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 epitope on the second 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 reductions 7 days after an initial dose of IBA when added to a failing ARV regimen. Here, we describe the sustained efficacy, safety and tolerability of IBA through 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 IV 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 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

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

Efficacy at Day 14

Following 2000 mg loading dose of IBA (Day 7):
• Mean and median VL decrease was 1.1 log10 (p<0.0001)

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

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.