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# IBALIZUMAB SUSCEPTIBILITY IN PATIENT HIV ISOLATES RESISTANT TO ANTIRETROVIRALS

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## Background

Ibalizumab (IBA) is a CD4-directed post-attachment HIV-1 inhibitor that blocks HIV entry into CD4+ T cells. Unlike other antiretroviral agents, IBA, a long-acting humanized immunoglobulin G4 monoclonal antibody, 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.

We sought to determine the IBA susceptibility in treatment-experienced HIV-infected patients with multidrug resistant (MDR) HIV-1, entered in a Phase 3 clinical trial (TMB-301). The IBA susceptibility was compared in patient HIV isolates that were sensitive and resistant to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), enfuvirtide (ENF) and maraviroc (MVC).

## Viral Resistance Testing

Blood plasma samples for viral resistance testing were collected at study entry for TMB-301. Susceptibility testing was performed for all enrolled patients and was used by treating physician to select OBR agents.

Viral resistance testing was performed by Monogram Biosciences (South San Francisco, CA) to determine susceptibility to IBA and all approved antiretroviral agents. PhenoSense GT (PSGT) assay was used to measure in vitro sensitivity to NRTIs, NNRTIs, or PIs and resistance associated mutations. PhenoSense Integrase and Integrase GeneSeq assays were used to assess the phenotypes and genotypes for approved INSTIs. PhenoSense HIV Entry assay was used to measure phenotypic sensitivity to IBA, EFV, and MVC. *Trofile* assay was used for phenotypic assessment of coreceptor tropism.

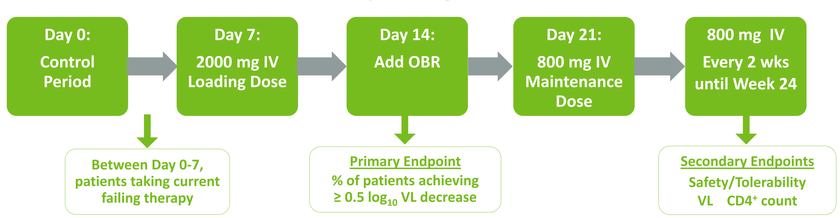
For IBA, Maximum Percent Inhibition (MPI) and ICHalfMax Fold Change (FC) from the dose-response curve were monitored as indicators of IBA susceptibility and potency. MPI is the maximum level of inhibition achieved and ICHalfMax FC occurs at the midpoint of the dose response curve.

## 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.

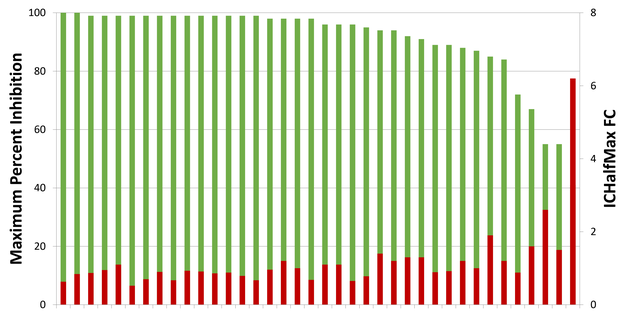
### Study Design




## Baseline Characteristics

- N = 40
- Median age of 53 years
- 85% male; 45% non-white
- Median duration of HIV infection of 23 years (range of 2-30)
- Median viral load of 35,350 copies/mL
  - 18% with viral load ≥ 100,000 copies/mL
- Median CD4+ T cell count was 73 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

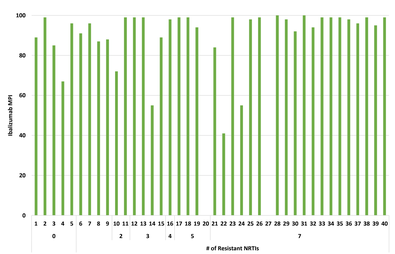
## IBA MPI and ICHalfMax FC at Study Entry



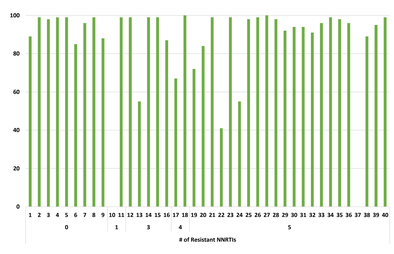

| | |
|---|---|
| **Mean / Median IBA MPI** | 91 ± 14 / 97 |
| **Mean / Median IBA HalfMax FC** | 1.2 ± 0.9 / 0.9 |
| **IBA MPI 90-100, %** | 71 |
| **IBA MPI 80-90, %** | 16 |
| **IBA MPI <80, %** | 13 |

## IBA MPI by ARV Classes at Study Entry

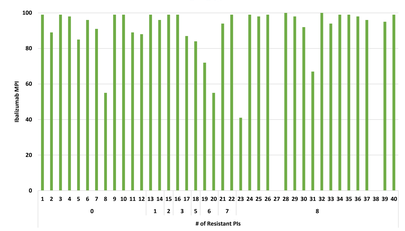
### NRTIs



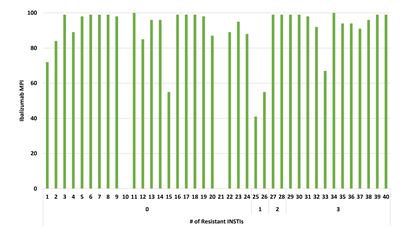

### NNRTIs




### PIs

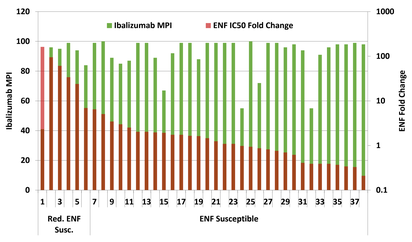



### INSTIs

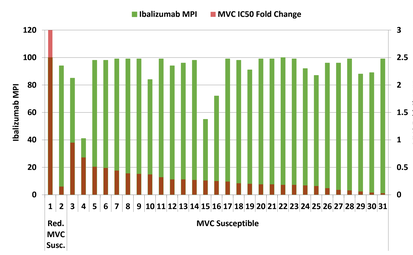



## IBA MPI and ENF & MVC ICHalfMax FC at Study Entry

### Enfuvirtide




### Maraviroc




In all ARV classes as well as EFV and MRV, IBA is equally active against resistant and sensitive HIV isolates.

## Efficacy at Day 14 and Week 24

### Day 14

| | Day 7 | Day 14 | |
|---|---|---|---|
| **Percent with ≥0.5 $\log_{10}$ reduction** | 3% | 83% | P<0.0001 |
| **Percent with ≥1.0 $\log_{10}$ reduction** | 0% | 60% | P<0.0001 |
| **Mean VL decrease** | | 1.1 $\log_{10}$ | P<0.0001 |

### Week 24

| | |
|---|---|
| **Percent with VL < 50 copies/mL** | 43% |
| **Percent with VL < 200 copies/mL** | 50% |
| **Mean VL decrease** | 1.6 $\log_{10}$ |
| **Percent with ≥1.0 $\log_{10}$ reduction** | 55% |
| **Percent with ≥2.0 $\log_{10}$ reduction** | 48% |

## Conclusion

Resistance to other ARVs does not impact the IBA susceptibility at study entry. Furthermore, IBA susceptibility at study entry does not seem to impact overall efficacy results. IBA is a potent new tool for the treatment of MDR HIV-1.