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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

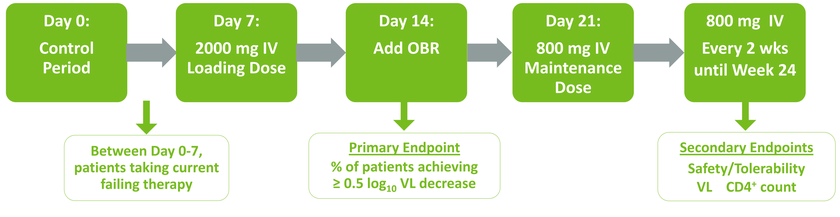
TMB-301 is a single arm, 24-week study of IBA plus optimized background regimen (OBR) in treatment-experienced patients infected with MDR HIV-1.

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 $\log_{10}$ 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.

Study Design



Key Criteria

Inclusion

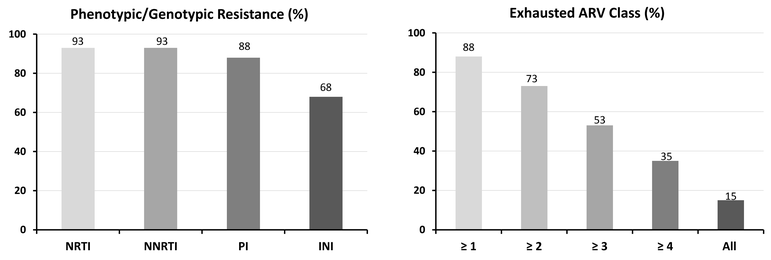
- HIV-1 viral load > 1000 copies/mL
- History of at least 6 months on ARV therapy
- Documented resistance to at least 1 ARV from 3 classes
- Have sensitivity to at least 1 ARV with which to construct an OBR
- Receiving stable ARV therapy for at least 8 weeks before Screening

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

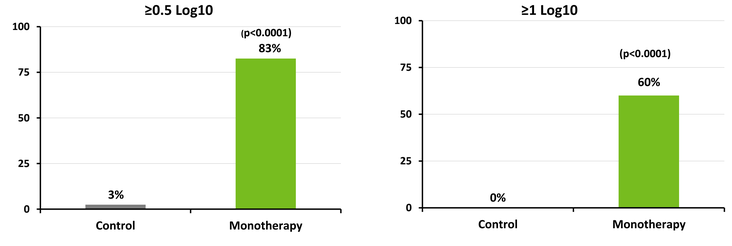
Baseline Characteristics

- 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 Day 14

Following 2000 mg loading dose of IBA (Day 7):



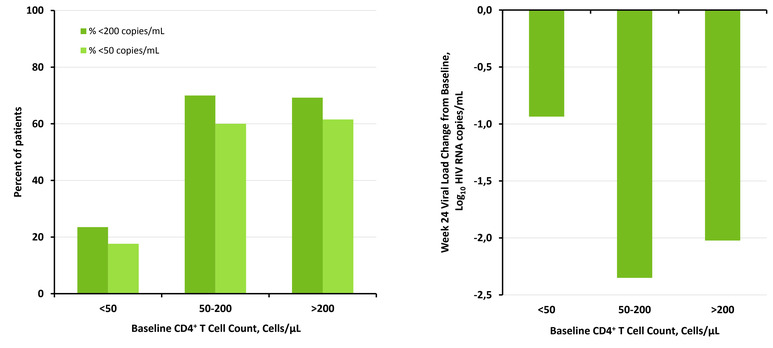
- Mean and median VL decrease was 1.1 $\log_{10}$ (p<0.0001)

CD4⁺ T Cell Counts at Week 24

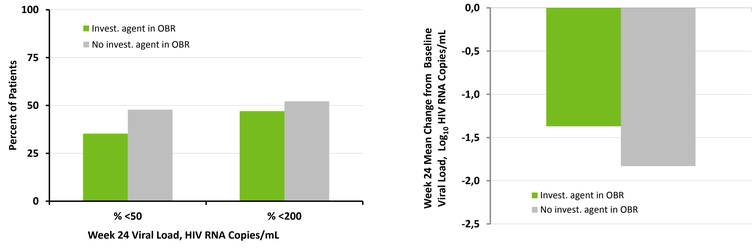
Baseline CD4⁺ T cell/µL (n; Mean BL Count)	**Week 24 - MEF** Mean increase in CD4⁺ T cell/µL (n)	**Week 24 - PP** Mean increase in CD4⁺ T cell/µL (n)
<50 (17; 12)	9 (17)	15 (7)
50-200 (10; 109)	75 (10)	75 (10)
>200 (13; 363)	78 (13)	81 (10)

Efficacy at Week 24

- Mean viral load decrease of 1.6 $\log_{10}$ from Baseline
- 55% and 48% of patients with a ≥1 and ≥2 $\log_{10}$ reduction, respectively
- Undetectable viral load in 43% of patients; 50% with <200 copies



Efficacy with (n=17) or without (n=23) investigational agent 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

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.