Primary Efficacy Endpoint and Safety Results of Ibalizumab in a Phase 3 Study of Heavily Treatment-Experienced Patients with Multi-Drug Resistant HIV-1 Infection

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Ibalizumab

- Humanized monoclonal antibody that primarily binds to second extracellular domain of CD4 receptor on T cells, away from binding site for MHC class II molecules

- Does not inhibit gp120 binding of HIV to CD4+ T cells

- Exerts its antiviral activity by blocking post-attachment conformational changes that are required for entry of virus into CD4+ cells

- Not immunogenic; not T cell depleting

Bruno and Jacobson, 2010, J Antimicrob Chemother
Ibalizumab – *In Vitro* Testing

- Broad spectrum anti-HIV activity
  - Active across clades
  - Active against CCR5, CXCR4 and dual/mixed tropic viruses

- No evidence of cross-resistance with existing ARTs
  - Synergistic with enfuvirtide
  - Additive or synergistic with all other classes of ARTs

- No drug-drug interactions with ARTs and/or other drugs
  - No significant liver or kidney metabolism
  - Metabolized by CD4 receptor internalization
Phase 2b: Antiretroviral Activity in Triple-Class Resistant Patients in Combination with OBR

Mean change from Baseline VL at Week 24

800 mg q2wk: -1.6 log10 HIV RNA copies/mL
2000 mg q4wk: -1.5 log10 HIV RNA copies/mL

NOTE: Designated Orphan Drug and awarded Breakthrough Designation by FDA
TMB-301: Study Design

Day 0: Control Period

Day 7: 2000 mg IV loading dose

Day 14: Add OBR

Day 21: 800 mg IV maintenance dose

800 mg IV q2 wks until week 23

Patients taking current failing therapy

Primary Endpoint
Proportion of patients achieving ≥ 0.5 log_{10} decrease in viral load

Secondary Endpoints
Safety/Tolerability
Viral Load CD4 count
CD4 receptor density/occupancy
TMB-301: Study design

Day 0-6 (Control period):
• Patients monitored on current failing therapy
  • Viral load determined at Day 0 and Day 7

Day 7-13 (Monotherapy period):
• Patients continued on current failing therapy
• Received 2000 mg IV dose of Ibalizumab on Day 7
  • Viral load determined at Day 14

Day 14- Week 25 (Maintenance period):
• OBR initiated on Day 14
• Ibalizumab dosed 800 mg IV on Day 21 and every 2 weeks thereafter
TMB-301: Key Inclusion criteria

- HIV-1 viral load > 1000 copies/mL
- History of at least 6 months on ART
- Documented resistance to at least 1 ARV from 3 classes
- Have sensitivity to at least 1 ARV with which to construct an OBR
- Receiving stable ART for at least 8 weeks before Screening
TMB-301: Key Exclusion criteria

• Active AIDS-defining illness
• Immunomodulatory therapy, systemic steroids, or systemic chemotherapy within 12 weeks before Enrollment
• Prior exposure to ibalizumab
• Any Grade 3 or 4 lab abnormality
TMB-301: Patient Baseline Characteristics

- N = 40
- 85% male; 45% non-white
- Mean duration of HIV infection 21 years
- Mean VL of $10^5$ copies/mL
  - 18% with VL $\geq 10^5$ copies/mL
- Mean CD4+ T cell count of 160 cells
  - 50% with <100 cells; 33% with <10 cells
- 28% treated with $\geq 10$ previous ARVs
- 43% used second investigational agent in OBR
TMB-301: Baseline Resistance Data

Phenotypic/Genotypic Resistance

- NRTI: 88%
- NNRTI: 88%
- PI: 85%
- INI: 58%

Major Resistance Mutations

- NRTI: 93%
- NNRTI: 85%
- PI: 83%
- INI: 61%

- 50% of patients had resistance to all drugs from at least 3 classes

Preliminary data pending verification of historical resistance testing
Primary Endpoint: VL Reduction at Day 14

Following 2000 mg loading dose of Ibalizumab (Day 7)

• Mean and median VL decrease of $1.1 \log_{10}$ ($p<0.0001$)
TMB-301: Safety (Day 0 - 14)

• No discontinuations

• No treatment-related SAEs

• Treatment-Emergent AEs include:
  • Dizziness 10%
  • Asthenia/Fatigue 5%
  • Nausea/Vomiting 5%
  • Rash 2.5%
Conclusion / Practice Improvement

• Long-acting ART, administered IV every 2 weeks

• Significant antiretroviral activity
  • 83% with $\geq 0.5 \log_{10} VL$ decrease after 7 days
  • Mean/median VL decrease of $1.1 \log_{10}$ after 7 days

• Excellent short-term safety profile

• Novel mechanism of action providing new treatment to patients with limited options
  • No drug-drug interactions
  • No known risk of cross resistance

• Future results to address longer term outcomes (up to Week 25)

• Expanded Access Program is open for enrollment
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Thank You
Entire TMB-301 Study Team and Patients