Optimization of Dose and Analytic Treatment Interruption for VRC07-523LS and PGT121.414.LS

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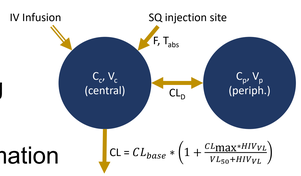
BACKGROUND

- A5388 is a placebo-controlled trial of VRC07-523LS and PGT121.414.LS administered at antiretroviral therapy initiation in adults with acute or early HIV.
- An analytical treatment interruption (ATI) is planned after bNab clearance to evaluate for a vaccinal-like effect.
- bNab levels above 1 mg/L may represent antiviral activity.
- Objective: To determine the optimal dosing and ATI timing to ensure <1 mg/L bNAb concentration in ≥90% of participants in an adaptive trial design.

METHODS

- Population PK analyses using maximum a posteriori estimation



- A two-compartmental PK analysis was applied to the first six participants (82 samples) in an interim sampling analysis at 24 and 36 weeks

Software & analysis **[Table 1] [Fig 1]**

- ADAPT 5 for analysis
- Bayesian priors initially included allometric scaling of animal data then remodeled when early first-in-human PK study data available[1]

Clinical trial simulation for dose determination

- 90% of participants at trough of 1 mg/L
- 1-2 dose, dynamic viral load to suppressed
- Correlations, covariates, and HIV RNA levels included in a stepwise manner **[Fig 2]**
- Covariates: baseline viral load and hematocrit for VRC07-523LS and none for PGT.121.414.LS
- Machine learning optimization

Time to target (1 mg/L)

- Dummy observations were added at 64 weeks to extrapolate out further than the target 48-week endpoint
- Participant-specific parameters were then used to identify each participant's own time to target

1. Gaudinski MR, et al. Lancet HIV 2019;6:e667-79.

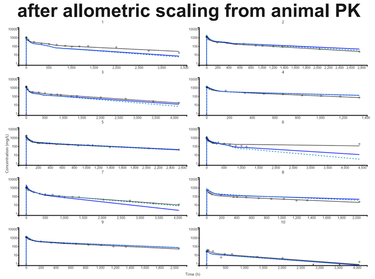
An adaptive trial design leveraged a dynamic PK approach to optimize dosage and determine time to ATI initiation of a bNAb combination by using clinical trial simulation based on real-world initial PK data.

MODELING

Table 1. Estimated Parameters – Excerpt from VRC07-523LS

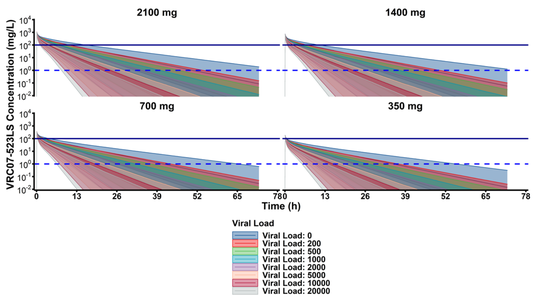
	Value	SE	RSE%
Parameters			
Bioavailability (F, %)	0.530	0.0840	15.9
Absorption Half-life (T_{abs}, d)	1.68	0.390	23.4
Clearance (CL, mL/d)	91.11	6.03	6.62
Central Volume (V_1, mL)	2202	130	5.92
BLHCT Effect on V_1 ($\beta V1BLHCT$, -)	1.76	0.520	29.3
Distributional Clearance (CL_D, mL/d)	586	98.51	16.8
Peripheral Volume (V_2, mL)	2791	261	9.36
BLHCT Effect on V_2 ($\beta V2BLHCT$, -)	2.01	0.830	41.3
Viral Load 50% CL_{max} (VL_{50}, copies/mL)	36307	0.190	4.13
Max Clearance (CL_{max}, -)	8.02	0.500	6.29
Shape parameter (γ, -)	0.510	0.0240	4.64
Standard Deviation of the Inter-individual Variability			
ω_F	0.7	0.29	41.8
ω_{Tabs}	0.45	0.19	41.5
ω_{CL}	0.33	0.044	13.6
ω_{V1}	0.28	0.045	16.0
ω_{CLD}	0.65	0.16	24.5
ω_{V2}	0.42	0.072	17.0
Correlations between Parameters			
V1~CL	0.32	0.2	62.3
Residual Error			
Proportional Error (a, -)	0.49	0.12	24.7
Additive Error (b, mg/L)	0.21	0.008	3.85

Fig 1. Model Diagnostics – Excerpt of observed (solid black) vs individual (dashed) and population (blue) predicted concentration-time profiles after allometric scaling from animal PK



*BLHCT = baseline hematocrit; RES% = Relative Standard Error; and ES = Standard Error.

Fig 2. Influence of Viral Load – Excerpt of modeled clearance with 90% CI, across a range of VL and for different doses for VRC07-523LS



RESULTS

Fig 3. Dose Simulation and Time to Target (1 mg/L) – Dose simulation prior to study initiation for VRC07-523LS and PGT121.414.LS. Median values with 90% CI in shaded areas for a range of doses. Horizontal dashed lines representing target concentrations and vertical dash line representing initial 48 week ATI.

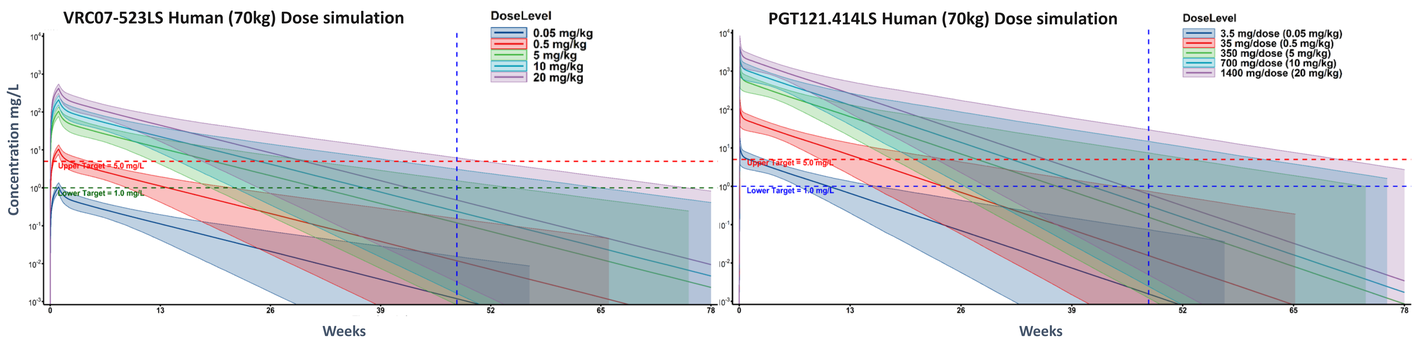


Fig 4. Interim Sampling Analysis - Performed on observed concentrations from 24 and 36 week accrued data for VRC07-523LS at 10mg/kg and PGT121.414.LS at 5 mg/kg, which were selecting from dose simulations. Individual concentration-time profiles for 6 participants. Horizontal dashed line indicating target concentration of 1 mg/L.

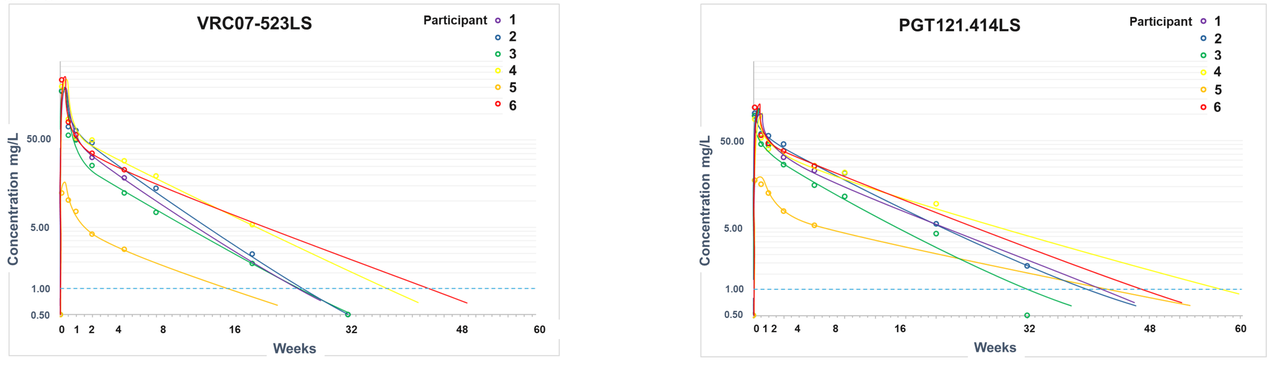


Table 2. Time to Target - Predicted time to target 1 mg/L from analyses at weeks 24 and 36 for individual participants

	VRC07-523LS		PGT.121.414.LS	
	Week 12	*Week 36*	*Week 12*	*Week 36*
1	23.4	25.6	40.4	42.8
2	30.3	29.6	44	44
3	28.6	29.0	33.6	35
4	36.6	41.6	56.4	61
5		20.5		43.5
6		47.1		48.5

FINDINGS

- Clinical trial simulations revealed VRC07-523LS at **10 mg/kg** and PGT121.414.LS at **5 mg/kg** resulted in 90% of predicted concentrations to reach 1 mg/L by week 48.**[Fig 3]**
- Interim PK analysis of the initial cohort confirmed that majority (5/6) would reach 1 mg/L by week 48, whereas 1 out of 6 would remain above until week 61 due to slower clearance of PGT121.414.LS. **[Table 2] [Fig 4]** The initiation of ATI was therefore adjusted from the originally planned week 48 to week 60.

CONCLUSION

- A dynamic PK approach was leveraged by an ***adaptive trial design*** for dosage optimization and determination of optimal time to ATI initiation of a bNAb combination by using clinical trial simulation with adjustments based on real-world initial PK data.

ADDITIONAL KEY INFORMATION

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- Acknowledgements: Elizabeth Woolley

PLAIN LANGUAGE SUMMARY

Modeling broadly neutralizing antibody drug levels was used to figure out their best dose and the best time to begin stopping anti-HIV treatment to evaluate the continued protective effects of combination broadly neutralizing antibodies. Clinical trials were computer simulated using real patient data collected early in the study.