antibodies for potential prophylactic and therapeutic self-administration of bnMAbs.

Pharmacokinetics Results

- PK following N6LS 5 mg/kg SC administration was similar with and without rHuPH20. Bioavailability of N6LS following SC administration was 50-65%.
- Estimated serum half-life ($t_{1/2B}$) for the SC route of N6LS alone is 36-46 days, with rHuPH20 is 42-57 days.

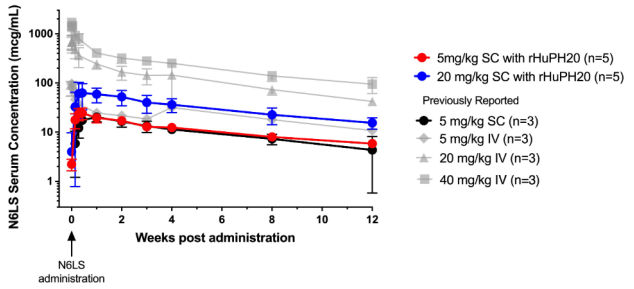

Figure 2. Serum concentrations of N6LS. Geometric mean serum concentrations with standard deviation (SD) indicated by bars after a single administration of N6LS with or without rHuPH20 on Day 0.

N6LS dose and route	rHuPH20 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]	Serum half-life $t_{1/2\beta}$ [days]
5 mg/kg IV (n=3)	-	101 (23)	0·04 (0·02)	32 (2.3)	11 (0.8)	1,876 (123)	44 (1.6)
5 mg/kg SC (n=8)	-	**27 (9.8)**	**6.4 (3.6)**	**15 (5.8)**	**6.3 (2.7)**	**1,101 (386)**	**42 (4.0)**
20 mg/kg IV (n=8)	-	601 (215)	0.1 (0·07)	95 (22)	38 (7.5)	8,803 (2,815)	45 (6.9)
40 mg/kg IV (n=3)	-	1,717 (50)	0·1 (0·07)	254 (38)	99 (34)	20,644 (2,996)	38 (5.2)
5 mg/kg SC (n=5)	**2000 U/mL**	**26 (5.9)**	**3.7 (1.8)**	**13 (2.3)**	**5.9 (0.7)**	**991 (118)**	**45 (2.8)**
20 mg/kg SC (n=5)	**2000 U/mL**	**83 (38)**	**5.6 (5.2)**	**38 (11)**	**16 (4.0)**	**2,989 (949)**	**50 (7.4)**

Table 1. PK parameters of N6LS. PK parameters (group means and SD) for all subjects who received at least one administration of N6LS and represent the first dose only except for $t_{1/2b}$ and CL (calculated from all doses).
[a] $AUC_{0\text{-}84D}$ shown for all dose groups.

Neutralization and ADA Results

- N6LS demonstrated broad and potent neutralization against multiple HIV-1 clades following administration (clades A, B, C, D, and AE evaluated in the trial to date, with additional analysis ongoing).
- There was no evidence of anti-drug antibody (ADA) development to N6LS observed following administration in any dose group, regardless of rHuPH20.

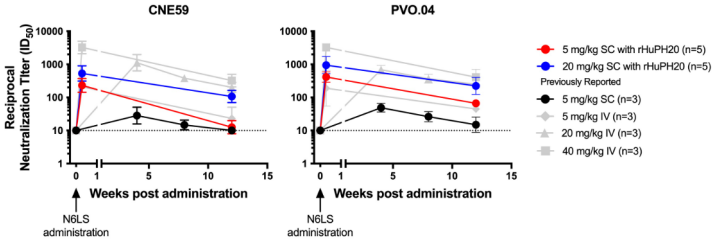

Figure 3. The addition of rHuPH20 does not inhibit the potent and broad neutralization activity of N6LS following administration. Geometric mean reciprocal neutralizing titers (ID50) with standard deviation (SD) are shown for participants who received a single SC or IV administration of N6LS alone (n=3) or with rHuPH20 (n=5). CNE59 (clade AE) and PVO.04 (clade B) pseudoviruses are shown here as examples. Dotted line indicated limit of detection for the assay.

Conclusions

- N6LS was safe and well tolerated when administered with or without rHuPH20 in this phase 1 trial.
- The addition of rHuPH20 did not appear to impact the pharmacokinetics or the broad and potent neutralizing activity of N6LS.
- Given its broad and potent neutralization of circulating HIV-1 clades, N6LS remains a promising candidate for HIV-1 prevention and therapy.
- SC delivery of biotherapeutics is a valuable alternative to IV administration that can result in reduced drug delivery-related healthcare costs and resource use. This proof-of-concept trial indicates that higher doses and volumes of N6LS with rHuPH20 can be safely delivered subcutaneously, which opens new potential avenues for prophylactic and therapeutic self-administration of bnMAbs.

Acknowledgements and VRC 609 Study Team

The VRC 609 Study Team: Joseph Casazza, John Misasi, Ingelise J Gordon, Cynthia Hendel, Karen Parker, Shinyi Telscher, Ro Shauna S Rothwell, Nina Berkowitz, Abidemi Ola, Pamela Costner, Jennifer Cunningham, Floreliz Mendoza, Laura Novik, Xiaolin Wang, William Whalen, Anita Arthur, Allison Beck, Aba Eshun, Pernell Williams, Preeti Apte, Catina Evans, Renunda Dyer, Justine Jones, Lashawn Requilman, Jumoke Gbadebo, Olympia Hotobah-During, Katherine Brooks, Eugenia Burch, Maria C Burgos Florez, Thuy Nguyen, Iris Pittman, Somia Hickman, Jason Sands, Kevin Carlton, Jason G Gall, Olga Vasilenko, Martha Nason, Sana Waheed, Galina Yamshchikov, Olga Trofymenko, Ellie Seo, Sarah Plummer, Julie E Ledgerwood, John R Mascola, and Barney S Graham.

We would also like to acknowledge the trial participants and Steve Knowles at Halozyme Therapeutics.