A 24-Week Phase II Maintenance Study of TMB-365/TMB-380 Q8W in People With Suppressed HIV-1 Infection

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Jacob P. Lalezari[1], Edwin DeJesus[2], Michael G. Sension[3], Gordon Crofoot[4], Moti Ramgopal[5], Mezgebe Berhe[6], Kuei-Ling Kuo[7], YingAn Lai[7], Chin-Ming Chang[7], Martin Markowitz[8]
[1]Quest Clinical Research, San Francisco, CA, USA, [2]Orlando Immunology Center, Orlando, FL, USA, [3]CAN Community Health, Fort Lauderdale, FL, USA, [4]Crofoot Research Center, Houston, TX, USA,
[5]Midway Immunology and Research Center, Fort Pierce, FL, USA, [6]North Texas Infectious Diseases Consultants, Dallas, TX, USA, [7]TaiMed Biologics Inc., Taipei City, Taiwan, [8]TaiMed Biologics Inc., Irvine, CA, USA

BACKGROUND

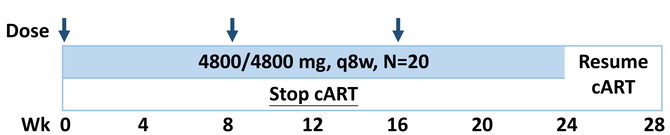
- TMB-365 is a second-generation post-attachment broadly neutralizing antibody (bNAb) of ibalizumab binds to the second domain of CD4. Previous clinical pharmacokinetics (PK), safety, and antiviral activity data show the potential for long-acting.
- TMB-380 (aka VRC07-523LS) is a bNAb that binds to the CD4 binding site of HIV Env and has potent antiviral activity and favorable safety and PK profile for long-acting.
- The combination of TMB-365/TMB-380 is designed as a long-acting complete regimen with complementary mechanisms of action for HIV maintenance therapy given every 8 weeks (q8w).
- This study was to evaluate the safety, efficacy, and PK 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 a phase 1b/2a trial (NCT05275998).
- The dose was determined by the results from the phase 1b part of the study[1].
- **Dose:** 4800 mg of each bNAb q8w; single IV infusion; n=20.
- **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.
- No susceptibility screen was conducted to either bNAb due to the high potency, broad breadth, and low risk of resistance based on preliminary data from precursor molecule studies.

	TMB-365[2]	TMB-380[3]
Geometric Mean IC_{50} (ug/mL)	0.014	0.055
Breadth %	100	97

- Participants switched to every 8-week TMB-365/TMB-380 treatment for 24 weeks (3 infusions), then restarted the oral cART at Week 24.
- TMB-365 and TMB-380 serum concentrations were measured using validated enzyme-linked immunosorbent assays (ELISAs).



[1] Lalezari et al. A Dose Escalation Study of Safety & PK of TMB-365 & TMB-380 in People With Suppressed HIV. CROI 2024; Abs 640
[2] Song et al. (2013). Strategic addition of an N-linked glycan to a monoclonal antibody improves its HIV-neutralizing activity. Nature Biotechnology 31(11):1047-52.
[3] Rudicell et al. (2014). Enhanced Potency of a Broadly Neutralizing HIV-1 Antibody In Vitro Improves Protection against Lentiviral Infection In Vivo. Journal of Virology 88(21):12669-82.

TMB-365/TMB-380, a long-acting combination of bNAbs, is a promising complete switch regimen for HIV **without the need to screen susceptibility**. A single infusion every 8 weeks is **safe** and can **maintain HIV suppression** with potential for wider application.

RESULTS - ENROLLMENT

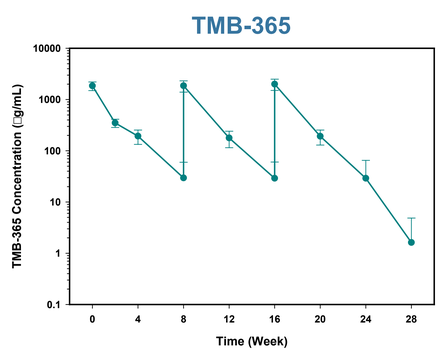
- 29 participants were screened. 21 were enrolled and dosed as least one infusion of TMB-365/TMB-380.
- 1 participant was requested to terminate their participation due to GI bleed between screen and the first infusion (not drug-related).
- 2 early discontinuations:
  - 1 due to Grade 2 generalized rash 32 days after the first infusion;
  - 1 withdrew consent after Grade 2 atypical rash 62 days after first infusion
- 18 participants completed the study; 1 without data at Week 24

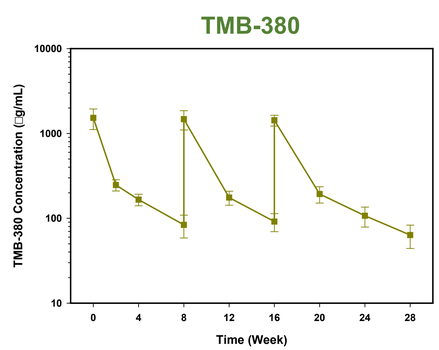
RESULTS – DEMOGRAPHIC

- Age range was 24 to 67 years; 1/21 were female; 10/21 were White (non-Hispanic); and median CD4 count was 706 cells/µl.

RESULTS - PHARMACOKINETICS

- The mean TMB-365 and TMB-380 concentrations at Week 24 are 29 and 107 µg/mL, respectively.





RESULTS - SAFETY

Events	# of participants (# of events)
SAE	0 (0)
Grade 3 or 4 AEs	0 (0)
Grade 1 or 2 AEs	14 (48)
Probably or definite related	8 (16)
Acute infusion reaction	0 (0)
TEAE leading to early discontinuation	1 (1)
TEAE leading to early discontinuation due to consent withdrawal	1 (1)

- 16 events deemed possibly or probably related to TMB-365/TMB380: rash (4), fatigue (4), headache (3), flushing (2), fever (1), chills (1), aches (1)
- Steady CD4 cell count throughout treatment period
- Low titer of anti-drug antibody (anti-TMB-365) were observed in 1 participant with no impact on PK and VL. Experienced Grade 1 AEs.

RESULTS - Efficacy

- No pre-defined virologic failures in 24-week treatment period
  - Definition: 2 consecutive HIV-1 RNA levels above 50 copies/mL

At Week 24	VL < 50 c/mL	VL ≥ 50 c/mL
# of participants (%), N=17*	16 (94%)	1 (6%)

*2 early discontinuations prior to Week 24; 1 no data at Week 24

- 1 participant had VL of 59 copies/mL at Week 24 prior to planned oral cART restart

CONCLUSIONS

- TMB-365/TMB-380 was safe and well-tolerated
  - No SAEs, Grade 3 or 4 AEs, acute infusion reactions
- TMB-365/TMB-380 maintained viral suppression throughout 24 weeks
  - No susceptibility screen needed
  - No confirmed virologic failures
- TMB-365/TMB-380 is a promising long-acting regimen for HIV maintenance therapy
- Without the need to screen susceptibility to either antibody, TMB-365/TMB-380 is a practical switch regimen with potential for wider application
- To further develop TMB-365/TMB-380 Q8W as a complete regimen in later phase studies

ADDITIONAL KEY INFORMATION

We convey our appreciation to all participants and their families.
We convey our appreciation to all participating investigators and their teams.
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