EXTENDED SAFETY AND PK OF ANTI-HIV MONOCLONAL AB VRC07-523LS IN HIV EXPOSED INFANTS

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BACKGROUND

Vertical HIV transmission continues to occur due to barriers to antiretroviral therapy (ART). Prevention of infection might be improved with a potent, broadly neutralizing, monoclonal antibody (bNAb) administered to exposed infants. VRC07-523LS is 5-fold more potent and has a prolonged $T_{1/2}$ compared to VRC01 and may provide protective levels over the duration of breastfeeding. *This study was designed to determine safety and pharmacokinetic properties of VRC07-523LS in HIV-exposed infants.*

METHODS

- Open label study of VRC07-523LS administered to HIV-exposed infants at increased risk of HIV infection
- Formula-fed infants receive 80 mg subcutaneous (SC) within 72 hrs of birth (Cohort 1) and breast-fed infants receive 80mg SC within 5d of birth and 100 mg SC at week 12 (Cohort 2), if still breastfeeding
- Infants and their mothers also receive ART to prevent HIV transmission
- Infant safety assessments and VRC07-523LS levels are collected out to 24 weeks
- The target week 12 (C_{12wk}) level is 10 mcg/mL: the level needed to neutralize >90% of tier II viruses (IC_{80}) in a multiclade panel

TABLE 1. Characteristics of infants enrolled. Age and weight are reported as mean and standard deviation.

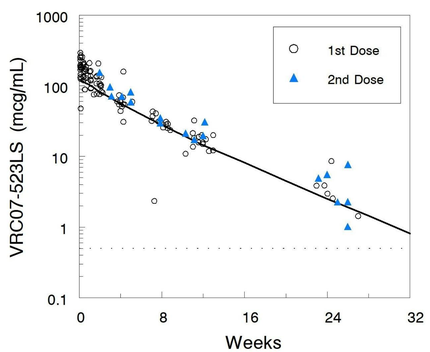
		Single Dose	Multi Dose
		(N=11)	(N=11)
Male gender		5 (45%)	8 (73%)
Race	Black	7 (64%)	11 (100%)
	Hispanic	2 (18%)	0
	Other	2 (18%)	0
Age (days) at immunization		1.5 (±0.7)	3.4 (±1.5)
Weight birth (g)		2830 (±272)	3228 (±571)
Weight week 12 (g)			5461 (±1601)

SC VRC07-523LS is *safe and well-tolerated* when administered to neonates. VRC07-523LS, with its enhanced potency, rapid absorption, and slow elimination, can quickly achieve and maintain plasma levels >10 mcg/mL with dosing every 3 months.

RESULTS

- All infants enrolled in Cohort 1 (formula fed) were at sites in the USA while all breastfed infants (Cohort 2) were enrolled at two African sites (Harare Family Care Clinical Research site, Zimbabwe and Pediatric Perinatal HIV Clinical Research Site, S. Africa).
- All infants and their mothers received standard-of-care ART to prevent vertical transmission of HIV.
- The 80mg dose resulted in an average dose of 26 mg/kg (range 18-35 mg/kg).
- Three infants in Cohort 2 did not receive a week 12 dose, two due to cessation of breastfeeding.
- All ≥Grade 3 events within 30 days of VRC07-523LS occurred after dose 1: 4 infants in Cohort 1 (vomiting [N=2], neutropenia, parainfluenza sepsis); and 1 infant in Cohort 2 (sepsis), none related to study treatment.
- C_{max} and C_{12WK} levels were lower than adults, suggesting infant SC bioavailability <1.
- Growth contributed to the fall in VRC07-523LS concentration, but levels remained over the target of 10 mcg/mL at week 12 in all participants.
- No children became HIV-infected.

Figure. VRC07-523LS plasma concentration post dose



First dose open circles, second dose triangles; prediction line is after 1st dose and very similar after dose 2.

TABLE 2. PK measures

PK parameters	
Cmax	203±48 mcg/mL
Tmax	1.8±1.6 d
C12wk	18.39±7.15 mcg/mL
C24wk (2 dose)	19.00±9.06 mcg/mL
T1/2	34 d
Dose 2/dose 1 ratio 4 weeks*	1.27 (±0.43)

*Dose 2 to dose 1 ratio compares level 4 weeks after each dose as a measure of product accumulation after dose 2.

TABLE 3. Number of infants with local/systemic reactions reported after injection.

	Reaction	Grade*		Percent Resolved ≤ 24 hours
		1	2	
Cohort 1	Erythema	1	0	0
N=11	Pain/tenderness	1	0	100
Cohort 2	Erythema	3	0	100
Dose 1	Induration	2	3	80
N=11	Edema	4	0	100
	Pain/tenderness	1	0	100
	Sleep changes	3	0	100
	Irritability	1	0	100
Cohort 2	Erythema	3	1	100
Dose 2	Induration	2	1	100
N=8	Edema	4	0	100
	Pain/tenderness	2	0	50
	Irritability	1	0	0

* All local and systemic reactions were <Grade 3.

CONCLUSIONS

- Local reactions after SC injection were common and usually very mild with rapid resolution.
- Grade 3 events occurred after dose 1 and were considered unrelated to study treatment.
- A VRC07-523LS dose of 80 mg results in favorable Week 12 concentrations, without significant accumulation.
- Our date support the need for further study to optimize dosing strategy.

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