LONG-ACTING IBALIZUMAB IN PATIENTS WITH MULTI-DRUG RESISTANT HIV-1: A 24-WEEK STUDY

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Background

Ibalizumab (IBA) is a long-acting humanized immunoglobulin G4 monoclonal antibody that blocks HIV to enter the CD4+ T cells. Unlike other antiretroviral agents, IBA binds to a conformational extracellular domain of the CD4 receptor, away from Major Histocompatibility Complex II molecule (MHC II) binding sites. It prevents HIV virus from infecting CD4+ immune cells while preserving normal immunological function. IBA has been shown to have potent activity against a broad spectrum of primary clinical isolates with no evidence of cross-resistance with existing antiretroviral (ARV) agents or drug-drug interactions. IBA was tested in a Phase 3 registration study in patients with multi-drug resistant (MDR) HIV-1 infection (TMB-301). We previously reported significant viral load change from Baseline and a mean increase in CD4+ T cell count at Week 24 of treatment.

Methods

TMB-301 is a single arm, 24-week study of IBA plus optimized background regimen (OBR) in treatment-experienced patients infected with MDR HIV-1. Patients receiving their current failing ARV therapy, or no therapy, were monitored during a 7-day control period. Thereafter, a loading dose of 2,000 mg of intravenous (IV) IBA was the only ARV agent added to their regimen for 7 days. IBA was continued at doses of 800 mg every 2 weeks through 24 weeks on study treatment. The primary efficacy endpoint was the proportion of patients achieving a ≥0.5 log₁₀ decrease in HIV-1 RNA 7 days after initiating IBA therapy (Day 14 of study). OBR was initiated at Day 14. Secondary endpoints included proportion of patients with RNA HIV-1 levels <50 and <200 copies/mL and mean change from Baseline in viral load and CD4+ T cell count at Week 24 as well as an assessment of safety and tolerability.

Key Criteria

Inclusion
- HIV-1 viral load > 1000 copies/mL
- History of at least 6 months on ARV therapy
- 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 ARV therapy for at least 8 weeks before Screening

Exclusion
- Active AIDS-defining illness
- Immunomodulatory therapy, systemic steroids, or systemic chemotherapy within 12 weeks before Enrollment
- Prior exposure to IBA
- Any Grade 3 or 4 lab abnormality

Baseline Characteristics

- N = 40
- Mean age of 51 ± 11 years
- 85% male; 45% non-white
- Mean duration of HIV infection of 21 years
- Mean viral load of 100,287 copies/mL
- 18% with viral load ≥100,000 copies/mL
- Mean CD4+ T cell count was 150 cells/µL
- 17 patients with <50 cells/µL (12 patients with <10 cells/µL)
- 10 patients with 50-200 cells/µL
- 13 patients with >200 cells/µL
- 28% were previously treated with ≥10 ARV agents
- 43% required investigational agent (fostemsavir) in OBR

Efficacy at Week 24

- Mean viral load decrease of 1.6 log₁₀ from Baseline
- 55% and 48% of patients with a ≥1 and ≥2 log₁₀ reduction, respectively
- Undetectable viral load in 43% of patients; 50% with <200 copies/mL

Safety and Tolerability

- Treatment-emergent Adverse Reactions – Most are mild to moderate
- 17 SAEs reported for 9 patients
- One drug-related (IRIS) that lead to discontinuation
- 9 Discontinuations (8 in <50 CD4+ count at BL group; 1 in >200 group)
- 4 Deaths
  - Liver failure (CD4+ cell count at BL: 1)
  - Kaposi sarcoma (CD4+ cell count at BL: 2)
  - End-stage AIDS (CD4+ cell count at BL: 3)
  - Lymphoma (CD4+ cell count at BL: 44)
- 3 Consent withdrawals
- 2 Lost to follow-up
- No patients with anti-IBA antibodies

Conclusion

In MDR HIV patients with very limited treatment options due to resistance to approved ARV agents, bi-weekly IBA plus OBR maintained virologic efficacy and was well tolerated through Week 24.