A DOSE ESCALATION STUDY OF SAFETY & PK OF TMB-365 & TMB-380 IN PEOPLE WITH SUPPRESSED HIV

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BACKGROUND

- TMB-365, a second generation post-attachment broadly neutralizing antibody (bNAb), binds to the second domain of CD4 and is designed to display improved pharmacokinetics (PK), antiviral activity, and breadth of coverage when compared to ibalizumab.
- TMB-380 (aka VRC07-523LS) is a bNAb that binds to the CD4 binding site of HIV Env and has potent antiviral activity and favorable safety and PK profile.
- The long-acting combination is designed as a complete regimen with complementary mechanisms of action for HIV maintenance therapy given every 8 weeks.
- This study was to evaluate the safety and PK results of the TMB-365 and TMB-380 combination given as a single IV infusion in people with suppressed HIV.

METHODS

- TMB-365/TMB-380 combination was administered to people with suppressed HIV in an ongoing phase 1b/2a trial (NCT05275998).
  - **Dose:** 2400 mg (Group 1), 3200 mg (Group 2), or 4800mg (Group 3) of each bNAb; single dose IV; n=10/group; dose escalation was approved by an independent Data Monitoring Committee.
  - **Participants:** suppressed with continuous oral cART for at least 6 months, clinically stable, without a history of severe allergies, and had no history of virologic failure on previous treatment regimens.
- TMB-365 and TMB-380 serum concentrations were measured using validated enzyme-linked immunosorbent assays (ELISAs).
- CD4 receptor occupancy (RO) was measured using flow cytometry.
- Trough PK targets were ≥0.3 and 65 µg/ml for TMB-365 and TMB-380, respectively in approximately 80% of participants in any group.

RESULTS: PHARMACOKINETICS

- All 30 participants completed the study. The participants were comprised of 28 males (93%) and 2 females (7%), with a mean age of 44 years and a mean weight of 85 kg. One Group 3 participant was erroneously dosed with 1600 mg of each antibody and is excluded from PK analysis.
- Duration of concentrations above trough targets is increased with increased dose.
- In Group 3 participants at week 8, approximately 80% of participants met pre-defined trough targets for both TMB-365 and TMB-380. TMB-365 CD4 RO was above 80% (efficacy indicator) in 8/9 of participants.

The long-acting combination of bNAbs (TMB-365/TMB-380) is safe. PK data suggests an every 8-week infusion for HIV maintenance therapy is feasible.

Figure 1. TMB-365 Concentration Post Dose

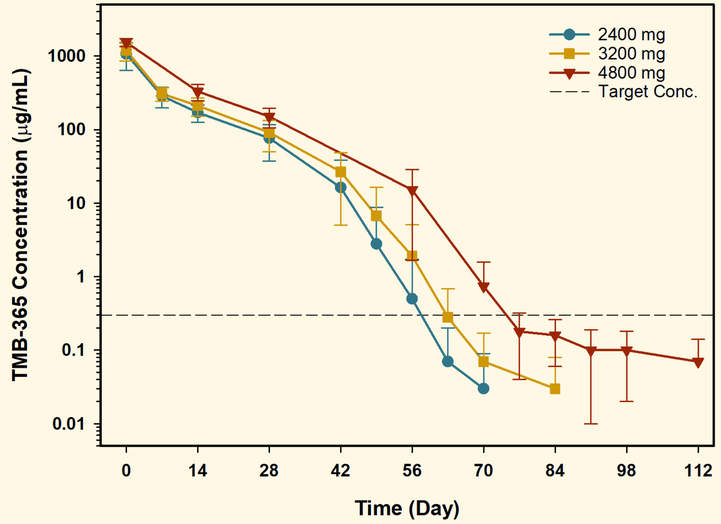

Table 1. TMB-365 PK Parameters

Dose (mg)	C_{max} (µg/mL)	C_{D56} (µg/mL)	AUC_{last} (µg*day/mL)	CL (mL/day)	$T_{1/2}$ (day)	
					Target saturated	Target partially saturated
2400	1067 ± 432	0.5 ± 1.2	7883 ± 2536	337 ± 117	10.0 ± 3.0	2.6 ± 0.5
3200	1192 ± 344	1.9 ± 3.2	9159 ± 2469	374 ± 105	10.5 ± 2.5	3.3 ± 0.9
4800	1536 ± 194	15.1 ± 13.5	15822 ± 2957	313 ± 58	9.3 ± 2.3	3.6 ± 0.5

C_{max}: maximum concentration; C_{D56}: Day 56 concentration; AUC_{last}: area under the curve from time 0 to the last measurement (2400, 3200 mg: Day 84; 4800 mg: Day 112); CL: clearance; $T_{1/2}$: half-life

Figure 2. TMB-380 Concentration Post Dose

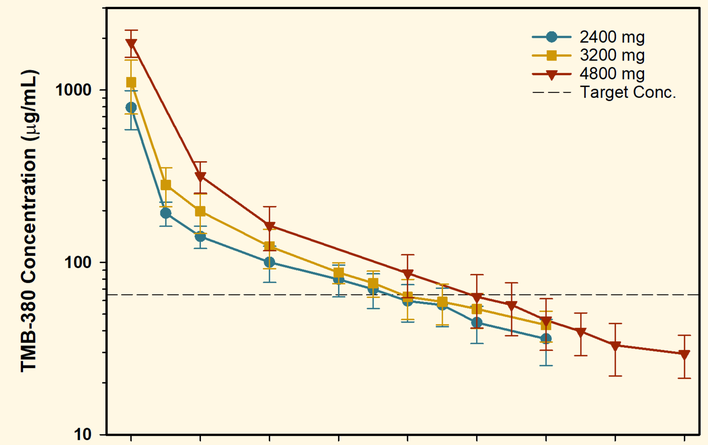

Table 2. TMB-380 PK Parameters

Dose (mg)	C_{max} (µg/mL)	C_{D56} (µg/mL)	AUC_{last} (µg*day/mL)	CL (mL/day)	$T_{1/2}$ (day)
2400	792 ± 202	59.6 ± 14.6	9145 ± 1527	224 ± 46	35 ± 5
3200	1110 ± 383	63.1 ± 16.5	12272 ± 2873	237 ± 59	32 ± 4
4800	1890 ± 340	86.4 ± 24.1	21798 ± 4146	214 ± 39	30 ± 2

C_{max}: maximum concentration; C_{D56}: Day 56 concentration; AUC_{last}: area under curve from time 0 to last measurement (2400, 3200 mg: Day84; 4800 mg: Day112); CL: clearance; $T_{1/2}$: half-life

RESULTS: SAFETY

- No SAEs, Grade 3 or 4 adverse events (AEs), or acute infusion events were observed.
- Total 32 cases of treatment emergent AEs were observed in 23 participants – 8 were mild and 24 were moderate.
- 5 AEs were probably or definitely related to the study drugs – 2 in low dose group and 3 in mid dose group. 2 participants in mid dose group experienced delayed onset of fatigue and chills interpreted as hypersensitivity. Other related AE were peripheral coldness, fatigue, and sneezing.

CONCLUSIONS

A single infusion of TMB-365 and TMB-380 in combination up to 4800 mg each is safe. Prolonged PK duration was observed for both TMB-365 and TMB-380 and results suggest that an every 8-week infusion is feasible and will be tested in a Phase 2a clinical study.