IV PUSH ADMINISTRATION OF IBALIZUMAB: PHARMACOKINETICS, SAFETY, AND EFFICACY

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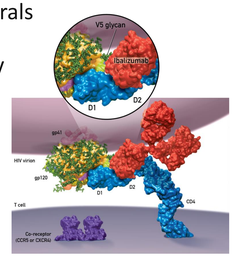
Edwin DeJesus[1], Gary Richmond[2], Mezgebe Berhe[3], Anthony Mills[4], Tanya Schreibman[5], Charlotte-Paige Rolle[1], Kuei-Ling Kuo[6], Mohammed Zogheib[7], Olivia G. Goss[7], R. Brandon Cash[8], YingAn Lai[6], Martin Markowitz[6], Pedro M. Mesquita[8]

[1]Orlando Immunology Center, Orlando, FL, United States, [2]Broward Health Medical Center, Fort Lauderdale, FL, United States, [3]North Texas Infectious Diseases Consultants, Dallas, TX, USA, [4]Men's Health Foundation, Los Angeles, CA, United States, [5]CAN Community Health, Sarasota, FL, [6]TaiMed Biologics Inc, Taipei City, Taiwan, [7]Syneos Health, Somerset, NJ, United States, [8]Theratechnologies, Inc., Montreal, Canada

Background

- Long-acting injectable antiretrovirals (LAIs) are becoming increasingly available for the treatment of HIV due to perceived reduction in pill burden, improved compliance through directly observed therapy, and patient preference.



- Ibalizumab (IBA) is a long-acting post-attachment inhibitor approved for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced (HTE) adults failing their current antiretroviral (ARV) regimen.[1]
- IBA is diluted in 250 mL of saline and administered via intravenous infusion (IVI) as a loading dose of 2000 mg over 30 minutes followed by 800 mg maintenance doses over 15 minutes every 2 weeks.[1]
- In TMB-302 we sought to evaluate the pharmacokinetics (PK), safety, and efficacy of administering IBA maintenance doses as undiluted IV push (IVP) or as intramuscular (IM) injections to improve convenience and offer patients more options. Here we present the IVP analysis.

OBJECTIVES

- **Primary: A)** Evaluate the safety of administering IBA maintenance doses as an undiluted intravenous push (IVP) over 30 seconds, compared to 15-minute IVI. **B)** Compare the area under the curve (AUC) and trough serum drug concentrations (C_{trough}) after IVP vs. IVI.
- **Secondary: A)** Assess efficacy of IVP IBA in people with HIV (PWH). **B)** Determine antidrug antibodies (ADA).

Methods

- In TMB-302, an open-label non-randomized phase 3 study, clinically stable PWH with viral load (VL) < 1000 c/mL while on IBA-containing ARV regimens for at least 3 months, and HIV-uninfected individuals (UI) were administered IBA as shown in Study Design.
- **Sentinel Group** participants (n=5 PWH) received IBA at progressively increasing concentrations over shortening intervals prior to IVP dosing. Following Data Monitoring Committee (DMC) review, **Core Group** (n=4 PWH and n=13 UI) participants were enrolled and administered IBA as shown.

Methods (cont'd)

- Blood samples were taken at various times pre- and post-administration to measure PK and viral load.
- Treatment-emergent adverse events (TEAEs) were recorded throughout, and the development of ADA was monitored.

STUDY DESIGN

Sentinel Group

800 mg 3.2 mg/mL 15 min	800 mg 3.2 mg/mL 15 min	800 mg 16 mg/mL 10 min	800 mg 50 mg/mL 5 min	800 mg 100 mg/mL 1 min	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 3.2mg/mL 15 min
Week: 0 (Baseline)	2	4	6	8	10	12	14

Core Group - PWH

800 mg 3.2mg/mL 15 min	800 mg 3.2mg/mL 15 min	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 3.2mg/mL 15 min	
Week: 0 (Baseline)	2	4	6	8	10	12	

Core Group - UI

2000 mg 8 mg/mL 30 min	800 mg 3.2mg/mL 15 min	800 mg 3.2mg/mL 15 min	800 mg 3.2mg/mL 15 min	800 mg 3.2mg/mL 15 min	800 mg 3.2mg/mL 15 min	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 150 mg/mL 30 sec	800 mg 3.2mg/mL 15 min	
Week: -8 (Pre-Steady-State)	-6	-4	-2	0 (Baseline)	2	4	6	8	10	12	

IV infusion IV bolus IV push

Results

- A total of 22 subjects were enrolled including 9 PWH.
- All PWH and 10 out of 13 UI completed the study.
- Reasons for treatment discontinuation included adverse events (AEs [mild nausea and tremors, and moderate headache, unrelated to study drug]), consent withdrawn, and noncompliance with study schedule in 1 UI each.

BASELINE CHARACTERISTICS

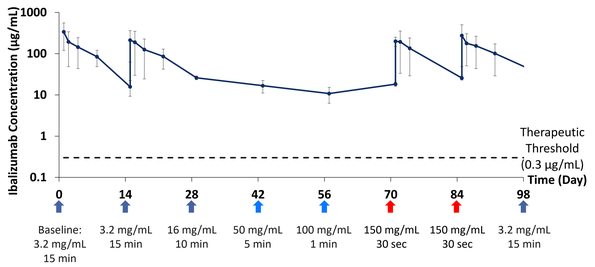
	Sentinel Group (N=5)	Core Group HIV-Infected (N=4)	Core Group HIV-Uninfected (N=13)	Total (N=22)
Sex, n (%)				
Male	5 (100.0%)	4 (100.0%)	9 (69.2%)	18 (81.8%)
Female	0	0	4 (30.8%)	4 (18.2%)
Ethnicity, n (%)				
Hispanic or Latino	0	2 (50.0%)	8 (61.5%)	10 (45.5%)
Neither Hispanic nor Latino	5 (100.0%)	2 (50.0%)	5 (38.5 %)	12 (54.5%)
Race, n (%)				
Black or African American	1 (20.0%)	0	0	1 (4.5%)
White	4 (80.0%)	4 (100.0%)	13 (100.0%)	21 (95.5%)
Age, years				
Mean (SD)	54.2 (5.72)	58.0 (6.38)	31.3 (6.76)	41.4 (13.88)
Median	58.0	56.0	30.0	39.0
Min, Max	47, 59	53, 67	19, 42	19, 67
Viral load, log_{10} copies/mL Mean (SD)	1.22 (0.319)	1.30 (0.245)	-	-
CD4 count, cells/mm³ Mean (SD)	440 (342)	307 (152)	956 (393)	-

Results (cont'd)

PHARMACOKINETICS

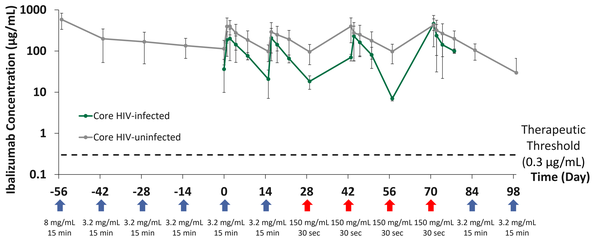
- Serum concentrations of IBA remained >5 µg/mL at all timepoints, which suggests that IVP administration is effective at maintaining drug concentrations above therapeutic levels (0.3 µg/mL).

Mean (±SD) Ibalizumab Serum Concentrations (Sentinel Group)*



*Two sets of Day 14 pre- and post-dose concentration data were determined to be apparently reversed and were excluded.

Mean (±SD) Ibalizumab Serum Concentrations (Core Group)



PK bridge between IVI and IVP was established:

- Proportion of subjects with average C_{trough} ≥0.3 µg/mL was 18/19 (94.7%) for both IVI and IVP.
- 90% CI of the AUC ratio of IVP to IVI was within the target value of 0.80-1.25 (0.9478-1.1226).

SAFETY

- Overall, 13 subjects (59.1%) reported TEAEs during the study, including 1 of 5 subjects (20.0%) in the Sentinel Group, 2 of 4 subjects (50.0%) in the HIV-Infected Core Group, and 10 of 13 subjects (76.9%) in the HIV-Uninfected Core Group.
- The most frequently reported TEAEs were nausea (2 mild AEs; 9.1%) and headache (1 mild; 1 moderate AE; 9.1%).
- There were no clinically significant differences in the occurrence of AEs during IVI or IVP. Importantly, infusion reactions and rashes were not observed when IBA was administered as IVP.
- No deaths or serious TEAEs were reported, and no subjects developed ADA.

Results (cont'd)

SUMMARY OF TEAEs

	Sentinel Group (N=5)	Core Group HIV-Infected (N=4)	Core Group HIV-Uninfected (N=13)	Total (N=22)
Number (%) of subjects with				
TEAEs	1 (20.0%)	2 (50.0%)	10 (76.9%)	13 (59.1%)
Serious TEAEs[a]	0	0	0	0
TEAEs with death outcome	0	0	0	0
TEAE leading to study drugs discontinuation	0	0	1 (7.7%)	1(4.5%)
Suspected adverse reaction[b]	0	1 (25.0%)	0	1 (4.5%)
Severe TEAE[c]	0	0	0	0
Class C TEAE[d]	0	0	0	0

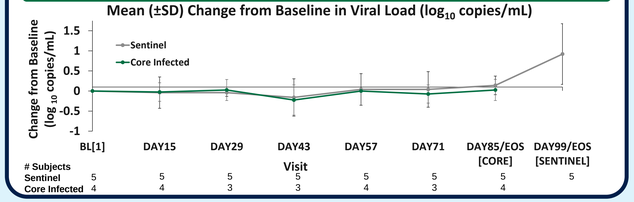
[a]Excluding Death; [b]Possibly related to study drug; [c]Severity / Grade 3 or 4 (severe or potentially life threatening); [d]Per the CDC classification system for HIV infection

EFFICACY

- Among PWH, there were no virologic failures. Mean (SD) VL (copies/mL) at baseline (BL) and end of study (EOS) were:
  - Sentinel Group: 21.6 (16.0) BL and 76,022 (169,928) EOS
  - Core Group: 21.3 (11.3) BL and 36 (46.2) EOS
- One Sentinel PWH experienced virologic rebound following the last IVP dose, which was linked to nonadherence to the oral ARV regimen
- Median VL at BL and EOS was <20 copies/mL for both groups

CHANGE FROM BASELINE IN VIRAL LOAD

Mean (±SD) Change from Baseline in Viral Load (log_{10} copies/mL)



Conclusions & Future Perspective

- Administration of IBA as an **undiluted IVP over 30 seconds was safe and well tolerated** in all participants and remained effective among PWH.
- **Bioequivalence between IVI and IVP administration** was demonstrated and supports IVP as a potential alternative for delivery of IBA.
- Reducing the time required for IBA administration may **improve patient acceptability** by increasing convenience.
- Assessment IM injection as an additional delivery option for HTE patients is ongoing in this study.

References:

1. Trogarzo®. Prescribing information. Theratechnologies Inc; 2021.