PHASE 1 TRIAL OF SUBCUTANEOUSLY ADMINISTERED VRC07-523LS AND PGT121

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CROI Conference on Retroviruses and Opportunistic Infections

BACKGROUND

- Effective, long-acting HIV prevention approaches are needed, especially for young women in Africa.
- We evaluated the safety and pharmacokinetics of monoclonal antibodies VRC07-523LS and PGT121.
- Study products were administered subcutaneously alone and in combination, as passive immunisation to young women in South Africa.

METHODS

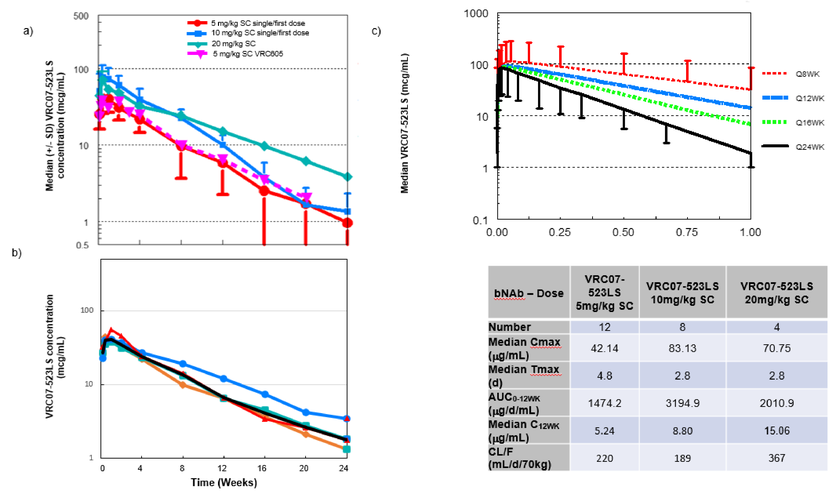
- 45 HIV-negative participants aged 18-40 years were randomised into 9 groups of 5 participants.
- In each group, 4 women were randomly assigned to the intervention and 1 to placebo.
- VRC07-523LS was administered at a dose of 5,10 or 20mg/kg once or at a repeat dose of 5 or 10 mg/kg at 12 or 24 weeks.
- PGT121 was administered at a dose of 3 and 10mg/kg once or at a repeat dose of 3 mg/kg at 12 weeks.
- VRC07-523LS at 5mg/kg and PGT121 at 3mg/kg were also administered in combination as two separate injections.
- Pharmacokinetic modelling was conducted to predict steady-state concentrations for 12- and 24-weekly dosing intervals.

RESULTS

Safety and PK Summary

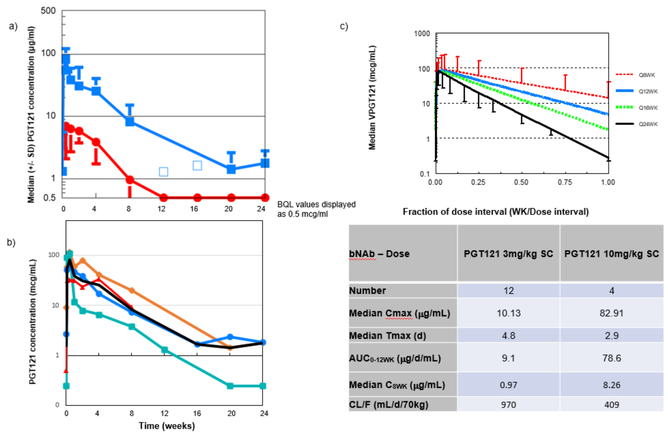
- The most common reactogenicity events were injection site tenderness and headaches.
- 9 related adverse events, including proteinuria, elevated alanine aminotransferase and aspartate aminotransferase, were mild and transient.
- Median VRC07-523LS concentrations following 20mg/kg doses were 9.65µg/ml and 3.86µg/ml at 16 and 24 weeks.
- The median week 8 concentration following the 10mg/kg PGT121 dose was 8.26µg/ml.
- Modelling of PGT121 at 20mg/kg showed median concentrations of 1.37µg/ml and 0.22µg/ml at 16 and 24 weeks.
- Half-lives of VRC07-523LS and PGT121 were 29 and 20 days.
- Both antibodies retained neutralizing activity post administration and no anti-drug antibodies were detected.

Subcutaneous administration of VRC07-523LS and PGT121 individually and in combination is safe and well tolerated. PK analysis shows that VRC07-523LS can be administered at 16 to 24-week dosing intervals while shorter intervals are appropriate for PGT121.



bNAb – Dose	VRC07-523LS 5mg/kg SC	VRC07-523LS 10mg/kg SC	VRC07-523LS 20mg/kg SC
Number	12	8	4
Median Cmax (µg/mL)	42.14	83.13	70.75
Median Tmax (d)	4.8	2.8	2.8
$AUC_{0\text{-}12WK}$ (µg/d/mL)	1474.2	3194.9	2010.9
Median C_{12WK} (µg/mL)	5.24	8.80	15.06
CL/F (mL/d/70kg)	220	189	367

Figure 1:
a) Observed VRC07-523LS median concentrations following 5, 10 and 20mg/kg
b) Observed VRC07-523LS concentrations following 20mg/kg dosing in Group 9, each coloured line represents concentrations for each participant and the black line represents the median concentration.
c) VRC07-523LS pharmacokinetic simulations at 20mg/kg showing median antibody concentrations at different dose intervals.
Table insert shows PK parameters following subcutaneous administrations of VRC07-523LS at 5,10 and 20mg/kg.



bNAb – Dose	PGT121 3mg/kg SC	PGT121 10mg/kg SC
Number	12	4
Median Cmax (µg/mL)	10.13	82.91
Median Tmax (d)	4.8	2.9
$AUC_{0\text{-}12WK}$ (µg/d/mL)	9.1	78.6
Median C_{8WK} (µg/mL)	0.97	8.26
CL/F (mL/d/70kg)	970	409

Figure 2:
a) Observed PGT121 median concentrations following 3 and 10mg/kg.
b) Observed PGT121 concentrations following 10mg/kg dosing in Group 8, each coloured line represents concentrations for each participant and the black line represents the median concentration.
C) PGT121 pharmacokinetic simulations at 20mg/kg showing median antibody concentrations at different dose intervals.
Table insert shows pharmacokinetic parameters following 3 and 10mg/kg subcutaneous administrations of PGT121.

CONCLUSIONS

- Antibody levels suggest that subcutaneous administration of high dose VRC07-523LS is appropriate at 16 to 24-week dosing intervals while shorter intervals (<8 weeks) are appropriate for PGT121.
- Subcutaneous administration of VRC07-523LS in combination with optimized versions of PGT121 or other antibodies should be further assessed for HIV prevention.

Acknowledgements

We thank the study participants enrolled in the CAPRISA 012A trial and acknowledge the participation and support of many colleagues and staff on the CAPRISA 012A teams. This study was supported principally by the European and Developing Countries Clinical Trials Partnership (EDCTP Grant number: RIA2017S). Funding was also provided by the South African Medical Research Council with funds from the South African Department of Science and Innovation and the Department of National Health through its Special Initiative on HIV Prevention Technology. In-kind support with study product was provided by the International AIDS Vaccine Initiative and by the Vaccine Research Centre of the National Institute of Allergy and Infectious Diseases, National Institutes of Health. The contents of this poster are the responsibility of the authors and do not necessarily reflect the views of USAID or the US Government.