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APPLICATION NUMBER:

761065Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY
REVIEW(S)

**DIVISION OF ANTIVIRAL PRODUCTS
CLINICAL VIROLOGY REVIEW**

BLA: [761065](#) **SDN:** 000 Addendum (Original BLA, SDN 012 in DARRTS) **REVIEW COMPLETED:** 01/19/2018
Clinical Virology Reviewer: Eric F. Donaldson, Ph.D.

BLA#: 761065 SDN 000 (Original BLA)

Reviewer Name(s): Eric F. Donaldson, Ph.D.

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Proprietary Name (Proposed): TROGARZO
Drug Names: ibalizumab, TNX-355, Hu5A8, Mu5A8, TMB-355
Drug Class: CD4 post-attachment HIV-1 inhibitor
Parent IND #: [IND009776](#)

Ibalizumab heavy chain primary structure (IgG4)

QVQLQQSGPEVVKPGASVKMSCKASGYTFTSYVIHWVRQKPGQGLDWIGYINPYNDGTDYDEKFKGKATLTSDTSTSTAYM
ELSSLRSEDTAVYYCAREKDNATGAWFAYWGQGLTTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS
WNSGALTSKVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYTCNVDPKPKNTKVDKRVESKYGPPCPSCPAPEFLGGPSVF
LFPPKPKDITLMISRTPVTCVVVDVSDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKGLPSSIEKTIISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKLSLSLGLK

Ibalizumab light chain primary structure (κ)

DIVMTQSPDLSAVSLGERVTMNCSSQSLLYSTNQKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTI
SSVQAEDVAVYYCQQYYSYRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKSTYLSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Amendments: none

Related/Supporting Documents: This BLA was submitted as a rolling submission starting with SDN 000. Additional/updated clinical virology information was submitted to the BLA in the following SDNs: [0003](#) (proprietary name review), [0011](#) (TMB-301 Clinical Virology Study Report), [0012](#) (Original BLA), [0015](#) (TMB-301 electronic database), [0018](#) (TMB-202 and TMB-301 neutralizing antibody ligand binding testing of clinical samples), [0020](#) (response to IR regarding resistance algorithm), [0023](#) (response to Clinical Virology IR requesting define files), [0026](#) (response to Clinical Virology IRs sent on 6/5/17 and 6/20/17), and [0033](#) (response to Clinical Virology IR sent on 7/20/1966). For this addendum review, the following submissions have been reviewed: [0055](#) (response to labeling comments), [0057](#) (Clinical Virology study reports for TMB 301 and TMB 202), [0059](#) (slides for Late Cycle Meeting), [0063](#) (update on pending review issues for Product Quality), [0064](#) (FASTQ files for Clinical Virology data submitted in 0057), [0065](#) (revised label), [0066](#) (product quality), [0068](#) (label revision), [0070](#) (label revision), [0071](#) (response to Virology and Pharm/Tox PMRs), [0073](#) (revised label).

Dosage Form and Route of Administration: A loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks; intravenous injection

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Dispensed: Rx

Proposed Indication(s): Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; CD4, cluster of differentiation 4 molecule; D2, domain 2 of CD4; DM, dual mix or dual tropic; Env, envelope protein; gp, glycoprotein; GSS, genotypic susceptibility score; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IV, intravenous; mAb, monoclonal antibody; MDR, multiple drug resistance; MHC-II, major histocompatibility complex class II; MPI, maximal percent inhibition; NGS, next generation sequencing; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NRS, non-recycled score; OBR, optimized background regimen; OSS, overall susceptibility score; PBMC, Peripheral blood mononuclear cell; PI, protease inhibitor; PNGS, potential N-linked glycosylation site; PSS, phenotypic susceptibility score; Q2W, administered once every two weeks; Q4W, administered once every 4 weeks; R5, CCR5 coreceptor; X4, CXCR4 coreceptor;

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EXECUTIVE SUMMARY

The original Biologics License Application (BLA) for ibalizumab (previously known as Mu5A8 [original mouse monoclonal antibody], Hu5A8, TNX-355, and TMB-355) which targets the CD4 HIV-1 receptor, was reviewed and archived on 10/3/2017 with a PDUFA goal date of 1/3/18. The goal date was extended to 4/3/18 due to a major Product Quality amendment. The submissions covered in this addendum Clinical Virology review were received after the original review was archived (see [BLA761065 SDN 000](#)). Of note, submissions [0057](#) (Clinical Virology study reports for TMB 301 and TMB 202), [0064](#) (FASTQ files for Clinical Virology data) provided additional information regarding the HIV-1 from subjects who failed treatment while on ibalizumab plus an optimized background regimen (OBR). Additional submissions pertained to the label or CMC issues, and were reviewed briefly and updated below.

In the BLA, the sponsor provided resistance data for TMB-301 ([NCT02475629](#)) and TMB-202 ([NCT00784147](#)); however, the dataset for TMB-202 was incomplete in that it was limited to 17 of the 30 subjects identified by the sponsor as treatment failures. The approval of ibalizumab was predominantly based upon the pivotal clinical trial TMB-301, with support from TMB-202, therefore, to better characterize the resistance pathways for ibalizumab we have consistently requested the resistance data for the remaining 13 subjects. New resistance data provided in submissions [0057](#) (Clinical Virology study reports for TMB 301 and TMB 202) and [0064](#) (FASTQ files for Clinical Virology data) expanded the resistance analysis of TMB-202 to include all subjects who failed treatment or who were poor responders.

Viral resistance monitoring for ibalizumab in clinical trials TMB-202 ([NCT00784147](#)) and TMB-301 ([NCT02475629](#)) included collecting blood samples at timepoints before treatment, at regular intervals during treatment, and at the end of study. (b) (4) performed drug susceptibility testing at baseline and at EOS to determine that subjects met the inclusion criteria of multiple class drug resistance, and to determine which drugs to include in the OBR. Samples selected for ibalizumab resistance analysis were collected at the time of confirmed virologic failure while the subject was still on treatment with the prescribed study drug regimen. Protocol-defined virologic failure was defined as follows:

- TMB-202: two consecutive viral load measurements with $<1 \log_{10}$ reduction from Baseline
- TMB-301: two consecutive viral load measurements with $<0.5 \log_{10}$ reduction from Baseline viral load

Overall, the sponsor reported totals of 25 subjects in TMB-202 and 7 in TMB-301 who experienced protocol-defined virologic failure. In addition, the sponsor reported that 5 subjects in TMB-202 and 3 in TMB-301 experienced virologic rebound or breakthrough, defined as $1 \log_{10}$ HIV-1 RNA copies/mL increase in viral load or increase from below to above 200 HIV-1 RNA copies/mL. In the BLA, Clinical Virology reviewed the sponsor's resistance analysis for the 17 subjects from TMB-202 and 10 subjects in TMB-301, which primarily focused on the absence or loss of a Potential N-linked Glycosylation Site (PNGS) in the V5 loop of HIV-1 gp120. The sponsor concluded, and Clinical Virology concurred, that genotypic analysis demonstrated the absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab maximal percent inhibition (MPI). Two post-marketing requirements (PMRs) were agreed upon in response to the review of the BLA to better assess the resistance pathways for ibalizumab.

For this addendum review, resistance analyses for 18 additional subjects from TMB-202 who were poor responders or who failed treatment with ibalizumab plus an optimized background regimen were reviewed. Several amino acid substitutions in the gp120 were identified and a Clinical Virology PMR will be added requiring the sponsor to determine the phenotypes of several substitutions in relation to ibalizumab activity in cell culture. In addition, baseline data provided for all subjects in TMB-301 and TMB-202 provided additional information that could be used to assess for baseline polymorphisms that could potentially be resistance-associated. However, the datasets submitted were not integrated with the original datasets, making it extremely difficult to compare the amino acid variation between the different datasets due to insertions and deletions that altered the numbering. A second PMR will be added to require integration of all datasets.

Overall, the data provided in these submissions provided additional support for the approval of the BLA.

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1. RECOMMENDATIONS

1.1 Recommendation and Conclusion on Approvability

The original BLA for ibalizumab (previously known as Mu5A8 [original mouse monoclonal antibody], Hu5A8, TNX-355, and TMB-355) was determined to be approvable from the Clinical Virology perspective for the treatment of HIV-1 infection in HIV-1 in heavily treatment-experienced adults with multidrug resistant HIV-1 infection and limited treatment options. There are no issues related with the submissions reviewed herein that would alter the approvability status.

1.2 Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

Based on the new information provided after the original BLA was reviewed and archived, the following additional post-marketing commitments will be communicated to the sponsor:

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.
2. Please provide integrated virology datasets for studies TMB-202 and TMB-301 to include all baseline sequences in one database for both studies, and at time of failure for all 35 subjects who failed and were examined for resistance in TMB-202.

2. SUMMARY OF OND VIROLOGY ASSESSMENTS

For a complete summary, please see the BLA review ([BLA761065 SDN 000](#)).

2.1 Nonclinical Virology

Ibalizumab is a recombinant, humanized IgG isotype 4 κ light chain monoclonal antibody that binds to domain 2 of CD4 and functions as a CD4 post-attachment inhibitor of HIV-1. Ibalizumab blocks the post-CD4-receptor-attachment steps required for viral and cellular membrane fusion leading to entry into CD4⁺ T cells. Cell culture antiviral activity was seen against all clades of HIV-1, regardless of co-receptor tropism (R5, X4, and dual tropic or dual mixed, abbreviated DM). The EC₅₀ values against Clade A, B, C, D, CRF01_AE, CRF_AG, G, AC, ACD, BC, and CD HIV-1 envelope pseudotypes ranged from 0.02 to 0.23 $\mu\text{g/mL}$. Among 82 clinical isolates obtained from a phase 2 study, ibalizumab exhibited antiviral activity with a median EC₅₀ value of 0.08 $\mu\text{g/mL}$ (range 0.02-0.16 $\mu\text{g/mL}$; n=43) against R5-tropic HIV-1, an EC₅₀ value of 0.11 $\mu\text{g/mL}$ against one R4-tropic virus, and a median EC₅₀ value of 0.08 $\mu\text{g/mL}$ (range 0.01-0.14 $\mu\text{g/mL}$; n=33) against DM-tropic HIV-1 assessed in R5 cells and a median EC₅₀ value of 0.09 $\mu\text{g/mL}$ (range 0.07-0.23 $\mu\text{g/mL}$; n=29) against DM-tropic HIV-1 assessed in X4 expressing cells. No antagonism was observed when ibalizumab was combined with approved HIV-1 drugs at concentrations spanning the EC₅₀ value of both drugs, including against the CCR5 co-receptor antagonist, maraviroc, and the gp41 fusion inhibitor, enfuvirtide.

Ibalizumab resistance was first observed in studies conducted in nonhuman primates infected with SIV that were treated with hu5A8. In those studies, it was shown that a 10-fold EC₅₀ value increase in ibalizumab susceptibility, as measured by quantification of SIV Gag p27, was observed after 17 days on ibalizumab; however, the viruses from this study were not characterized genotypically. Further cell culture characterization of ibalizumab resistance was performed in an experiment comparing 116 HIV-1 envelope sequences derived from clinical isolates selected to represent envelope diversity by geography, clade, tropism, and stage of infection that were assessed for ibalizumab susceptibility using an HIV-1 envelope sequence pseudotype assay. Genotypic characterization of HIV-1 envelope sequences that were less susceptible to ibalizumab indicated that changes in the V5 loop that altered PNGSs were associated with lower ibalizumab susceptibility. HIV-1 envelope sequences with no PNGSs in the V5 loop were the least susceptible to ibalizumab with a median MPI <50% (n=4, MPI 37.2 \pm 16%, P <0.001). HIV-1 envelope sequences with one V5 PNGS were less

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susceptible to ibalizumab compared with those with 2 V5 PNGS (n=59, MPI $77.8 \pm 18.3\%$ vs n=51, $89.2 \pm 12.5\%$, P= 0.001). HIV-1 envelope sequences with one N-terminal V5 PNGS had higher MPIs compared with viruses with one central or C-terminal V5 PNGS (n=29, MPI of $83.4\% \pm 18.3\%$ vs n=30, MPI of $72.4\% \pm 16.8\%$, P=0.02). Changes to the V5 loop did not have an impact on CD4 receptor usage or the antiviral activity of the CCR5 co-receptor antagonist, maraviroc, or the gp41 fusion inhibitor, enfuvirtide.

2.2 Clinical Virology

Clinical Trial TMB-301

The approval of ibalizumab was based predominantly upon the results from clinical trial TMB-301, as this was the only clinical trial that assessed the dose approved for the indication. TMB-301 was conducted with 40 subjects infected with HIV-1 with documented resistance to at least one drug in three different drug classes. The study design was for treatment-experienced subjects infected with multi-drug resistant HIV-1 to receive a 2,000 mg loading dose of ibalizumab at Day 7 (Baseline) in combination with their failing regimen followed by 800 mg doses of ibalizumab every other week in combination with OBR starting at Day 14. The trial was designed to establish the efficacy of ibalizumab as a monotherapy during the first week of the trial, and then add-on an optimized background regimen. Here are the stages of this trial:

- During Days 0 through 6 subjects were monitored on current failing therapy (or no therapy) as a comparator to assess efficacy.
- Day 7-13 (functional monotherapy period). During Days 7 through 13 subjects continued on current failing therapy and received one 2,000 mg dose (loading dose) of ibalizumab on Day 7. Day 7 is Baseline for the treatment period (Day 7-Week 25).
- Day 14-Week 25 (maintenance period). On Day 14 (primary endpoint), the optimized background regimen was initiated and was to include at least one agent to which the subject's virus was fully susceptible. Beginning at Day 21, 800 mg of ibalizumab was administered every 2 weeks through Week 23.
- All subjects were to complete the Week 25/EOS visit and the Week 29/Follow-up visit procedures.

A statistically significant number of subjects achieved the primary endpoint for this study, which was a ≥ 0.5 \log_{10} reduction in viral load from Baseline (Day 7) to Day 14 (n=33; 82.5%; p<0.0001). Other clinically meaningful reductions in viral load observed at Day 14 and Week 25 (EOS) in the ITT population included:

- 25 (62.5%) subjects achieved ≥ 0.5 \log_{10} reduction in viral load from Baseline (Day 7) to Week 25 (EOS)
- 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at Week 25 (EOS)
- 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at Week 25 (EOS)
- 22 (55%) subjects achieved ≥ 1.0 \log_{10} reduction in viral load from Baseline (Day 7) to Week 25 (EOS)

Virologic failure was defined as 2 consecutive viral load measurements of less than a 0.5 \log_{10} decline from the baseline viral load beginning at Day 14. Five subjects did not have a robust response to ibalizumab monotherapy, including subjects 04-001, 05-001, 05-003, 17-003, and 27-001. Two additional subjects only achieved a 0.3 \log_{10} reduction during ibalizumab monotherapy and these subjects were 08-001 and 21-002. However, despite the poor response during the monotherapy phase of this clinical trial, overall, these subjects fared equal to or better than other subjects in this trial when comparing secondary endpoints indicating that the OBR drove response in these subjects. Of note, 17 of the 40 subjects treated in TMB-301 received the experimental HIV-1 entry inhibitor, fostemsavir, in their OBR, which further confounded the resistance analysis.

The durability of ibalizumab was difficult to assess directly because of the addition of an OBR that was added-on after 1 week of essential monotherapy with ibalizumab in TMB-301. However, comparing the secondary endpoint of percent of subjects with <50 HIV-1 RNA copies/mL at the end of the study, which was 42.5%, to the same endpoint that was the primary endpoint at the end of ibalizumab monotherapy and was reached by

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82.5% of subjects, it is clear that ibalizumab (and probably other drugs in the OBR) was not durable in this population. In addition, given that ibalizumab exhibited a low barrier to resistance during nonclinical development and in clinical trials that explored the use of ibalizumab as a monotherapy, it appears that ibalizumab rapidly selects for variants of HIV-1 that are less susceptible to this drug, and therefore, this drug should not be used as a monotherapy. Resistance to ibalizumab was analyzed for 10 subjects who failed treatment with ibalizumab in TMB-301 and in general, these subjects exhibited changes in the V5 loop region that altered PNGSs consistent with results observed previously.

Clinical Trial TMB-202

In addition, to data reviewed from TMB-301, Clinical Virology data from clinical trial TMB-202 were also analyzed as part of the approval for ibalizumab, and the data reviewed from the original BLA submission and in subsequent submissions reviewed in this addendum review indicate that the general trends in efficacy and resistance were similar in both trials, indicating that the new data provided support the approvability of ibalizumab.

No additional changes to the Microbiology section of the label were necessary based on the additional data reviewed.

3. ADMINISTRATIVE

3.1 Reviewer's Signature

Eric F. Donaldson, Ph.D.
Clinical Virology Reviewer, Division of Antiviral Products

3.2 Concurrence

Julian J. O'Rear, Ph.D.
Clinical Virology Team Leader, Division of Antiviral Products

OND CLINICAL VIROLOGY REVIEW

Please see the [BLA761065 SDN 000](#) for the complete description of data provided in the BLA. Sections pertinent to this review are included below.

4. IBALIZUMAB RESISTANCE IN CLINICAL TRIALS

4.1 Overview of Ibalizumab Resistance Mechanism

A decrease in susceptibility to ibalizumab, as determined by a shift in EC₅₀ value and a decrease in MPI, has been associated with the loss or shifting of PNGS in the V5 loop of the envelope gp120. Presumably, the alteration of PNGS in this region impacts the carbohydrate moieties that can interact with the amino acids in this region, and these moieties may play a role in the anti-HIV-1 activity of ibalizumab. Hypothetically, the presence of multiple glycans in the V5 loop or glycans in the N-terminal region of the V5 loop in particular contribute to the steric hindrance that prevents the HIV-1 envelope protein from interacting with the co-receptor. Shifting the PNGS toward the C-terminal region of the V5 loop or eliminating it all together would likely allow the HIV-1 gp120 to engage with the co-receptor while ibalizumab is still bound to domain 2 of CD4, representing a resistance pathway.

The sponsor used next generation sequencing of the envelope gene to determine what changes occurred in

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the HIV-1 gp120 of subjects who met the criteria of protocol defined virologic failure, by comparing the V5 loop region at baseline to that at the time of failure in clinical trials TMB-202 and TMB-301. To date, the sponsor has only submitted NGS files that were limited to sequence fragments that contained reads spanning the V5 loop; however, in response to a PMR, the sponsor has agreed to submit the per protocol raw NGS sequence reads for the entire envelope sequence. The sponsor also provided resistance tables wherein the envelope sequences, as determined by quantitative NGS analysis using a greater than or equal to 10% cutoff, were populated. Of note, many of the amino acid positions in these tables were marked with an 'X' indicating a lack of consensus or a problem with the nucleotides in the codon. Resistance analyses were performed by the sponsor by looking at the number and positions of the PNGS in the V5 loop, comparing the genotype and baseline to the genotype from the sample collected close to the time of failure.

Clinical Virology looked at the PNGS composition of the HIV-1 gp120 V5 loop derived from subjects at baseline and time-of-failure to confirm what the sponsor reported. Hypothetically, amino acid changes elsewhere in the envelope protein could allow for HIV-1 to interact with the co-receptor in the presence of ibalizumab. In addition to the PNGS analysis, DAVP also compared gp120 amino acid sequences that were detected by quantitative NGS analysis and derived at baseline and at the time-of-failure from subjects who met protocol defined virologic failure to determine if amino acids that evolved over the course of treatment could be associated with ibalizumab resistance. These analyses identified several potential resistance-associated substitutions that occurred in 2 or more subjects.

5. PRIOR TMB-202 AND TMB-301 RESISTANCE ANALYSES

Baseline Resistance Characteristics

Baseline resistance-associated substitutions could not be assessed with the data in the original BLA submission because the sponsor did not provide the baseline gp120 sequences for all subjects who were enrolled in TMB-202 and TMB-301; however, these data were provided in the submissions reviewed here and will be discussed below. In addition, the clinical trial designs employed in TMB-202 (no monotherapy arm) and TMB-301 (limited monotherapy arm) made it nearly impossible to determine baseline substitutions associated with a lower susceptibility specifically to ibalizumab but not to other drugs in the OBR. However, the EC₅₀ values derived at baseline and assessed via cell culture did not show any appreciable changes in ibalizumab susceptibility to HIV-1 strains with 1 PNGS site in the gp120 V5 loop at baseline versus those with 2 PNGS sites in the V5 loop (Table 1), indicating that no clear genotype could be associated with ibalizumab resistance.

Table 1. Baseline EC₅₀ values for subsets of subjects in TMB-202 (DAVP Analysis). EC₅₀ values are shown in µm/mL.

	ALL	EFF=Yes	EFF=No	RESIST	2 PNGS	1 PNGS
N	104	37	67	17	9	8
Mean	0.032	0.035	0.031	0.034	0.044	0.022
SD	0.031	0.031	0.030	0.032	0.041	0.006
Median	0.025	0.027	0.023	0.024	0.026	0.022
Min	0.009	0.014	0.009	0.015	0.016	0.015
Max	0.218	0.188	0.218	0.150	0.150	0.033

ALL is all subjects in TMB-202, **EFF=Yes** represents subjects who were determined to be treatment successes, **EFF=No** represents subjects who failed treatment, **RESIST** represents subjects for whom resistance analysis was performed, **2 PNGS** represents subject from the RESIST subgroup whose virus had two PNGS at baseline, and **1 PNGS** represents subjects from the RESIST subgroup whose virus had one PNGS at baseline.

By contrast, the median EC₅₀ values for ibalizumab against the HIV-1 strains derived at baseline and assessed via cell culture for TMB-301 were higher than those determined for TMB-202 (Table 2). In addition, the baseline EC₅₀ values for ibalizumab against viruses derived from the 10 subjects who were determined to have

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failed treatment were >18-fold higher, indicating that baseline differences might account for variation in ibalizumab susceptibility.

Table 2. Baseline EC₅₀ values for subsets of subjects in TMB-301 (DAVP Analysis). EC₅₀ values are shown in µm/mL.

	ALL	RESIST	2 PNGS	1 PNGS
N	38	10	5	4
Mean	0.039	11.768	22.119	1.607
SD	0.035	21.650	26.847	1.669
Median	0.031	0.566	0.298	0.802
Min	0.013	0.148	0.148	0.370
Max	0.212	55.000	55.000	4.453

ALL is all subjects in TMB-301 for which BL EC₅₀ values were determined, **RESIST** represents subjects for whom resistance analysis was performed, **2 PNGS** represents subject from the RESIST subgroup whose virus had two PNGS at baseline, and **1 PNGS** represents subjects from the RESIST subgroup whose virus had one PNGS at baseline.

Treatment-Emergent Resistance

A decrease in susceptibility to ibalizumab, as determined by a shift in EC₅₀ value and a decrease in MPI, has been associated with the loss of PNGS in the V5 loop of the envelope gp120. Presumably, the alteration of PNGS in this region impacts the carbohydrate moieties that can attach to the amino acids in this region, and these moieties may play a role in the anti-HIV-1 activity of ibalizumab.

An independent assessment of the NGS data provided for the HIV-1 from the 10 subjects from TMB-301 who were assessed for the development of resistance indicated that the results reported by the sponsor were in agreement with the results observed by DAVP. The predominant changes occurred in the V5 loop and resulted in altered PNGS in this region. However, there were a couple of additional HIV-1 gp120 amino acid substitutions that emerged on-treatment in at least two subjects that were noted in different regions of the gp120 protein sequence (Table 3). Phenotyping these substitutions was recommended and agreed to be performed as a PMR.

Table 3: Potential resistance-associated substitutions that emerged in 2 or more subjects who failed treatment in TMB-301 (DAVP analysis).

Substitution	No	Ratio	Subjects	CDS
V75I	2	2-0	17001, 18002	C1cons
E229G/Q229P/R	2	1-1	22001, 17001	gp41cons
L274V/A274T	2	1-1	21001, 32001	gp41cons
N12K	2	2-0	17001, 21001	V1V2
N14D,V14M/deletion	2	1-1	18002, 22001	V1V2
T23N/deletion	2	1-1	4001, 9002	V4

CDS terms represent domains of envelope protein: C, constant region; V, variable region; cons, conserved; ratio, the number of occurrences of each substitution at a given position.

There were a total of 25 subjects in TMB-202 and 7 in TMB-301 who experienced protocol-defined VF. In addition, 5 subjects in TMB-202 and 3 in TMB-301 experienced virologic rebound or breakthrough, defined as 1 log₁₀ increase in viral load or increase from below to above 200 copies/mL. The sponsor performed resistance analysis for 17 subjects from TMB-202 and 10 subjects in TMB-301, looking primarily at the

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absence or loss of a PNGS in the V5 loop of HIV-1 gp120. The sponsor concluded that genotypic analysis demonstrated the absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab MPI.

For the 10 subjects from TMB-301 who were analyzed for resistance, the virus of five subjects started with two V5 PNGS in the V5 loop of the HIV-1 gp120 and each lost one PNGS over the course of treatment. Of the remaining 5 subjects, 4 had one V5 PNGS in their HIV-1 at baseline and 1 of these subjects lost the V5 PNGS in their HIV-1 at the time of failure, and 1 subject had no V5 PNGS in their HIV-1 at baseline but had one PNGS at the time of failure (Table 4).

Table 4: TMB-301 PNGS among VF at baseline and failure (Table 15, page 22, TMB-301 Virology Report).

Subject ID	Baseline				Virologic Failure				VF/BL IC _{HalfMax} FC
	MPI	# V5 PNGS motif, %			MPI	# V5 PNGS motif, %			
		0	1	2		0	1	2	
Majority V5 2 PNGS at Baseline									
01-001	72	0	4	96	48	1	87	12	0.4
08-001	99	0	1	98	63	25	75	0	1.9
17-001	98	0	2	97	72	1	98	0	2.0
21-001	94	0	2	98	63	8	78	14	0.7
32-001	95	0	2	98	43	1	99	0	1.5
Majority 1 PNGS at Baseline									
04-001	55	6	64	30	55	1	58	41	2.5
09-002	99	1	99	0	60	100	0	0	1.9
18-002	67	3	97	0	52	84	16	0	0.3
27-002	96	2	98	0	55	99	1	0	2.8
Majority 0 PNGS at Baseline									
22-001	91	97	1	2	52	3	97	0	1.7

By comparison, in the 17 TMB-202 subjects, nine started with two V5 PNGS in their HIV-1 at baseline and six of these had only one V5 PNGS in their HIV-1 at VF (Table 5). Eight subjects had one V5 PNGS in their HIV-1 at baseline and half of these had no V5 PNGS in their HIV-1 at the time of failure.

Table 5: TMB-202 PNGS among VF at baseline and failure (Table 14, page 26, TMB-202 Virology Report).

Subject ID	Baseline				Virologic Failure				VF/BL IC _{HalfMax} FC
	MPI	# V5 PNGS motif, %			MPI	# V5 PNGS motif, %			
		0	1	2		0	1	2	
Majority V5 2 PNGS at Baseline									
32007	96	0	2	97	94	0	8	92	0.4
14004	97	5	2	93	92	7	29	64	1.9
51003*	98	0	12	88	81	1	92	7	2.0
51006*	98	0	28	72	76	26	56	18	0.7
32002	99	0	8	92	65	1	88	10	1.5
42017	97	2	1	96	61	0	2	98	1.1
17003	100	0	27	73	49	34	66	0	3.2
33003	99	0	2	98	44	2	95	3	1.3
51008*	99	0	5	95	38	2	97	1	3.4
Majority 1 PNGS at Baseline									
28003	94	1	99	0	72	30	70	0	1.9
25004*	78	0	100	0	61	0	100	0	0.3
45002	96	1	99	0	61	0	86	14	2.8
15005	89	1	99	0	58	100	0	0	2.5
51004	88	1	78	22	55	42	58	0	1.7
16003*	99	0	99	0	54	96	4	0	2.8
52001*	99	2	88	10	51	100	0	0	1.8
48007*	86	27	73	0	47	99	1	0	1.3

* Experienced viral load rebound with high mean receptor occupancy

In addition, tropism changes at the EOS did not appear to correlate with treatment failure supporting the observation that ibalizumab has antiviral activity against HIV-1 regardless of tropism. Of note, there was no

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evidence of cross-resistance between ibalizumab and the CCR5 co-receptor antagonist maraviroc or the gp41 fusion inhibitor enfuvirtide.

6. ADDITIONAL SUBMISSIONS TO BLA761065

The following submissions were received after 10/3/17, which was the date that the original Clinical Virology review for BLA761065 was due to be completed and archived. These submissions fall into three categories: 1) Resistance analyses (see section [6.1](#)), 2) Labeling communications (see section [6.2](#)); and 3) Product quality information (see section [6.3](#)). All of these are reviewed in this addendum review.

6.1 Resistance Analyses

During the original review of the virology study report for clinical trial TMB-202, it was noted that resistance data were only provided for 17 of the 30 subjects who were defined as subjects who likely failed due to the development of resistance. In review of this study report (see [BBI009776 SDN 199](#)), Clinical Virology requested that the sponsor submit data for all subjects who failed treatment. This request was also communicated to the sponsor at the time of and after the pre-BLA meeting (see [BBI009776 SDN 336](#)). On October 19 and 23, 2017, the sponsor provided these data in two submissions, including SDN [0057](#) (received 10/19/2017) which contained supplemental study reports for TMB-202 and TMB-301 and submission SDN [0064](#) (received 10/23/2017) which contained the FASTQ files for these data.

6.1.1 Submission [0057](#) (Clinical Virology study reports for TMB 301 and TMB 202)

In this submission, the sponsor provided supplemental data for 18 additional subjects in TMB-202 who failed treatment and baseline genotypic data generated by quantitative NGS for all subjects in clinical trials TMB-202 and TMB-301. The sponsor summarized the results of the analyses reported in this supplement as follows:

For TMB-202, all treatment failure isolates had ibalizumab MPI values that were numerically lower than their paired Baseline value, except for one isolate with no change in MPI; the magnitude of MPI changes ranged from -1 to -71%. The $IC_{HalfMax}$ Fold Change increased slightly at treatment failure with average change = 1.8 ± 0.8 compared to baseline (median = 1.5, range 0.7-3.5). There was no association between changes in ibalizumab susceptibility and susceptibility to enfuvirtide or maraviroc, consistent with previous conclusions that ibalizumab-resistant HIV-1 is not cross-resistance to other antiretrovirals.

Genotypic analysis indicated that larger reductions in ibalizumab MPI at treatment failure were associated with a reduction in the number of potential N-linked glycosylation site sites (PNGSs) in the V5 loop of gp120 (Asn-XSer/Thr is the canonical 3-amino acid sequence motif for N-linked glycosylation). For samples exhibiting lower magnitude shifts in MPI at treatment failure, minimal genotypic shifts in the overall number of V5 PNGS were observed. These results are consistent with the conclusions from previous studies (TMB-202 Clinical Virology Report, TMB-301 Clinical Virology Report).

Genotypic analysis of baseline samples revealed no direct correlation between the extent of V5 glycosylation and ibalizumab susceptibility at baseline. A similar analysis of baseline samples from TMB-301 revealed the same general trends, though the highest and lowest ibalizumab MPI values may have been associated with more and less V5 glycosylation, respectively. Overall, genotypic test results demonstrated that the loss of a PNGS in the V5 loop of HIV gp120 is the primary genetic change associated with reduced susceptibility to ibalizumab, and there was no evidence of cross-resistance between ibalizumab and other HIV entry inhibitors such as enfuvirtide and maraviroc.

In addition to the data provided for 17 subjects from TMB-202 that were already analyzed for resistance, the sponsor provided data for 18 additional TMB-202 subjects who were identified for testing. These included samples collected at baseline and the time of treatment failure from the remaining 14 subjects who experienced virologic failure (defined as two consecutive viral load measurements that do not show a reduction from the baseline measurement of at least 1 \log_{10} beginning at Week 12-14) – 13 of these subjects met the

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criteria for protocol defined virologic failure but actually experienced treatment failure at study time points prior to Week 12. Also tested were samples from the remaining 4 subjects who experienced virologic breakthrough (defined as consecutive viral load measurements >200 HIV RNA copies/mL after first achieving virologic suppression at <50 HIV RNA copies/mL)(Table 6).

Table 6: Additional subjects for whom resistance data were provided in this submission Table 1, page 7, TMB-202-TIM-301 Clinical Virology Supplement).

Subject ID	Visit Week at VF/ BT	Viral Load, HIV RNA Copies/mL				Change from Baseline, Log10 HIV RNA Copies/mL		
		Baseline	Nadir	VF/ BT	Week 24/ EOS	Nadir	VF/ BT	Week 24/ EOS
Virologic breakthrough								
14003	8	101933	47	5760	6490	-3.3	-1.2	-1.2
17002	24	231000	47	590	590	-3.7	-2.6	-2.6
25006	20	15077	47	204	254	-2.5	-1.9	-1.8
45001	16	17600	47	744	261	-2.6	-1.3	-1.8
Virologic failure								
15001	4	1517	227	288	293	-0.8	-0.7	-0.7
25007	4	329333	62100	342000	889000	-0.7	0.0	0.4
28002	4	134667	31200	315000	100000	-0.6	0.4	-0.1
32004	4	111333	721	33500	69900	-2.2	-0.5	-0.2
34001	4	827333	321000	918000	321000	-0.4	0.1	-0.4
34002	4	92833	27800	276000	189000	-0.5	0.4	0.3
39001	8	849000	894	2230000	1060000	-3.0	0.4	0.1
39002	4	254667	26700	7770000	50800	-1.0	-0.8	-0.7
45004	4	161333	868	77100	51900	-2.3	-0.3	-0.5
47002	4	37250	21500	21500	46700	-0.2	-0.3	0.1
50001	4	10470	4150	5030	5420	-0.4	-0.3	-0.3
51002	4	53375	3120	34000	13600	-1.2	-0.2	-0.6
51005	4	7230	355	1970	1290	-1.3	-0.6	-0.7
51007	16	30550	583	17700	6940	-1.7	-0.2	-0.6

VF=virologic failure; BT=virologic breakthrough; EOS=end of study

Analysis of PNGS in the V5 Loop of HIV-1 gp120

In the original BLA, the sponsor performed resistance analyses for 17 subjects from TMB-202 and 10 subjects in TMB-301, looking primarily at the absence or loss of a PNGS in the V5 loop of HIV-1 gp120. The sponsor concluded that genotypic analysis demonstrated the absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab MPI.

For the 10 subjects from TMB-301 who were analyzed for resistance, the virus of five subjects started with two V5 PNGS in the V5 loop of the HIV-1 gp120 and each lost one PNGS over the course of treatment. Of the remaining 5 subjects, 4 had one V5 PNGS in their HIV-1 at baseline and 1 of these subjects lost the V5 PNGS in their HIV-1 at the time of failure, and 1 subject had no V5 PNGS in their HIV-1 at baseline but had one PNGS at the time of failure (see Table 4). By comparison, among the 17 subjects from in TMB-202, 9 subjects

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started with two V5 PNGS in their HIV-1 at baseline and six of these had only one V5 PNGS in their HIV-1 at VF (see Table 5). Eight subjects had one V5 PNGS in their HIV-1 at baseline and half of these had no V5 PNGS in their HIV-1 at the time of failure (see Table 5). This information was expanded with data from 16 of the 18 additional subjects from TMB-202 (PNGS data were not available for two subjects: 15-001 and 17-002). Of these 16 subjects, eleven started with 2 or more V5 PNGS and 7 of these lost one PNGS, and, five started with 1 PNGS and 2 had no PNGS at the time of failure. In summary, among the HIV-1 V5 sequences derived from 33 subjects analyzed from TMB-202, 20 had two or more PNGS at baseline and 14 of these lost one PNGS by the time of failure. Of the HIV-1 gp120 V5 sequences from the remaining 13 subjects, 7 subjects had 0 at the time of failure (Table 7).

Table 7: TMB-202 PNGS analysis of VF samples at baseline and failure for 33 of 35 subjects (DAVP Analysis). Black font indicates substitutions identified in the original 17 subjects; Blue font identifies substitutions that were detected in the HIV-1 envelope sequence in the additional 18 subjects.

USUBJID	Baseline					Virologic Failure					MPI Diff	V5 BL	V5 VF	V5 Diff
	BL MPI	#V5 PNGS motifs, %				VF MPI	#V5 PNGS motifs, %							
		0	1	2	3		0	1	2	3				
39002	96	0.2	1.5	80	18	58	3.9	92	0.7	3.8	-38	2.2	1	-1.2
51002	95	0.1	2.6	81	16	64	2.5	97	0.5	0	-31	2.1	1	-1.1
25007	100	0.1	2	98	0.3	79	2.3	94	3.3	0.4	-21	2	1	-1
25006	100	0.1	1.3	99	0.1	89	0.1	2.3	98	0.1	-11	2	2	0
28002	100	0.1	3.6	96	0.1	94	7.2	40	53	0.5	-6	2	1.5	-0.5
45004	99	0.1	0.6	99	0	98	0.5	7.1	92	0.2	-1	2	1.9	-0.1
32004	97	0.1	3.2	97	0	97	0.2	3.6	96	0	0	2	2	0
32007	96	0	2	97	0	94	0	8	92	0	-2	2	1.9	-0.1
33003	99	0	2	98	0	44	2	95	3	0	-55	2	1	-1
51008	99	0	5	95	0	38	2	97	1	0	-61	2	1	-1
51007	99	0.2	14	86	0	52	2.8	96	1.3	0	-47	1.9	1	-0.9
47002	100	0.2	4.5	95	0	76	25	71	3.4	0	-24	1.9	0.8	-1.1
39001	82	0.2	10	89	1.1	79	0.2	4.2	95	0.2	-3	1.9	1.9	0
14004	97	5	2	93	0	92	7	29	64	0	-5	1.9	1.6	-0.3
51003	98	0	12	88	0	81	1	92	7	0	-17	1.9	1.1	-0.8
32002	99	0	8	92	0	65	1	88	10	0	-34	1.9	1.1	-0.8
42017	97	2	1	96	0	61	0	2	98	0	-36	1.9	2	0.1
34001	96	0.2	29	71	0	63	22	73	4.3	0	-33	1.7	0.8	-0.9
51006	98	0	28	72	0	76	26	56	18	0	-22	1.7	0.9	-0.8
17003	100	0	27	73	0	49	34	66	0	0	-51	1.7	0.7	-1
34002	92	0.9	56	43	0	63	72	15	13	0	-29	1.4	0.4	-1
51005	76	0.4	66	34	0	72	2.9	92	5.4	0	-4	1.3	1	-0.3
51004	88	1	78	22	0	55	42	58	0	0	-33	1.2	0.6	-0.6
50001	95	2.5	88	9.5	0.1	24	89	11	0.1	0	-71	1.1	0.1	-1
52001	99	2	88	10	0	51	100	0	0	0	-48	1.1	0	-1.1
45001	97	1	99	0.1	0	83	2.3	98	0.2	0	-14	1	1	0
14003	88	7.6	92	0.2	0	84	1.9	98	0	0	-4	1	1	0
28003	94	1	99	0	0	72	30	70	0	0	-22	1	0.7	-0.3
25004	78	0	100	0	0	61	0	100	0	0	-17	1	1	0
45002	96	1	99	0	0	61	0	86	14	0	-35	1	1.1	0.1
15005	89	1	99	0	0	58	100	0	0	0	-31	1	0	-1
16003	99	0	99	0	0	54	96	4	0	0	-45	1	0	-1
48007	86	27	73	0	0	47	99	1	0	0	-39	0.7	0	-0.7

USUBJID, unique subject id; BL MPI, baseline; VF, at the time of virologic failure; V5, number of PNGS sites in the V5 loop

Consistent with the observations reported in the original BLA, the PNGS analysis of the larger dataset for TMB-202 showed similar trends in that the loss of a PNGS in the V5 loop of HIV gp120 appeared to be the primary genetic change associated with reduced susceptibility to ibalizumab. In TMB-202, the HIV-1 envelope from all subjects had approximately 2 PNGS in the V5 loop and these viruses were susceptible to ibalizumab with starting MPIs of approximately 97 (Figure 1). At the time of failure, on average, the PNGS decreased by 1 and the MPI decreased by more than 20%, indicating that these viruses were less susceptible to ibalizumab and that the PNGS sites in the V5 loop were altered in this population (Figure 1).

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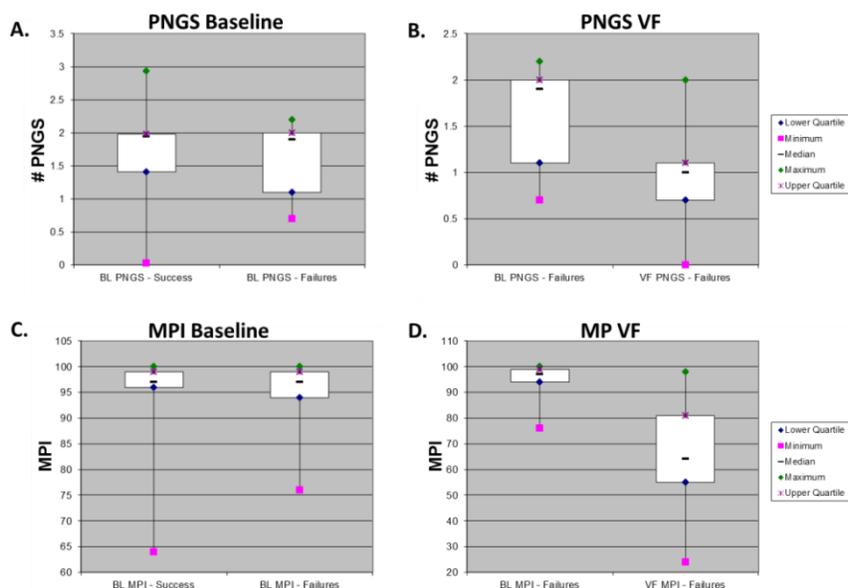


Figure 1. PNGS and MPI analysis of HIV-1 from subjects in TMB-202 (DAVP Analysis).

The same trends were observed for TMB-301, where the virus from subjects infected with HIV-1 had >1.7 PNGS in the V5 loop at baseline and these viruses were susceptible to ibalizumab with starting MPIs of approximately 98 (Figure 2). At the time of failure, on average, the PNGS decreased by >0.5 and the MPI decreased by more than 40%, indicating these viruses were less susceptible to ibalizumab and that the PNGS sites in the V5 loop were altered in this population consistent with the development of resistance (Figure 2).

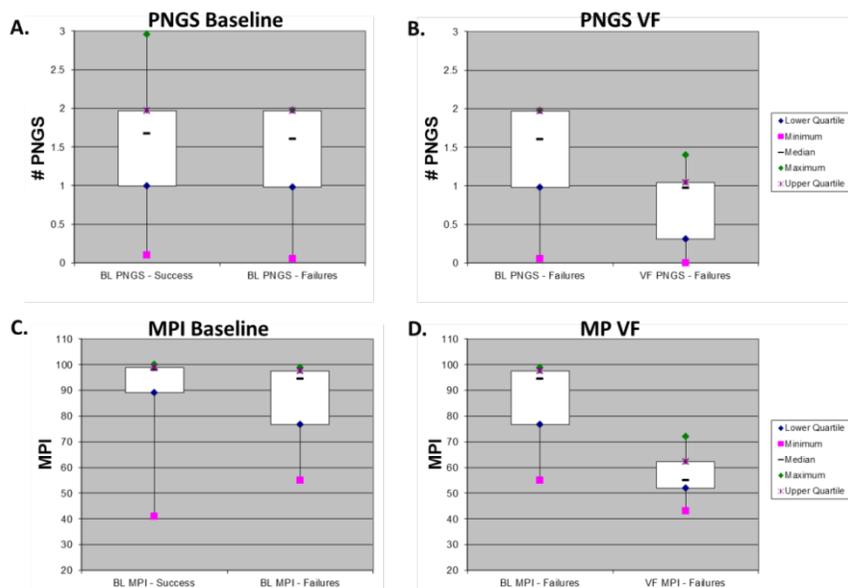


Figure 2. PNGS and MPI analysis of HIV-1 from subjects in TMB-202 (DAVP Analysis).

Importantly, some subjects who failed treatment with ibalizumab maintained two PNGS in the V5 loop of their HIV-1 and still showed a reduction in MPI indicating that additional unidentified genotypic factors may play a role in resistance against ibalizumab. Of note, there was no evidence of cross-resistance between ibalizumab and the CCR5 co-receptor antagonist maraviroc or the gp41 fusion inhibitor enfuvirtide.

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Baseline Resistance Analysis for TMB-202

In the TMB-202 resistance data submitted, the sponsor provided baseline envelope sequences in table format for the remaining 96 out of 113 subjects in TMB-202 (17 baseline sequences were included in the data submitted for those subjects who failed treatment). In addition, 18 additional time-of-failure envelope sequences were submitted for a total of 35 subjects who either did not respond or were poor responders to ibalizumab + OBR treatment. Of note, the new datasets were not compatible with the previously submitted sequence databases for subjects from TMB-202 and TMB-301 because different insertions and deletions altered the alignments and therefore the tables submitted by the sponsor. Therefore, it was not possible to merge the tables to conduct analyses. In addition, the data in the tables included several ambiguous amino acid calls, identified as 'X', and some sequences had insertions or deletions.

A comparison of baseline envelope sequences from the 96 subjects from TMB-202 was made, comparing subjects who were considered treatment successes to those who were defined by the sponsor as Suboptimal (SUB) or Non-responders (NON). Of note, for this comparison of baseline sequences, the amino acid calls that were designated as ambiguous (X) or associated with insertions or deletions were ignored. Baseline polymorphisms that were potentially associated with ibalizumab resistance, known as resistance-associated polymorphisms (RAPs), were identified using the following criteria:

1. Polymorphisms that were present at baseline in the NON and SUB populations but not in the HIV-1 envelope of subjects who were successfully treated;
2. Polymorphisms that occurred in the HIV-1 gp120 of 2 or more subjects in NON, SUB, or both.

Using these criteria, 13 potential RAPs were identified in the TMB-202 clinical trial, but this analysis did not include the original 17 subjects identified as treatment failures (Table 8).

Table 8. Potential baseline resistance-associated polymorphisms from TMB-202 (DAVP Analysis).

AAPOS	SUBS	Ratio	Explanation
221	F221Y	2	RAP 2SUB
299	N299R/Q/T	2-1-1	RAP 3SUB, 1NON
325	R325K/G	2-1	RAP 2SUB, 1NON
393	W393L/F	3-1	RAP 2SUB, 2NON
453	T453V/M	4-1	RAP 3NON, 2SUB
522	G522S/A	2-1	RAP 2NON, 1SUB
539	A539T	3	RAP 2NON, 1SUB
697	F697C	2	RAP 2SUB
735	G735S/D	2-1	RAP 2SUB, 1NON
739	D739G/N	3-1	RAP 3NON, 1SUB
770	R770T/I	2-1	RAP 2NON, 1SUB
823	G823W	2	RAP 2SUB
841	I841V	4	RAP 2SUB, 2NON

AAPOS, amino acid position; **SUBS**, substitutions; **Ratio**, the number of times a substitution occurred in the **SUBS** column; **NON**, non-responder; **RAP**, potential resistance-associated polymorphism; **SUB**, suboptimal responder;

Note: Because the datasets were incompatible, it was not possible to conduct a robust assessment of baseline resistance for all 113 envelope sequences derived from subjects in TMB-202. Instead of submitting an information request asking for integrated baseline databases for each clinical trial, we note that the sponsor has agreed to provide complete envelope sequences for each subject in a PMR, and so baseline resistance will be fully examined at the time that those sequences are provided. A new PMR will be sent requiring the datasets to be integrated.

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Baseline Resistance Analysis of TMB-301

Because the datasets were not compatible, it was not possible to perform a robust assessment of baseline resistance for all subjects in TMB-301. A comparison of baseline sequences based upon MPI did not identify any gp120 amino acid substitutions that correlated with lower MPIs or less susceptibility to ibalizumab.

Treatment-Emergent Resistance Analysis of TMB-202

The resistance data for the original 17 subjects was submitted with the original BLA and data for 18 additional subjects who failed treatment were provided in this submission. Of note, the datasets were not compatible because of differences in insertions and deletions between the two datasets and so, each of these datasets was examined individually and the results were then compared. In both cases, the baseline and time-of-failure HIV-1 full-length envelope sequences for each of the subjects in each dataset were compared to identify substitutions that emerged while on treatment. A total of 19 resistance-associated substitutions were identified using the following criteria (Table 9):

1. A substitution that was present in time-of-failure sequences but not present in baseline sequences that occurred in more than one subject was considered resistance-associated;
2. Substitutions that occurred at polymorphic sites that were not observed as polymorphisms at baseline in the HIV-1 envelope sequences of any of the 35 treatment failures were considered potentially resistance-associated if the RAP was detected in more than one subject.

Table 9: Potential resistance-associated substitutions that emerged while on treatment in TMB-202 (DAVP Analysis). Black font indicates substitutions identified in the original 17 subjects; Blue font identifies substitutions that were detected in the HIV-1 envelope sequence in the additional 18 subjects. Bold lines represent substitutions that are potentially resistance-associated.

AAPOS	SUBS	Ratio	Explanation	RESIST Status	PMR
78	D78N	2	Only detected at time of failure	Polymorphic site	
141	N141K/I	2-1	Polymorphic site with K and I only observed in TF	Polymorphic site	
143	S143T/P	3-2	Polymorphic position with N/R T and P only present at time of failure	S143P is potentially RESIST	S143P
144	S144D/A	2-1	Polymorphic site with D and A only observed in TF	Polymorphic site	
163	T163S	2	Only detected at time of failure	Polymorphic site	
171	K171E/I	2-1	Polymorphic site with E and I only observed in TF	K171E is potentially RESIST	K171E
184	I184M/L	1-1	Only detected at time of failure	Polymorphic site	
186	N186K/S/R	1-1-1	Polymorphic site with K,S,R only observed in TF	Potentially RESIST	N186K/S/R
188	S188R/N/Y	1-1-1	Only observed in treatment failures	Polymorphic site	
304	S304R	4	Polymorphic site with R only observed in TF	Polymorphic site	
308	Q308H/P	2-1	Polymorphic site with H and P only observed in TF	Potentially RESIST	Q308H/P
309	R309I	3	Polymorphic site with I only observed in TF	Polymorphic site	
320	K320Q/G/T	2-1-1	Polymorphic site with Q, G, T only observed in TF	Polymorphic site	
352	G352K/E	4-1	Substitutions only detected at time of failure	Potentially RESIST	G352K/E
358	I358T/F	2-1	Polymorphic with V,A,K,Y; T and F only observed at time of failure	Polymorphic site	
406	T406G/D	2-1	Polymorphic site with G and D only observed in TF	Polymorphic site	
515	A515V	2	Only detected at time of failure	Polymorphic site	
547	V547A/G	1-1	Only detected at time of failure	Potentially RESIST	V547A/G
638	S638N	3	Polymorphic site with N only observed in TF	Polymorphic site	

AAPOS, amino acid position; SUBS, substitutions; TF, at the time of treatment failure; RESIST, substitutions associated with resistance; PMR, substitutions to be included in a PMR requiring the sponsor to determine the phenotypes.

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Six additional potentially resistance-associated substitutions were identified in the resistance analysis (noted in bold in Table 9), and these will be included in a PMR requiring the sponsor to determine if these substitutions have an impact on ibalizumab susceptibility.

Additional Recommended PMRs:

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.
2. Please provide integrated virology datasets for studies TMB-202 and TMB-301 to include all baseline sequences in one database for both studies, and time-of-failure sequences for all 35 subjects who failed and were examined for resistance in TMB-202.

Treatment-Emergent Resistance Analysis of TMB-301

For TMB-301, there were several HIV-1 gp160 amino acid substitutions identified by Clinical Virology that emerged on treatment in at least two subjects that were noted in different regions of the gp120 protein sequence. Phenotyping these substitutions was recommended and agreed upon as a PMR. These were the substitutions identified:

1. P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V.

6.1.2 Submission [0064](#) (FASTQ files for Clinical Virology data submitted in 0057)

This submission contained the NGS data the sponsor used for making determinations about the development of resistance to ibalizumab. The NGS analyses were conducted by (b) (4) and the methods are provided in the original BLA review (see [BLA761065 SDN 000](#)).

The fastq sequences contained in this submission were limited to the V5 loop region used to assess for PNGS shifts and deletions. These files were analyzed in depth to confirm that they were reviewable, but given that the information contained therein would not provide additional information on alternative resistance pathways for ibalizumab, a complete independent review of these data was not performed. The sponsor has agreed to a PMR that would provide all of the NGS data for the envelope sequences derived from all subjects at baseline and at the time of failure from subjects who failed treatment from TMB-202 and TMB-301. A complete analysis of these NGS data will be performed at the time these data are submitted.

6.2 Labeling Communications, Revisions, and Agreements

The Microbiology section of the label (section 12.4) that was included in the BLA review was modified slightly in the following submissions.

6.2.1 Submission [0055](#) (response to labeling comments)

The pharmacologic class proposed by Clinical Virology was: **CD4 post-attachment HIV-1 inhibitor**, but the sponsor did not like this class description and proposed (b) (4) instead.

Sponsor Comment: Post attachment does not represent the unique mechanism of action of ibalizumab in consideration of other post attachment HIV-1 inhibitors on the market. Furthermore, its biological function is not inhibition rather it is a physical blocking. Hence we are recommending the following wording: (b) (4)

In addition, the sponsor suggested a few minor modifications to section 12.4, and most of these were accepted (see Section 8 for the finalized version of the label). Clinical Virology responded with the following comment:

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Comment to Applicant- The pharmacological drug class should be succinct and descriptive to capture the target and mechanism of action of the drug. Given that ibalizumab exerts its antiviral activity at an undefined step after attaching to CD4 domain 2, we recommend that “**CD4 directed post-attachment HIV-1 inhibitor**” be the class used.

6.2.2 Submission [0059](#) (slides for Late Cycle Meeting)

This submission contained slides that the sponsor prepared and presented at the Late Cycle Meeting.

6.2.3 Submission [0065](#) (revised label)

The sponsor agreed to all other Clinical Virology modifications to section 12.4 of the label, but still did not like the pharmacological class suggested. They sent the following comment:

Sponsor Comment:

(b) (4)
For the above reason and the examples below we suggest that the first part of the indication reads as: TROGARZO, (b) (4), in combination....

Wording for other monoclonal antibodies approved by the FDA:

Efalizumab - CD11a-directed humanized IgG1 antibody

Obinutuzumab - CD20-directed cytolytic antibody

Dinutuximab - GD2-binding monoclonal antibody

Ipilimumab - human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody

Palivizumab - RSV anti-F protein monoclonal (mAb)

In their reply, the sponsor wanted to use (b) (4) as the pharmacological class. In response, Clinical Virology sent the following comment:

Comment to Applicant: As previously stated, the pharmacological drug class should be succinct and describe medically relevant information, i.e., the target and mechanism of action of the drug. We have had a multidisciplinary discussion of your proposed class description: (b) (4) and have the following comments:

- From our perspective, the most important descriptors of ibalizumab activity are:
 - It specifically inhibits HIV-1 infection
 - It binds to CD4 but does not prevent HIV-1 attachment to CD4, does not interfere with normal CD4 function, and exerts its antiviral activity post-attachment
 - It may not compete with other drugs that directly block CD4-gp120 interactions

None of these points are captured in the proposed pharmacologic class description provided by the sponsor.

- As described in the Guidance entitled [Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information](#), the pharmacologic class is a group of drugs that share scientifically documented properties. Therefore, the pharmacologic class is not designed to specifically describe the

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drug being labeled, but instead should capture the pharmacologic activity that may be used to describe other drugs with similar properties.

- The significance of the (b) (4) descriptor is not likely to be appreciated by most clinicians; it is more appropriate to describe this under the mechanism of action section of the label, as is currently the case. (b) (4)
- Mentioning CD4 without describing the post-attachment mechanism would imply to many that ibalizumab is an HIV-1 attachment inhibitor, and, mentioning it without mentioning HIV-1 might imply that it targets normal CD4 activity
- In general, we do not disagree with using (b) (4)”; however, adding that to the proposed class description would increase the length to the point that it would no longer be succinct. Using the descriptor ‘inhibitor’ captures that it inhibits HIV-1 infection, whereas (b) (4), speaks more to (b) (4).

Therefore, given that ibalizumab exerts its antiviral activity at an undefined step after attaching to CD4 domain 2 to block HIV-1 infection, “**CD4 directed post-attachment HIV-1 inhibitor**” will be the class used.

6.2.4 Submission [0068](#) (label revision)

Sponsor Comment: We accept the FDA proposed wording for the pharmacologic class as stated in the FDA fax dated Nov. 16, 2017.

With this agreement, the sponsor and clinical virology were in agreement with the information to be presented in the pharmacological class and in section 12.4 of the label. See section 8 for the current agreed upon version of the label.

6.2.5 Submission [0070](#) (label revision)

This submission contained minor changes to the label but did not alter the wording of any of the virology sections.

6.2.6 Submission [0071](#) (PMR response)

This submission contained the sponsor’s agreement and dates by which the two virology PMRs would be completed. The dates provided by the sponsor were acceptable to Clinical Virology

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.
 - a. **Final Report Submission: November 30, 2018**
2. Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment in clinical trials TMB-202 and TMB-301 to better characterize the HIV-1 gp120 sequence at the time of failure.
 - a. **Final Report Submission: April 30, 2018**

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6.2.7 Submission [0073](#) (label revision)

This submission contained minor changes to the label but did not alter the wording of any of the virology sections.

6.3 Product Quality (major amendment to BLA)

6.3.1 Submission [0063](#) (update on pending review issues for Product Quality)

This submission contained a summary of the outstanding review issues and these were related to Product Quality.

6.3.2 Submission [0066](#) (product quality)

This submission contained product quality information, for which a major amendment was invoked resulting in a new PDUFA goal date of April 3, 2018. There were no virology data included in this submission.

7. CONCLUSIONS

In conclusion, ibalizumab administered in clinical trial TMB-301 at a loading dose of 2,000 mg followed with 800 mg Q2W resulted in a statistically significant number of subjects achieving $\geq 0.5 \log_{10}$ reduction in HIV-1 RNA copies/mL from BL (Day 7) to Day 14 ($n=33$; 82.5%; $p<0.0001$) during the essential monotherapy treatment phase. When ibalizumab was combined with an OBR, 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from BL to EOS, 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at EOS, 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at EOS and 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from BL to EOS. The seven subjects who failed to meet the primary endpoint did not fare any better or worse by EOS than those who achieved the primary endpoint in this study.

Resistance analyses were performed on samples collected from 10 subjects who failed treatment with ibalizumab + OBR, and the predominant ibalizumab resistance pathway was associated with altered potential N-link glycosylation sites (PNGS) in the V5 loop of the HIV-1 envelope. Experiments performed during nonclinical development combined with susceptibility testing performed before and after treatment in TMB-301 indicated that the emergence of ibalizumab resistance did not have an impact on the antiviral activity of the CCR5 co-receptor antagonist, maraviroc, or with the gp41 fusion inhibitor, enfuvirtide.

Additional resistance data for TMB-202 and TMB-301 were reviewed under this addendum review, and an accounting of labeling changes was made. Overall the data reviewed provided additional support for approval of ibalizumab; however, two additional PMRs will be required of the sponsor to better characterize potential resistance pathways for ibalizumab.

This original BLA is approvable from a Clinical Virology perspective, pending final agreement on the prescribing information. The information reviewed in this addendum BLA review was supportive of the approval of ibalizumab.

Additional Recommended PMRs:

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.
2. Please provide integrated virology datasets for studies TMB-202 and TMB-301 to include all baseline sequences in one database for both studies, and at time of failure for all 35 subjects who failed and were examined for resistance in TMB-202.

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8. PRESCRIBING INFORMATION (LABEL)

8.1 Proposed Prescribing Information (with initial Reviewer-recommended changes)

The sponsor and Clinical Virology have reached agreement on the label for sections related to Clinical Virology (see Section 8.2).

8.2 Agreed Upon Prescribing Information (clean)

INDICATIONS AND USAGE

TROGARZO, a CD4 directed post-attachment HIV-1 inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen. (1)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibalizumab-uiyk is an HIV-1 antiretroviral drug [see *Microbiology (12.4)*].

12.4 Microbiology

Mechanism of Action

Ibalizumab-uiyk, a recombinant humanized monoclonal antibody, blocks HIV-1 from infecting CD4⁺ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

Ibalizumab-xxxx Does Not Impact CD4 Function

The binding specificity of ibalizumab-uiyk to domain 2 of CD4 allows ibalizumab-uiyk to block viral entry into host cells without causing immunosuppression. Epitope mapping studies indicate that ibalizumab-uiyk binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and therefore does not interfere with CD4-mediated immune functions. Additionally, ibalizumab-uiyk does not interfere with gp120 attachment to CD4.

Antiviral Activity

Ibalizumab-uiyk inhibits the replication of CCR5- and CXCR4-tropic laboratory strains and primary isolates of HIV-1 in phytohemagglutinin stimulated peripheral blood lymphocytes. The median EC₅₀ value (50% effective concentration) for ibalizumab-uiyk against HIV-1 group M isolates (subtypes A, B, C, D, E, or O) was 8 ng/mL (n = 15, range of 0.4 to 600 ng/mL) in cell culture, with lower susceptibility observed in macrophage-tropic HIV-1 strains (BaL, JR-CSF, YU2, and ADA-M). In a single-cycle infection assay, ibalizumab-uiyk inhibited 17 clinical isolates of subtype B with a median EC₅₀ value of 12 ng/mL (range of 8.8 to 16.9 ng/mL; mean 12 ± 3 ng/mL) and a median maximum percentage inhibition (MPI) of 97% (range of 89 to 99%; mean 97 ± 3%). Three CCR5-tropic clinical isolates from subtypes B, C, and D, were inhibited with EC₅₀ values ranging from 59-66 ng/mL and 3 CXCR4-tropic clinical isolates from subtypes B, C, and D, with EC₅₀ values ranging from 44-59 ng/mL.

Antiviral Activity in Combination with Other Antiviral Agents

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No antagonism was observed when PBMCs or MAGI-CCR5 cells infected with the subtype B Ba-L or ADA variants of HIV-1 were incubated with ibalizumab-uiyk in combination with the CCR5 co-receptor antagonist maraviroc or when PBMCs infected with the subtype B HT/92/599 variant of HIV-1 were incubated with ibalizumab-uiyk in combination with the gp41 fusion inhibitor enfuvirtide; a nonnucleoside reverse transcriptase inhibitor (efavirenz); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, tenofovir, or zidovudine); or a protease inhibitor (atazanavir).

Antiviral Activity in Antiretroviral-Resistant Virus

Subjects enrolled in TMB-301 were heavily treatment-experienced subjects infected with multidrug resistant HIV-1. Ibalizumab-uiyk inhibited 38 baseline isolates at a median EC₅₀ value of 31 ng/mL (range of 13 to 212 ng/mL; mean 39 ± 35 ng/mL) with a median MPI of 97% (range of 41-100%; mean 91 ± 14%). For 10 subjects in TMB-301 who failed treatment, at the time of failure the median ibalizumab-uiyk EC₅₀ value was 566 ng/mL (range of 148 to >54,900 ng/mL; mean 11,768±21,650 ng/mL) representing an EC₅₀ value shift of >18-fold. For the HIV-1 derived from the same subjects, the median MPI was 55% (range of 43-72%; mean 56 ± 8%) representing a 42 percentage point reduction.

Decreased Susceptibility

Decreased susceptibility to ibalizumab-uiyk, as defined by a decrease in MPI, has been observed in some subjects experiencing virologic failure and may be associated with genotypic changes in the HIV-1 envelope coding sequence that results in the loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120. The clinical significance of decreased susceptibility to ibalizumab-uiyk has not been established.

Cross-Resistance

Phenotypic and genotypic test results revealed no evidence of cross-resistance between ibalizumab-uiyk and any of the approved classes of anti-retroviral drugs (CCR5 co-receptor antagonists, gp41 fusion inhibitors, integrase strand transfer inhibitors [INSTIs], non-nucleos(t)ide reverse transcriptase inhibitors [NNRTIs], nucleos(t)ide reverse transcriptase inhibitors [NRTIs], or protease inhibitors [PIs]). Ibalizumab-uiyk is active against HIV-1 resistant to all approved antiretroviral agents and exhibits antiretroviral activity against R5-tropic, X4-tropic, and dual-tropic HIV-1.

Decreased susceptibility to ibalizumab-uiyk following multiple dose administrations of ibalizumab-uiyk has been observed in some subjects. Cell culture studies performed with HIV-1 variants with reduced susceptibility to ibalizumab-uiyk indicate that phenotypic changes associated with resistance to ibalizumab-uiyk do not alter susceptibility to other approved agents and do not result in the selection of CD4-independent viral isolates.

CD4 Polymorphisms and Ibalizumab-xxxx Activity

CD4 polymorphisms reported in public databases were analyzed to determine if any naturally occurring amino acid substitutions in the CD4 molecule from different human populations would potentially impact the antiviral activity of ibalizumab-xxxx. None of the known CD4 polymorphisms are likely to have an impact on ibalizumab-xxxx binding to CD4.

8.3 Final Approved Package Insert

Due to the timing of NDA milestones and PDUFA goal deadlines, the final approved package insert was not available at the time of finalization of this review.

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9. RECOMMENDATIONS

This reviewer recommends the following post-marketing commitments or requirements (as appropriate):

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: S143P, K171E, N186K/S/R, Q308H/P, G352K/E, and V547A/G.
2. Please provide integrated virology datasets for studies TMB-202 and TMB-301 to include all baseline sequences in one database for both studies, and at time of failure for all 35 subjects who failed and were examined for resistance in TMB-202.

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/s/

ERIC F DONALDSON
01/22/2018

JULIAN J O REAR
01/22/2018

**DIVISION OF ANTIVIRAL PRODUCTS
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Clinical Virology Reviewer: Eric F. Donaldson, Ph.D.

BLA#: 761065 SDN 000 (Original BLA)
Reviewer Name(s): Eric F. Donaldson, Ph.D.

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Correspondence Date: 5/3/2017
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Review Complete Date: 10/03/2017
PDUFA Date: 1/3/2018

Proprietary Name (Proposed): TROGARZO
Drug Names: ibalizumab, TNX-355, Hu5A8, Mu5A8, TMB-355
Drug Class: CD4 post-attachment HIV-1 inhibitor
Parent IND #: [IND009776](#)

Ibalizumab heavy chain primary structure (IgG4)

QVQLQQSGPEVVKPGASVKMSCKASGYTFTSYVIHWVRQKPGQGLDWIGYINPYNDGTDYDEKFKGKATLTSDTSTSTAYM
ELSSLRSEDTAVYYCAREKDNATGAWFAYWGQGLTIVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTKYTCNVDPKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVF
LFPPPKKDTLMISRTPEVTCVVDVDSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKLSLSLGLK

Ibalizumab light chain primary structure (κ)

DIVMTQSPDLSAVSLGERVTMNCKSSQSLLYSTNQKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFSGSGSGTDFTLTI
SSVQAEDVAVYYCQQYYSYRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKSTYLSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Amendments: none

Related/Supporting Documents: This BLA was submitted as a rolling submission starting with SDN 000. Additional/updated clinical virology information was submitted to the BLA in the following SDNs: [0003](#) (proprietary name review), [0011](#) (TMB-301 Clinical Virology Study Report), [0012](#) (Original BLA), [0015](#) (TMB-301 electronic database), [0018](#) (TMB-202 and TMB-301 neutralizing antibody ligand binding testing of clinical samples), [0020](#) (response to IR regarding resistance algorithm), [0023](#) (response to Clinical Virology IR requesting define files), [0026](#) (response to Clinical Virology IRs sent on 6/5/17 and 6/20/17), and [0033](#) (response to Clinical Virology IR sent on 7/20/1966).

Dosage Form and Route of Administration: A loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks; intravenous injection

Dispensed: Rx

Proposed Indication(s): Treatment of adults infected with HIV-1 resistant to at least one agent in three different classes

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Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; CD4, cluster of differentiation 4 molecule; D2, domain 2 of CD4; DM, dual mix or dual tropic; Env, envelope protein; gp, glycoprotein; GSS, genotypic susceptibility score; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IV, intravenous; mAb, monoclonal antibody; MDR, multiple drug resistance; MHC-II, major histocompatibility complex class II; MPI, maximal percent inhibition; NGS, next generation sequencing; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NRS, non-recycled score; OBR, optimized background regimen; OSS, overall susceptibility score; PBMC, Peripheral blood mononuclear cell; PI, protease inhibitor; PNGS, potential N-linked glycosylation site; PSS, phenotypic susceptibility score; Q2W, administered once every two weeks; Q4W, administered once every 4 weeks; R5, CCR5 coreceptor; X4, CXCR4 coreceptor;

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EXECUTIVE SUMMARY

This original Biologics License Application (BLA) for ibalizumab (previously known as Mu5A8 [original mouse monoclonal antibody], Hu5A8, TNX-355, and TMB-355) is seeking approval for an indication to treat adults infected with HIV-1 which is resistant to at least one anti-retroviral drug in three different drug classes. Ibalizumab is a recombinant humanized IG4 κ monoclonal antibody (mAb) that binds to domain 2 (D2) of the human cluster of differentiation 4 (CD4) molecule. CD4, an integral, membrane glycoprotein found on the surface of immune cells, such as T helper cells, is the receptor for HIV-1. HIV-1 envelope glycoprotein 120 (gp120) interacts with CD4 domain 1 for attachment to T-cells. Upon interaction with CD4, gp120 undergoes a conformational change which opens the co-receptor binding site on gp120, allowing it to then interact with the CCR5 (R5) or CXCR4 (X4) chemokine co-receptor, which is required for fusing the viral and cell membranes to facilitate viral entry into the cell. The interaction of gp120 with CD4 domain 1 necessary for attachment is not altered by the presence of ibalizumab bound to domain 2 of CD4, but the positioning of ibalizumab on domain 2 of CD4 blocks all of the downstream steps required for membrane fusion and viral entry. Based on this mechanism of action, ibalizumab will be the first biologic agent approved for a new class of drugs that will be referred to as CD4 post-attachment HIV-1 inhibitors.

In humans, CD4 serves as a co-receptor involved with helping T cells communicate with antigen presenting cells (APCs). To initiate inter-cell signaling, major histocompatibility complex (MHC) class II (-II) molecules, normally found only on antigen-presenting cells, bind to the T cell receptor and to CD4 domain 1. Importantly, ibalizumab binding to domain 2 of CD4 occurs distal to the MHC-II binding site in domain 1, and does not appear to interrupt its ability to bind MHC-II. Known amino acid polymorphisms that have been identified in CD4 among different human populations do not occur in the region of domain 2 of CD4 that interacts with ibalizumab and therefore, are not likely to represent differences in efficacy to this drug.

Clinical trial TMB-301 was the only clinical trial that enrolled subjects who received doses of ibalizumab that were consistent with the indication being sought, and so this trial was the only pivotal clinical trial for this application. TMB-202 was used as a supportive clinical trial given that subjects in that trial received similar doses in one arm.

TMB-301, entitled *A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1*, was conducted with 40 subjects infected with HIV-1 (all were clade B with no restrictions based on tropism) with documented resistance to at least one drug in three different drug classes. The trial was designed to establish the efficacy of intravenous (IV) ibalizumab as a monotherapy during the second week of the trial, and then add-on an optimized background regimen (OBR). The study consisted of three periods: a 6 day control period (Days 0–6), an essential 6 day monotherapy period (Days 7–13), and a 23 week maintenance period (Day 14–Week 25). During the control period (Days 0–6) subjects were monitored on current failing therapy (or no therapy, if the subject had failed and discontinued treatment within the 8 weeks preceding Screening). During the essential monotherapy period (Days 7–13) subjects continued on current failing therapy, receiving one 2,000-mg dose (loading dose) of ibalizumab on Day 7. Day 7 was considered Baseline (BL) for the treatment period (Day 7–Week 25). Day 14 through Week 25 of the study represented the maintenance period. On Day 14 (primary endpoint), the OBR was initiated and was required to include at least one agent to which the subject's virus was fully susceptible (as determined at Screening, in combination with historical resistance testing). Beginning at Day 21, 800 mg of ibalizumab was administered every 2 weeks (Q2W) through Week 23.

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All subjects were to complete the Week 25/End of Study (EOS) visit and the Week 29/Follow-up visit procedures.

The sponsor reported a statistically significant number of subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from Baseline (Day 7) to Day 14 ($n=33$; 82.5%; $p<0.0001$). Other clinically meaningful reductions in viral load observed at Day 14 and Week 25 (EOS) in the intend-to-treat (ITT) population included:

- 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from Baseline (Day 7) to Week 25 (EOS)
- 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at Week 25 (EOS)
- 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at Week 25 (EOS)
- 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from Baseline (Day 7) to Week 25 (EOS)

TMB-202 was entitled “A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1” (Amended to 24 Week Study). This multicenter, randomized, double-blind study evaluated the effectiveness and safety of ibalizumab in highly treatment-experienced subjects infected with HIV-1. Subjects received one of two dose regimens: 1) 800 mg of ibalizumab every 2 weeks (Q2W) plus OBR or 2) 2,000 mg of ibalizumab every 4 weeks (Q4W) and placebo on the intervening 2-week period visit, plus OBR. The primary objectives were to evaluate effectiveness of a regimen based on the proportion of subjects achieving undetectable viral loads at Week 24 defined as <50 HIV-1 RNA copies/mL and to evaluate the safety and tolerability of two dose regimens of ibalizumab for dose selection. Secondary endpoints related to clinical virology included changes from Baseline in viral load, CD4⁺ T-cell counts, and time to loss of virologic response, HIV-1 susceptibility changes associated with ibalizumab administration in combination with an OBR, assessment of anti-ibalizumab antibodies and CD4 receptor density and occupancy. The sponsor summarized the results for TMB-202 as follows:

- viral load <50 copies/mL: 44% (26/59) for the 800 mg Q2W arm and 27.8% (15/54) for the 2,000 mg Q4W arm
- viral load <200 copies/mL: 53% (31/59) for the 800 mg Q2W arm and 43% (23/54) for the 2,000 mg Q4W arm
- viral load <400 copies/mL: 58% (34/59) for the 800 mg Q2W arm and 46% (25/54) for the 2,000 mg Q4W arm
- a $1.0 \log_{10}$ reduction in viral load: 63% (37/59) for the 800 mg Q2W arm and 59% (32/54) for the 2,000 mg Q4W arm
- a $0.5 \log_{10}$ reduction in viral load: was 68% (40/59) for the 800 mg Q2W arm and 59% (32/54) for the 2,000 mg Q4W arm.

Viral resistance to ibalizumab monitoring included collecting blood samples at timepoints before treatment, at regular intervals during treatment, and at the end of study. (b) (4) performed drug susceptibility testing at baseline and at EOS to determine that subjects met the inclusion criteria of multiple class drug resistance, and to determine which drugs to include in the OBR. Samples selected for ibalizumab resistance analysis were collected at the time of confirmed virologic failure while the subject was still on treatment with the prescribed study drug regimen. Protocol-defined virologic failure was defined as follows:

- TMB-202: two consecutive viral load measurements with $<1 \log_{10}$ reduction from Baseline
- TMB-301: two consecutive viral load measurements with $<0.5 \log_{10}$ reduction from Baseline viral load

Overall, there were totals of 25 subjects in TMB-202 and 7 in TMB-301 who experienced protocol-defined virologic failure. In addition, 5 subjects in TMB-202 and 3 in TMB-301 experienced virologic rebound or breakthrough, defined as $1 \log_{10}$ HIV-1 RNA copies/mL increase in viral load or increase from below to above 200 HIV-1 RNA copies/mL. The sponsor performed resistance analysis for 17 subjects from TMB-202 and 10 subjects in TMB-301, looking primarily at the absence or loss of a Potential N-linked Glycosylation Site (PNGS)

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in the V5 loop of HIV-1 gp120. The sponsor concluded that genotypic analysis demonstrated the absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab maximal percent inhibition (MPI). For the 10 subjects from TMB-301 who were analyzed for resistance, five started with two V5 PNGS in their HIV-1 and all of these lost one over the course of treatment. Of the remaining 5 subjects, 4 had one V5 PNGS in their HIV-1 at baseline and 1 of these subjects lost the V5 PNGS in their HIV-1 at the time of failure, and 1 subject had no V5 PNGS in their HIV-1 at baseline but had one PNGS at the time of failure. Of note, despite several requests for the sponsor to submit resistance data for the additional 13 subjects who experienced treatment failure or rebound/breakthrough in TMB-202, these data were never submitted to the IND or the BLA. Other pathways to ibalizumab resistance may therefore exist.

Given that ibalizumab exhibited a low barrier to resistance during nonclinical development and in clinical trials that explored the use of ibalizumab as a monotherapy, it appears that ibalizumab rapidly selects for variants of HIV-1 that are less susceptible to this drug, and therefore, this drug should not be used as a monotherapy.

In conclusion, ibalizumab administered in clinical trial TMB-301 at a loading dose of 2,000 mg followed with 800 mg Q2W resulted in a statistically significant number of subjects achieving $\geq 0.5 \log_{10}$ reduction in HIV-1 RNA copies/mL from BL (Day 7) to Day 13 ($n=33$; 82.5%; $p<0.0001$) during the essential monotherapy treatment phase. When ibalizumab was combined with an OBR, 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from BL to EOS, 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at EOS, 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at EOS and 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from BL to EOS. The seven subjects who failed to meet the primary endpoint did not fare any better or worse by EOS than those who achieved the primary endpoint in this study indicating that the OBR drove the response. Resistance analyses were performed on samples collected from 10 subjects who failed treatment with ibalizumab + OBR, and the predominant ibalizumab resistance pathway was associated with altered PNGSs in the V5 loop of the HIV-1 envelope. Experiments performed during nonclinical development combined with susceptibility testing performed before and after treatment in TMB-301 indicated that the emergence of ibalizumab resistance did not have an impact on the antiviral activity of the CCR5 co-receptor antagonist, maraviroc, or with the gp41 fusion inhibitor, enfuvirtide. Antiviral activity assessments performed with clinical isolates support ibalizumab activity against clade B HIV-1. In addition, ibalizumab is active against R5-tropic, dual-tropic, and X4-tropic HIV-1. Mechanism of action studies supported the class designation for this drug as a CD4 post-attachment HIV-1 inhibitor.

1. RECOMMENDATIONS

1.1 Recommendation and Conclusion on Approvability

This original BLA for ibalizumab (previously known as Mu5A8 [original mouse monoclonal antibody], Hu5A8, TNX-355, and TMB-355) is approvable from the Clinical Virology perspective for the treatment of HIV-1 infection in HIV-1 in heavily treatment-experienced adults with multidrug resistant HIV-1 infection and limited treatment options.

1.2 Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

This reviewer recommends the following post-marketing commitments or requirements (as appropriate):

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.
2. Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment to better characterize the HIV-1 gp120 sequence at the time of failure. (We note that the Sanger sequencing data contained a lot of positions that could not be adequately called.)

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2. SUMMARY OF OND VIROLOGY ASSESSMENTS

2.1 Nonclinical Virology

Ibalizumab is a recombinant, humanized IgG isotype 4 κ light chain monoclonal antibody that binds to domain 2 of CD4 and functions as a CD4 post-attachment inhibitor of HIV-1. Ibalizumab blocks the post-CD4-receptor-attachment steps required for viral and cellular membrane fusion leading to entry into CD4⁺ T cells. Cell culture antiviral activity was seen against all clades of HIV-1, regardless of co-receptor tropism (R5, X4, and dual tropic or dual mixed, abbreviated DM). The EC₅₀ values against Clade A, B, C, D, CRF01_AE, CRF_AG, G, AC, ACD, BC, and CD HIV-1 envelope pseudotypes ranged from 0.02 to 0.23 $\mu\text{g/mL}$. Among 82 clinical isolates obtained from a phase 2 study, ibalizumab exhibited antiviral activity with a median EC₅₀ value of 0.08 $\mu\text{g/mL}$ (range 0.02-0.16 $\mu\text{g/mL}$; n=43) against R5-tropic HIV-1, an EC₅₀ value of 0.11 $\mu\text{g/mL}$ against one R4-tropic virus, and a median EC₅₀ value of 0.08 $\mu\text{g/mL}$ (range 0.01-0.14 $\mu\text{g/mL}$; n=33) against DM-tropic HIV-1 assessed in R5 cells and a median EC₅₀ value of 0.09 $\mu\text{g/mL}$ (range 0.07-0.23 $\mu\text{g/mL}$; n=29) against DM-tropic HIV-1 assessed in X4 expressing cells. No antagonism was observed when ibalizumab was combined with approved HIV-1 drugs at concentrations spanning the EC₅₀ value of both drugs, including against the CCR5 co-receptor antagonist, maraviroc, and the gp41 fusion inhibitor, enfuvirtide.

Ibalizumab resistance was first observed in studies conducted in nonhuman primates infected with SIV that were treated with hu5A8. In those studies, it was shown that a 10-fold EC₅₀ value increase in ibalizumab susceptibility, as measured by quantification of SIV Gag p27, was observed after 17 days on ibalizumab; however, the viruses from this study were not characterized genotypically. Further cell culture characterization of ibalizumab resistance was performed in an experiment comparing 116 HIV-1 envelope sequences that were assessed for ibalizumab susceptibility using an HIV-1 envelope sequence pseudotype assay. Genotypic characterization of HIV-1 envelope sequences that were less susceptible to ibalizumab indicated that changes in the V5 loop that altered PNGSs were associated with lower ibalizumab susceptibility. HIV-1 envelope sequences with no PNGSs in the V5 loop were the least susceptible to ibalizumab with a median MPI <50% (n=4, MPI 37.2 \pm 16%, $P < 0.001$). HIV-1 envelope sequences with one V5 PNGS were less susceptible to ibalizumab compared with those with 2 V5 PNGS (n=59, MPI 77.8 \pm 18.3% vs n=51, 89.2 \pm 12.5%, $P = 0.001$). HIV-1 envelope sequences with one N-terminal V5 PNGS had higher MPIs compared with viruses with a central or C-terminal V5 PNGS (n=29, MPI of 83.4% \pm 18.3% vs n=30, MPI of 72.4% \pm 16.8%, $P = 0.02$). Changes to the V5 loop did not have an impact on CD4 receptor usage or the antiviral activity of the CCR5 co-receptor antagonist, maraviroc, or the gp41 fusion inhibitor, enfuvirtide.

2.2 Clinical Virology

Clinical Trial TMB-301

The approval of ibalizumab was based predominantly upon the results from clinical trial TMB-301, as this was the only clinical trial that assessed the dose approved for the indication. TMB-301 was conducted with 40 subjects infected with HIV-1 with documented resistance to at least one drug in three different drug classes. The study design was for treatment-experienced subjects infected with multi-drug resistant HIV-1 to receive a 2,000 mg loading dose of ibalizumab at Day 7 (Baseline) in combination with their failing regimen followed by 800 mg doses of ibalizumab every other week in combination with OBR starting at Day 14. The trial was designed to establish the efficacy of ibalizumab as a monotherapy during the first week of the trial, and then add-on an optimized background regimen. Here are the stages of this trial:

- During Days 0 through 6 subjects were monitored on current failing therapy (or no therapy) as a comparator to assess efficacy.
- Day 7-13 (functional monotherapy period). During Days 7 through 13 subjects continued on current failing therapy and received one 2,000 mg dose (loading dose) of ibalizumab on Day 7. Day 7 is Baseline for the treatment period (Day 7-Week 25).
- Day 14-Week 25 (maintenance period). On Day 14 (primary endpoint), the optimized background regimen was initiated and was to include at least one agent to which the subject's virus was fully

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susceptible. Beginning at Day 21, 800 mg of ibalizumab was administered every 2 weeks through Week 23.

- All subjects were to complete the Week 25/EOS visit and the Week 29/Follow-up visit procedures.

A statistically significant number of subjects achieved the primary endpoint for this study, which was a ≥ 0.5 \log_{10} reduction in viral load from Baseline (Day 7) to Day 14 (n=33; 82.5%; p<0.0001). Other clinically meaningful reductions in viral load observed at Day 14 and Week 25 (EOS) in the ITT population included:

- 25 (62.5%) subjects achieved ≥ 0.5 \log_{10} reduction in viral load from Baseline (Day 7) to Week 25 (EOS)
- 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at Week 25 (EOS)
- 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at Week 25 (EOS)
- 22 (55%) subjects achieved ≥ 1.0 \log_{10} reduction in viral load from Baseline (Day 7) to Week 25 (EOS)

Virologic failure was defined as 2 consecutive viral load measurements of less than a 0.5 \log_{10} decline from the baseline viral load beginning at Day 14. Five subjects did not have a robust response to ibalizumab monotherapy, including subjects 04-001, 05-001, 05-003, 17-003, and 27-001. Two additional subjects only achieved a 0.3 \log_{10} reduction during ibalizumab monotherapy and these subjects were 08-001 and 21-002. However, despite the poor response during the monotherapy phase of this clinical trial, overall, these subjects fared equal to or better than other subjects in this trial when comparing secondary endpoints indicating that the OBR drove response in these subjects.

The durability of ibalizumab was difficult to assess directly because of the addition of an OBR that was added-on after 1 week of essential monotherapy with ibalizumab. However, comparing the secondary endpoint of percent of subjects with <50 HIV-1 RNA copies/mL at the end of the study, which was 42.5%, to the same endpoint that was the primary endpoint at the end of ibalizumab monotherapy and was reached by 82.5% of subjects, it is clear that ibalizumab (and probably other drugs in the OBR) was not durable in this population. In addition, given that ibalizumab exhibited a low barrier to resistance during nonclinical development and in clinical trials that explored the use of ibalizumab as a monotherapy, it appears that ibalizumab rapidly selects for variants of HIV-1 that are less susceptible to this drug, and therefore, this drug should not be used as a monotherapy. Resistance to ibalizumab was analyzed for 10 subjects who failed treatment with ibalizumab and in general, these subjects exhibited changes in the V5 loop region that altered PNGSs consistent with results observed previously.

In addition, to data reviewed from TMB-301, clinical virology data from clinical trial TMB-202 were also analyzed as part of this approval for ibalizumab, and the data collected in that clinical trial supported the approval.

3. ADMINISTRATIVE

3.1 Reviewer's Signature

Eric F. Donaldson, Ph.D.
Clinical Virology Reviewer, Division of Antiviral Products

3.2 Concurrence

Julian J. O'Rear, Ph.D.
Clinical Virology Team Leader, Division of Antiviral Products

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OND CLINICAL VIROLOGY REVIEW

1. INTRODUCTION AND BACKGROUND

Ibalizumab targets the human CD4 protein necessary for HIV-1 replication. CD4 is an integral membrane glycoprotein found on the surface of T cells and other immune cells, and it functions as a receptor for HIV-1. HIV-1 envelope gp120 interacts with CD4 domain 1 for attachment to T-cells. Upon interaction with CD4, gp120 undergoes a conformational change which opens the co-receptor binding site on gp120, allowing it to then interact with the CCR5 or CXCR4 co-receptor, which is required for fusing the viral and cell membranes to facilitate viral entry into the cell. Ibalizumab binds to CD4 domain 2 and blocks post attachment steps that are necessary for viral and cell membrane fusion and viral entry.

The CD4 glycoprotein found on the surface of immune cells where it serves as a co-receptor involved with helping T cells communicate with APCs. To initiate inter-cell signaling, MHC-II molecules, normally found only on APCs, bind to the T cell receptor and to CD4 domain 1. Ibalizumab binds to domain 2 of CD4 distal to the MHC-II binding site in domain 1, and does not appear to interrupt its ability to bind MHC-II. In addition, the interaction of gp120 with CD4 domain 1 is not altered by the presence of ibalizumab bound to domain 2 of CD4.

Ibalizumab was first reported in a 1992 paper that detailed the early characterization of a murine mAb that was originally named 5A8, and was generated in BALB/c mice ([Burkly et al., 1992](#)). A humanized version of 5A8 was described in 1997 with the goal of generating a mAb that could be studied in nonhuman primates without generating a strong anti-mouse IgG response ([Reimann et al., 1997](#)). Ibalizumab development was originally initiated by Tanox, Inc. with an IND submitted to the Center for Biologics Evaluation and Research in 2001 but the company was acquired by Genentech in 2006, and subsequently, the patent for ibalizumab was sold to TaiMed Biologics in 2007.

1.1 Important Milestones in Product Development

- Ibalizumab was discovered in 1992 when it was generated in a BALB/c mouse injected with soluble CD4.
- Ibalizumab was humanized in 1997 to allow for studies in nonhuman primates
- First IND submission date was April 17, 2001 to the Center for Biologics Evaluation and Research
- The IND was granted Fast Track status in 2003
- IND was transferred to CDER in 2005
- In 2014 the IND was granted Orphan Drug status
- In 2015, the ibalizumab IND was granted Breakthrough Therapy Designation for i.v. infusion dosage

1.2 Methodology Used for TMB-301

Baseline Resistance Testing and Tropism

Most subjects underwent genotypic and phenotypic testing to determine baseline resistance to all classes of approved HIV-1 drugs, including INSTIs, NNRTIs, NRTIs, PIs, and the CCR5 co-receptor antagonist, maraviroc, and the gp41 fusion inhibitor, enfuvirtide, and phenotypic testing to determine tropism before and after treatment with ibalizumab. For subjects who did not have this testing performed, historical data were used. Viral resistance testing was performed by (b) (4) to determine susceptibility to ibalizumab and all approved ARV agents using the following assays:

1. **The PhenoSense GT assay** was used to measure susceptibility to NNRTIs, NRTIs, and PIs and evaluate genotypic changes associated with resistance to these agents.
2. **The PhenoSense Integrase assay** was used to measure susceptibility to INSTIs

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3. **The GeneSeq Integrase assay** was used to evaluate genotypic changes associated with INSTI resistance
4. **The Trofile assay** was used for phenotypic assessment of co-receptor tropism to determine the potential for susceptibility to maraviroc
5. **The PhenoSense HIV Entry assay** was used to measure phenotypic susceptibility to ibalizumab, maraviroc, and enfuvirtide

OSS Algorithm

- **GSS** - Score '1' if virus from a subject is "sensitive" in the Geneseq assessment and '0' if it is "partial" or "resistant".
- **PSS** - Score '1' if virus from a subject is "sensitive" in the Phenosense assessment and 0 if it is "partial" or "resistant".
- **OSS** - If GSS=1 and PSS=1 then OSS=1 otherwise OSS=0.
- **INSTIs, NNRTIs, NRTIs, and PIs** – Scored using Phenosense and Geneseq assessments.
- **Entry inhibitors:** Score '1' for enfuvirtide if virus from subject is 'Sensitive' in HIV Entry report Enfuvirtide Assessment; Score '1' for maraviroc if virus from subject is only CCR5-tropic in the HIV Trofile report; all else score '0'.
- **Investigational agent (fostemsavir):** Score '1' for fostemsavir if no prior experience. Score '0' for fostemsavir if historical resistance testing reveals an EC₅₀ value ≥10 nM in HIV Entry report from

(b) (4)

Drugs Assessed for Baseline Resistance

Table 1. HIV-1 drugs and classes evaluated for resistance assessments (DAVP analysis).

HIV-1 Drugs and Classes	
<p>Co-receptor Antagonist Maraviroc (MVC, Selzentry)</p> <p>gp41 fusion inhibitor Enfuvirtide (ENF, Fuzeon)</p> <p>INSTI Dolutegravir (DTG, Tivicay) Elvitegravir (EVG, Vitekta) Raltegravir (RAL, Isentress)</p> <p>Investigational Fostemsavir (BMS-663068) Ibalizumab</p> <p>NNRTI Delavirdine (DLV, Rescriptor) Efavirenz (EFV, Sustiva) Etravirine (ETV, Intelence) Nevirapine (NVP, Viramune) Rilpivirine (RPV, Edurant)</p>	<p>NRTI Abacavir (ABC, Ziagen) Azidothymidine (AZT) Didanosine (ddI, Videx) Emtricitabine (FTC, Emtriva) Lamivudine (3TC, Epivir) Stavudine (d4T, Zerit) Tenofovir AF (TAF, part of Genvoya) Tenofovir DF (TDF, Viread, part of Stribild) Zalcitabine (ddC, Hivid) Zidovudine (ZDV, Retrovir)</p> <p>PI Atazanavir (ATV, Reyataz) Darunavir (DRV, Prezista) Fosamprenavir (FPV, fAPV, fAMP; Lexiva) Indinavir (IDV, Crixivan) Lopinavir/ritonavir (LPVr, Kaletra) Nelfinavir (NFV, Viracept) Saquinavir (SQV, Invirase) Tipranavir (TPV, Aptivus)</p>

HIV-1 RNA Assessments (Viral Load)

HIV-1 RNA levels in serum collected from subjects were measured using the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test version 2.0 to quantify HIV-1 RNA over the range of 20-10,000,000 copies/mL. HIV-1 RNA values <20 were reported as either "Target detected" or "Target not detected".

Ibalizumab Resistance Testing by Next Generation Sequencing

HIV-1 envelope gp160 sequences were determined for subject isolates using next generation sequencing (NGS) methods as performed by (b) (4). Briefly, the entire envelope gene was determined for each envelope-expression library using standard dideoxynucleotide

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triphosphate chain terminator chemistry. Sixteen proprietary primers were used to generate sequence spanning the entire gp160 region. Plasmids containing the subject-derived HIV-1 gp160 gene were purified and DNA concentrations were normalized (AxyPrep Mag PCR Normalizer Kit, Corning). Sequence-ready libraries were prepared for NGS using the Illumina Nextera XT library preparation process and sequenced at a targeted coverage of 5000x, with a minimum allowed coverage of 1000x (although exceptions were permitted on a case-by-case basis for regions of low coverage). Library preparation was performed using the Nextera XT system and the resulting libraries were subjected to 2x250 bp MiSeq sequencing (Illumina; v2 chemistry). Sequence reads were quality trimmed such that both ends of reads were trimmed until the quality scores of 5 consecutive terminal nucleotides were ≥ 25 ; low quality reads and reads less than 50 nucleotides in length were discarded, and reads > 150 nucleotides in length were trimmed to 150 nucleotides. The trimmed MiSeq reads were aligned to a reference and a de novo consensus sequence using Bowtie 2. Variants were determined based on the reads that aligned to the de novo sample-specific env reference sequence and the results were tabulated in a codon-by-codon manner. An average Phred quality score ≥ 30 was required to report a codon variant. Codon variants present at $> 10\%$ frequency were reported for each amino acid position in gp160. Of note, the raw NGS data for the entire envelope sequence was not provided in the BLA, only segments of the sequence that contained the V5 loop were provided.

Protocol Defined Treatment Failure for TMB-301

Protocol-defined virologic failure was defined as:

- Two consecutive viral load measurements with $< 1 \log_{10}$ reduction from Baseline
- Viral load rebound was defined as a viral load rebound $\geq 1 \log_{10}$ from nadir without virologic failure

1.3 Prior FDA Virology reviews

This is the original NDA submission and initial Clinical Virology review of BLA 761065 for ibalizumab. Previous Clinical Virology reviews of the individual IND 009776 were conducted by Dr. Jules O'Rear, Ph.D. and Dr. Damon Deming, Ph.D. Since 2012, the IND and BLA have primarily been reviewed by Dr. Eric Donaldson, Ph.D.

1.4 Major Virology Issues that Arose during Product Development

Ibalizumab development spanned nearly two decades and was performed by three different companies. These transfers made it difficult for TaiMed to acquire some of the early study reports that were required for the BLA submission. Additionally, the original IND was reviewed by CBER prior to its transfer to CDER in 2005 and therefore initial reviews were not readily available. Because of this history, some areas of the IND review process were not fully understood at the time the BLA was submitted.

CD4 polymorphisms

Given that ibalizumab binds to the CD4 molecule on T cells, Clinical Virology requested that the sponsor conduct a bioinformatics study looking at naturally occurring polymorphisms in the CD4 of different races and ethnic groups to see if any CD4 polymorphisms mapped to the CD4-ibalizumab binding site. Polymorphisms in the binding site would potentially prevent the binding of ibalizumab to CD4 and a subpopulation that had this polymorphism could be less susceptible to ibalizumab treatment.

Ibalizumab resistance

The development of resistance to ibalizumab was noticed early in its development, but the study reports describing the experiments performed to characterize ibalizumab resistance were not available to DAVP reviewers until the BLA submission. Therefore, discussions regarding the development of resistance were ongoing, and it was not until the BLA was submitted that the full story on ibalizumab resistance was understood. Because of this, there will be a couple of post-marketing actions geared toward better understanding the mechanism of ibalizumab resistance.

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Clinical trial populations

Ibalizumab was developed for the highly treatment-experienced HIV-1 population based on several factors:

1. The mechanism of action of ibalizumab was found to target a highly conserved host protein (CD4) to prevent HIV-1 interaction with its co-receptor; a step that is essential for HIV-1 entry into host cells. This blockage would allow the drug to potentially have activity against all HIV-1 isolates;
2. The relatively long half-life of ibalizumab (3 to 3.5 days) compared to other antiretroviral drugs indicated that the drug could be dosed less frequently, making it easier for patients to comply with the appropriate treatment regimens;
3. The studied route of administration was as an IV infusion, which would provide a means for better managing adherence; and
4. Cross-resistance was unlikely since ibalizumab was a novel drug with a novel target, meaning that it could be combined with other HIV-1 drugs as part of a highly active ant-retroviral combination regimen.

1.5 State of Antivirals Used for the Indication(s) Sought

Ibalizumab (previously known as Mu5A8, Hu5A8, TNX-355, and TMB-355) is seeking approval with an indication for the treatment of adults infected with HIV-1 which is resistant to at least one anti-retroviral drug in three different drug classes. This patient population is typically defined as one of the following: highly treatment-experienced (HTE), multiple drug resistant (MDR), or the HIV salvage population. While there are currently 6 classes of approved drugs to treat HIV-1 infection (INSTIs, NNRTIs, NRTIs, PIs, gp41 fusion inhibitors, and CCR5 co-receptor antagonists), construction of an effective regimen for some of these patients can be difficult due to loss of classes from resistance, tropism change, and intolerance.

The emergence of MDR HIV-1 has been attributed to a number of factors, including but not limited to, poor patient adherence, transmission of resistant HIV-1, and exposure to suboptimal HIV regimens due to interactions with other medications, food, or dietary supplements. Ibalizumab has two advantages for this population. First, it is administered by intravenous injection (IV) starting with a loading dose of 2,000 mg at initiation of treatment and followed with 800 mg doses every two weeks. It is believed that this dosing regimen will likely help with adherence. Second, ibalizumab utilizes a novel target and therefore, resistance that develops against ibalizumab is not likely to impact other approved HIV-1 drugs.

The FDA granted Breakthrough Therapy and Orphan Drug designation for ibalizumab based largely on the fact that this drug will be the first licensed biologic or drug indicated for patients with MDR HIV-1.

2. NONCLINICAL VIROLOGY

2.1 Introduction

Overview of CD4 and MHC-II signaling

CD4 is an integral membrane glycoprotein with four protein structural domains exposed on the surface of T cells, monocytes, macrophages, and dendritic cells. One of the primary functions of CD4 is to serve as a co-receptor for the interaction of APCs presenting antigens with T cells to initiate signaling with professional APCs to recruit immune cells, such as T helper cells and CD8 killer cells that are part of the adaptive immune response. To initiate inter-cell signaling, MHC-II molecules, normally found only on APCs, bind to the T cell receptor and to the CD4 co-receptor, with binding occurring in domain 1 of CD4, which is the domain of the protein most distal to the cell membrane (Figure 1).

In humans, the CD4 protein is encoded by the *CD4* gene, and naturally occurring polymorphisms in this gene have been associated with interferon-dependent diabetes mellitus ([Ghabanbasani et al., 1994](#)), susceptibility to HIV-1 infection ([Lu et al., 2015](#); [Choi et al., 2012](#); [Choi et al., 2010](#)), and potentially have an impact on HIV-2 viral load and CD4⁺ T cell counts ([Wang et al., 2011](#)). [CD4 knockout mice](#) have a defective CD4 gene that

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leads to a CD4 deficiency and these animals exhibit a deficit in helper T cell activity and a reduction in other T cell responses. A similar immunodeficiency is seen in humans with advanced AIDS who have very low CD4⁺ T cell counts as a result of the virus killing these cells.

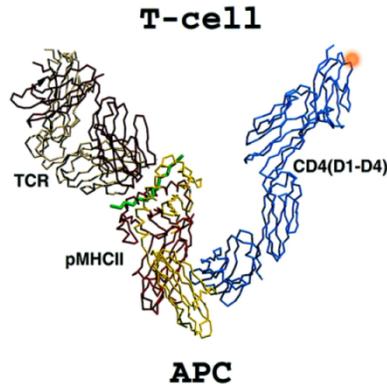


Figure 1: CD4 and T cell receptor binding to MHC-II on an APC ([Wang et al., 2001](#)).

There are at least two concerns associated with drugs that target CD4 molecules: 1) drugs that bind to CD4 could potentially block the MHC-II epitope, preventing signaling required to recruit the adaptive immune response; and 2) drugs that bind to CD4 might be unable to bind to specific human subpopulations that carry polymorphism in the *CD4* gene.

Ibalizumab binds to domain 2 of CD4 distal to the MHC-II binding site in domain 1, and does not appear to interrupt its ability to bind MHC-II. In addition, the interaction of gp120 with CD4 domain 1 is not altered by the presence of ibalizumab bound to domain 2 of CD4, but the positioning of ibalizumab on domain 2 of CD4 blocks all of the downstream steps required for viral and cellular membrane fusion and viral entry.

HIV-1 background

The human immunodeficiency virus (HIV) is a member of the *genus Lentivirus* and part of the family *Retroviridae*. Two types of HIV have been characterized: HIV-1 and HIV-2, and almost all of the cases of HIV infection in the United States are a result of infection with HIV-1. HIV-1 exhibits very high genetic variability which is driven by two factors: 1) high fecundity, which allows the virus to replicate about 10^{10} virions every day, and 2) low fidelity, due to an error prone reverse transcriptase with a high mutation rate of approximately 1.5×10^{-5} mutations per base per cycle of replication ([Abram et al., 2010](#)). There are three groups of HIV-1 that have been identified based on differences in the envelope (*env*) region and these are known as M, N, and O. Group M is the most prevalent HIV-1 group and it is further subdivided into eight subtypes (or clades), based on the whole genome sequence similarity. The most prevalent HIV-1 in the US is Group M, subtype B which is found mainly in North America and Europe.

According to the UNAIDS Organization, in 2016 there were 36.7 million people around the globe who were living with HIV-1 infection, with only 19.5 million of those infected having access to antiretroviral therapy ([UNAIDS website](#)). An additional 1.8 million people became infected in 2016, and 1 million of those suffering with HIV-1 infection died from the disease in 2016. To date, 76.1 million people have been infected with HIV-1 over the course of the AIDS epidemic and 35 million have died.

Treatment with antiretroviral therapy (ART) has allowed many of those infected with HIV-1 in the US to survive the infection and live reasonably normal lives; however, with long-term treatment there is a risk for the development of resistance to the drugs in a treatment regimen. In fact, there has been an association observed between long-term ART and the development of drug resistance, but as drugs have improved, more drugs from different classes have become available, and combination treatment regimens have become easier to tolerate this trend has decreased.

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HIV-1 life cycle

There are seven stages to the HIV-1 life cycle and these include:

1. **Viral Attachment** – The gp120 protein of the HIV-1 virus attaches to the CD4 receptor on a T cell, which causes a conformational change in gp120 allowing it to interact with the CCR5 or CXCR4 co-receptor.
2. **Fusion** – Interaction of gp120 with CD4 and the co-receptor triggers the Fusion Peptide to insert into the cell membrane, which leads to a Hairpin Formation and fusion of cellular and viral membranes releasing the viral ribonucleocapsid complex into the cytoplasm (Figure 2).
3. **Reverse Transcription** – During this stage the positive sense, single-stranded, linear viral RNA genome is reverse transcribed into DNA. Reverse transcription occurs while the RNA is in the viral capsid, which is transported to the nucleus.
4. **Integration** – Once inside the nucleus, the newly formed linear, double-stranded viral DNA is integrated into the host genome by a viral encoded integrase protein (that was packaged in the virion) resulting in the formation of the provirus.
5. **Replication** – Viral replication is driven by a viral promoter that expresses the provirus, generating mRNAs for the viral proteins necessary for replication, including the protease, reverse transcriptase, integrase, the viral structural proteins, and the viral genomic RNA required for HIV-1 particle formation.
6. **Assembly** – Viral Gag polyproteins containing the nucleocapsid proteins, protease, reverse transcriptase, and integrase, assemble with the HIV-1 RNA genome at the cellular membrane.
7. **Budding** – Immature, noninfectious viral particles bud through the cellular membrane, which contains the viral envelope glycoproteins, to form viral particles. The Gag polyprotein in immature viral particles is cleaved by the viral protease and rearranges to form the mature infectious virion.

HIV-1 viral attachment

The gp120 protein of the HIV-1 virus attaches to the CD4 receptor on a T cell, which causes a conformational change in gp120, opening up the co-receptor binding site and allowing it to interact with the CCR5 or CXCR4 co-receptor. Ibalizumab binds to the HIV-1 CD4 receptor on the host cell, which does not prevent binding of CD4 to gp120 or presumably co-receptor site exposure, but apparently prevents co-receptor interaction and the triggering of fusion (Figure 2).

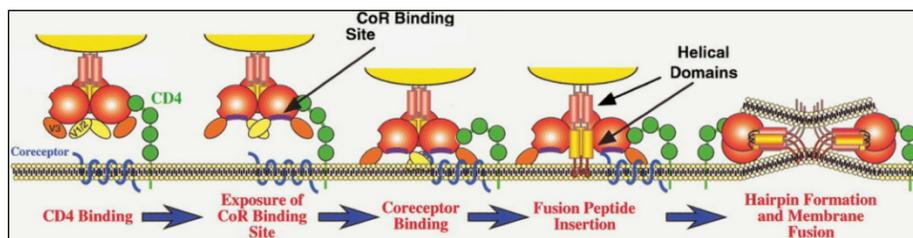


Figure 2: HIV-1 entry overview (from [Stuart's Science Blog](#)).

HIV-1 tropism

HIV-1 tropism is defined by the cell type the virus can infect and within which the virus can replicate. HIV-1 can infect several cells that express the CD4 receptor on the cell surface, including T cells and macrophages, and one of two chemokine co-receptors. The beta-chemokine receptor CCR5 is used by nearly all primary HIV-1 isolates regardless of subtype, and HIV-1 that infects cells with the CCR5 co-receptor are known as R5-tropic. The alpha co-receptor, CXCR4, is less frequently used by HIV-1 isolates and viruses that exclusively use CXCR4 are known as X4-trophic virus. HIV-1 that uses both R5 and X4 co-receptors are known as dual-tropic HIV-1. Importantly, HIV-1 transmitted founder viruses are predominantly R5-tropic ([Keele et al., 2008](#)).

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HIV-1 gp160, gp120, gp41, and gp120 glycosylation

The HIV-1 envelope glycoprotein polyprotein is encoded by the *env* gene and is known as gp160. It is cleaved into two functional domains by cellular proteases during transport through the secretory pathway, with gp120 being the surface protein and gp41 being the transmembrane portion of the envelope protein (Figure 3). The gp120 portion of the envelope is comprised of 5 variable regions (labeled V1-V5) that are flanked by conserved or constant regions (often referred to as C1, C2, etc.) (Figure 3). The variable regions contain highly variable amino acid sequences that are exposed on the surface of the virus, where they are thought to contribute to evasion of the immune response against HIV-1 infection. Three gp120s and three gp41s combine in a trimer of heterodimers to form the envelope spike ([Zhu et al., 2008](#)) which mediates attachment to and entry into the host cell.

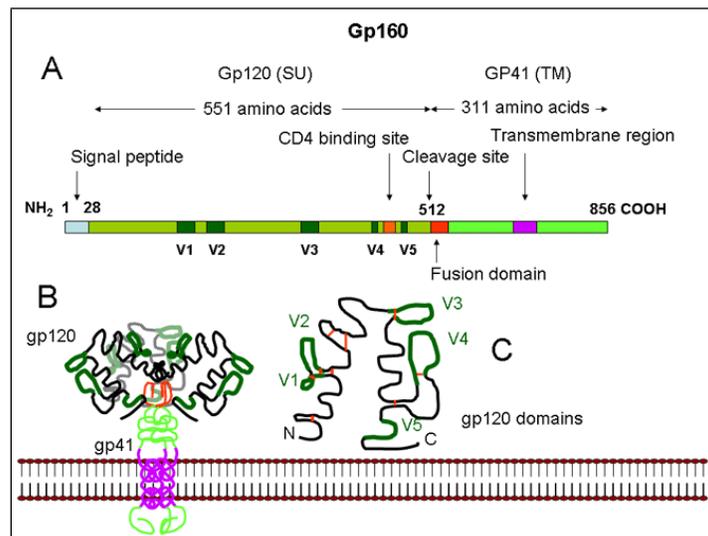


Figure 3. The HIV-1 envelope protein (copied from [Microbiology and Immunology Online, Chapter 7, part 9](#)). (A) The linear domain structure of gp160 is shown at the top. gp160 is cleaved into gp120 (the surface protein) and gp41 (the transmembrane fusion protein). (B) A trimer of gp120/gp41 is associated with the viral membrane. (C) gp120 has a number of hypervariable domains (V1-V5). The red bars show disulfide bridges.

The gp120 variable regions are thought to be sites of potential neutralizing antibody binding, and high variability in these regions likely allows the virus to escape the memory immune response. In addition, there are several PNGSs that could allow for the attachment of long-chain carbohydrates to the highly variable regions of gp120, and the presence of large carbohydrate chains extending from gp120 might obscure possible antibody binding sites ([Novitsky et al., 2009](#)) (see Figure 4).

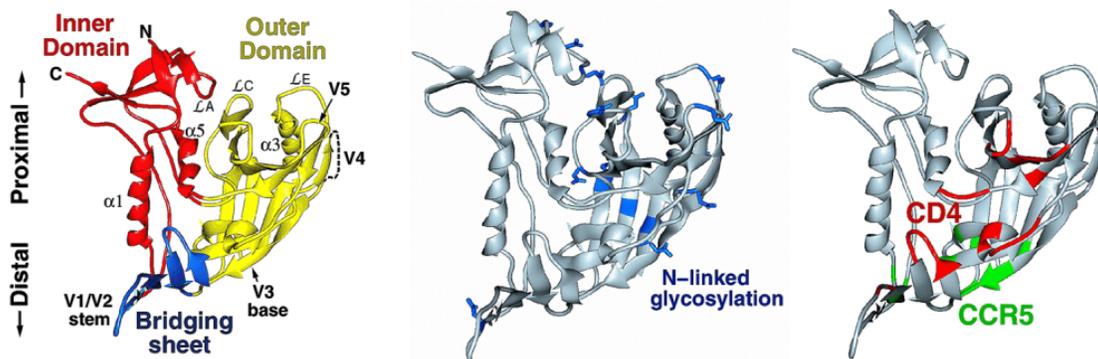


Figure 4: HIV-1 gp120 monomer structure and elements important for resistance ([Wyatt et al., Los Alamos website](#)). CD4 and CCR5 indicate the gp120 residues involved with binding to the CD4 receptor and the CCR5 chemokine co-receptor, respectively.

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HIV-1 drugs

There are currently 26 drugs approved for the treatment of HIV-1 infection that are frequently combined to create highly-active antiretroviral therapy (HAART) regimens. The approved anti-HIV-1 drugs include integrase strand transfer inhibitors (INSTIs) (dolutegravir, elvitegravir and raltegravir), NNRTIs (delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine), NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine), PIs (atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir), the gp41 fusion inhibitor enfuvirtide, and the CCR5 coreceptor antagonist maraviroc. Maraviroc inhibits the interaction between the viral envelope glycoprotein gp120 and the human CCR5 receptor membrane protein and thereby prevents fusion of the viral and cellular membranes necessary for entry of the virus into the cell. Enfuvirtide is a gp41 fusion inhibitor preventing the joining of the viral and cellular membranes. NRTIs mimic nucleosides and target HIV-1 RT by competing with natural deoxynucleoside triphosphates for binding to RT and by incorporating into newly synthesized viral DNA resulting in chain-termination. NNRTIs inhibit HIV-1 RT by binding near the catalytic site of RT and acting as noncompetitive inhibitors. Integrase catalyzes the integration of linear viral DNA into host cell DNA forming the provirus. INSTIs bind to the integrase active site and block the strand transfer step of retroviral DNA integration. PIs work at the late stage of viral replication to prevent virus production from infected cells. They block the HIV-1 protease enzyme, which is necessary for the maturation of the noninfectious virions released from cells, resulting in defective particles which are unable to infect new cells. This BLA application for ibalizumab, a mAb that is a CD4 post attachment HIV-1 inhibitor, establishes a new HIV-1 drug class.

Additionally, there are multiple fixed dose combinations (FDCs) of anti-HIV-1 drugs where multiple antiretroviral drugs are combined into a single pill. Prior to 2006, the FDCs only included drugs from the same class (NRTIs); however, more recently several FDCs have been approved that contain antiretroviral drugs from multiple HIV-1 drug classes. Four of these FDCs, Genovoya™, Odefsey™, Stribild™, and Trimeq™, have reduced the pill burden to one pill taken once per day. One advantage of these FDCs is that one pill/day has improved adherence and thereby reduced the development of resistance against the drugs in these regimens.

HIV-1 resistance

Since HAART regimens have been introduced, the number of AIDS cases has decreased dramatically; however, HAART does not clear HIV-1 from subjects and even though the number of serum HIV-1 RNA copies is reduced to undetectable levels, HIV-1 re-emerges quickly after discontinuation of HAART. Therefore, with the currently available regimens, it is likely that HIV-infected subjects will require antiretroviral therapy throughout their lives. The longer a patient is on a HAART regimen the greater the chance of selecting for resistance against one or more drugs in the regimen. Therefore, new drugs in established classes and novel drugs targeting unique viral targets are needed to ensure that the armamentarium against HIV-1 is robust.

HIV-1 salvage population

There are several terms used to describe patients who have experienced the development of resistance to several different HIV-1 drugs, including multidrug resistance, triple class resistant (TCR), highly treatment-experienced and the HIV-1 salvage population. Ibalizumab was developed for the HTE population with MDR in three classes.

2.2 Ibalizumab

Ibalizumab (formerly known as Mu5A8, Hu5A8, TNX-355, and TMB-355) is a recombinant, humanized immunoglobulin G (IgG) isotype 4 κ light chain mAb that has a constant region comprised of two heavy chains of the gamma 4 subclass and two κ light chains. The four chains are stabilized by multiple disulfide bonds and the constant region of each heavy chain has a single N-linked oligosaccharide chain. Ibalizumab is a humanized version of a murine progenitor known as Mu5A8.

Mechanism of Action

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Ibalizumab blocks HIV-1 virions from infecting CD4⁺ T cells by binding to domain 2 of CD4 where it interferes with post-attachment conformational changes required for entry of HIV-1 virus particles into host cells via co-receptor binding and initiation of virus-cell membrane fusion. It is active against CCR5-utilizing, dual-tropic and CXCR4-utilizing viruses. The sponsor provided several studies to support the mechanism of action for ibalizumab.

Binding Affinity of Ibalizumab to CD4

The binding affinity and kinetics of ibalizumab binding to CD4 domain 2 were assessed using a Kinetic Exclusion Assay that measured the free concentration of either the receptor or the ligand without perturbing the equilibrium. This assay used the recombinant, humanized IgG4 monoclonal antibody Hu5A8 (also known as TNX-355, ibalizumab), against soluble human CD4 as a surrogate for membrane-bound human CD4 receptor, which is the actual target of ibalizumab. Hu5A8 (ibalizumab) bound to soluble human CD4 with an optimal value of the equilibrium dissociation constant (K_d) of 82.2 pM (46.6pM-109 pM), indicating that Hu5A8 binds to soluble CD4 with high affinity (Table 2).

Table 2: Hu5A8 (ibalizumab) equilibrium measurements by dual curve analysis (Table 4a, page 8, TMB-RD-R2017013).

Equilibrium Measurements (Dual Curve Analysis)	
Kd	82.2 pM (46.4 pM - 109 pM)
Antibody Activity	87.1% (52.1% - 120%)
Overall Error	3.05%
Low [Ab] Equilibrium Experiment (Curve 1)	
Parameters	
Nominal [Binding Site]	300 pM
Nominal [Ag]	10 nM - 9.77 pM, 2-fold dilution
Incubation Time	4 hours
Samples	120 sec, 0.5 mL, 0.25 mL/min
Label	240 sec, 1 mL, 0.25 mL/min, 0.5 mg/mL
Reagents used:	
5A8 MAb	0.563 microgram
CD4 peptide antigen	1.32 microgram
High [Ab] Equilibrium Experiment (Curve 2)	
Parameters	
Nominal [Binding Site]	790 pM
Nominal [Ag]	10 nM - 9.77 pM, 2-fold dilution
Incubation Time	5 hours
Samples	60 sec, 0.5 mL, 0.5 mL/min
Label	240 sec, 1 mL, 0.25 mL/min, 0.5 g/mL
Reagents used:	
5A8 MAb	1.48 microgram
CD4 peptide antigen	1.32 microgram

From the results of this study, the sponsor concluded that Hu5A8 (ibalizumab) bound with high affinity to soluble human CD4.

Monovalency versus Bivalency of Ibalizumab

Based on previously reported results, the sponsor expected that only bivalent forms of Mu5A8 would be effective in blocking HIV-1 entry and an experiment was performed to assess the valence of ibalizumab activity in cell culture neutralization of HIV-1 pseudotyped viruses. In this experiment, a panel of 12 HIV-1 Env pseudoviruses was used, including three laboratory-adapted isolates and nine primary isolates from clades A, B, and C, to test inhibition of ibalizumab in its bivalent IgG form and its monovalent Fab fragment form. Contrary to the results observed in previous studies, both the bivalent IgG and the monovalent Fab fragment of ibalizumab blocked infection by most pseudoviruses; however, inhibition strengths of bivalent IgG and monovalent Fab varied greatly for different isolates, and in some instances, did not fully inhibit the pseudovirus (Figure 5 and Figure 6).

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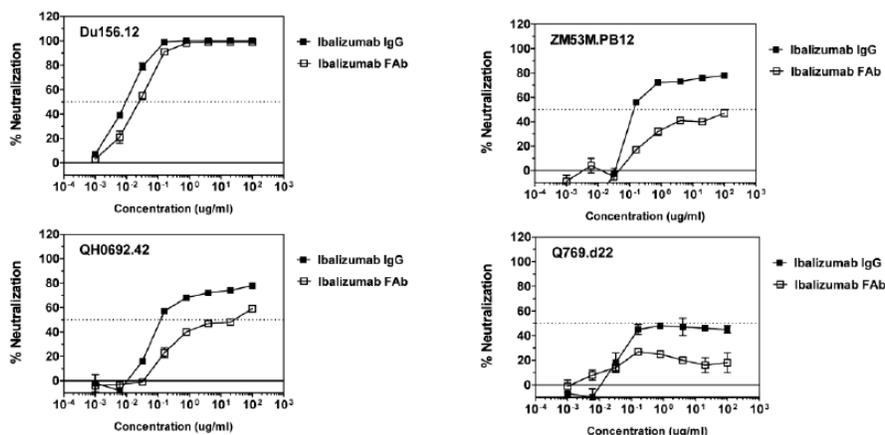


Figure 5: Inhibition of representative HIV-1 isolates by ibalizumab IgG and Fab (Figure 1, page 7, TMB-RD-R2017002). HIV-1 primary isolates, Du156.12 (clade C), QH0692.42 (clade B), ZM53M.PB12 (clade C), and Q769.d22 (clade A) were analyzed for inhibition by the anti-CD4 monoclonal antibody ibalizumab using a luciferase-based virus neutralization assay with TZM.bl cells. Serial dilutions of ibalizumab in the bivalent IgG form (filled square) or the monovalent Fab form (open square) were tested for neutralization against each virus. Fifty percent of inhibition is indicated by a dashed, horizontal line.

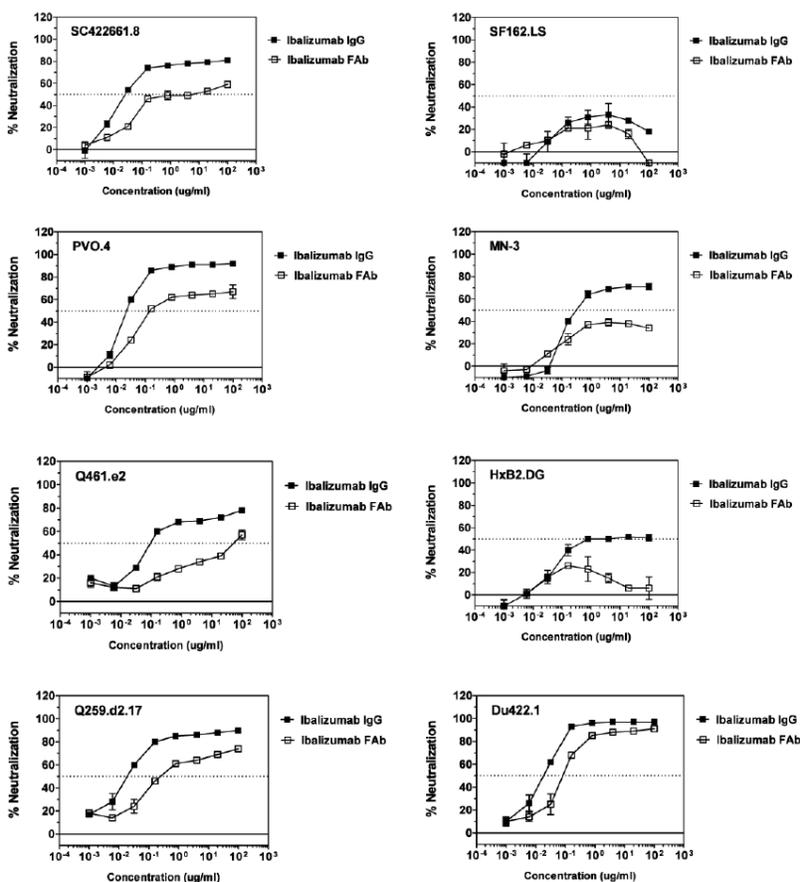


Figure 6: Inhibition of representative HIV-1 isolates by ibalizumab IgG and Fab (Figure 2, page 8, TMB-RD-R2017002). HIV-1 laboratory-adapted strains (clade B), SF162.LS, MN-3, HxB2.DG; and primary isolates, SC422661.8 and PVO.4 from clade B, Q461.e2 and Q259.d2.17 from clade A, Du422.1 from clade C, were analyzed for inhibition by ibalizumab using a luciferase-based virus neutralization assay with TZM.bl cells. Serial dilutions of ibalizumab in the bivalent IgG form (filled square) or the monovalent Fab form (open square) were tested for inhibition against each virus. A dashed, horizontal line indicates 50% of neutralization.

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This study indicated that the bivalency of ibalizumab is not required for ibalizumab antiviral activity. The sponsor reported that the discrepancy between this work and the published results was likely caused by the limited number of laboratory-adapted strains and the cell-cell fusion assay used.

X-ray Crystallography Studies of Ibalizumab in Complex with CD4

The x-ray crystal structure of the ibalizumab Fab in complex with soluble domain 2 of CD4 was solved in an effort to further define the residues in CD4 that interact with ibalizumab, defined as the ibalizumab epitope. This study was also performed to gain molecular insights on whether ibalizumab binding of domain 2 of CD4 could block CD4 receptor function, particularly the interaction site in domain 1 of CD4 where MHC Class II molecules interact with CD4. The structure of ibalizumab Fab in complex with soluble CD4 domain 2 was solved at a 2.2 Å resolution.

The x-ray structure showed that ibalizumab binds to CD4 mainly by direct contacts between both its heavy and light chains, and the BC loop of domain 2 of CD4, which is comprised of residues 121–125 (Figure 7 and Figure 8). The sponsor noted that these interactions were consistent with previous mutagenesis results ([Burkly et al., 1992](#); [Song et al., 2010](#)), and reported that the x-ray crystal structure also revealed that another segment in CD4, comprised of residues 127–134, which had previously been predicted to be critical for mAb 5A8 binding, barely makes contact with the antibody (Figure 7). Mutational analysis of CD4 domain 2 also predicted that the following CD4 amino acids were also part of the ibalizumab epitope: E77, S79, P121, P122, and Q163 ([Song et al., 2010](#)); however, these positions were not consistent with the x-ray structure. In addition, a more recent epitope-mapping study on ibalizumab by point mutation indicated that the segment (residues 127–134) is less critical.

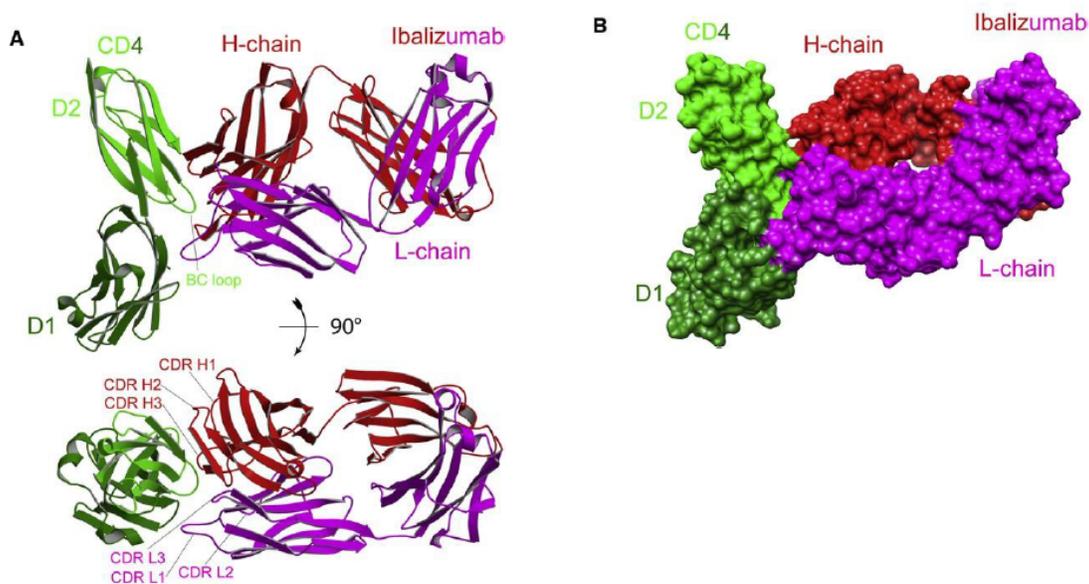


Figure 7: Structure of the complex of domain 2 of CD4 and the Fab fragment of ibalizumab (Figure 3, page 11, TMB-RD-R2017002). (A) Top and side views of the overall structure of CD4 domain 2 in complex with ibalizumab Fab, shown in ribbon representation. CD4 is in green (lighter green for domain 2 and darker green for domain 1), the heavy chain of ibalizumab in red, and the light chain in magenta. The BC-loop in the second domain of CD4, which constitutes the core epitope, and the CDR loops of ibalizumab are all indicated. (B) Surface representation of the complex. CD4 and ibalizumab are shown in the same color scheme as in (A).

There is a distorted disulfide (S-S) bond between residues Cys130 and Cys159, which are located in two antiparallel beta strands, respectively, and the geometry required for the S-S bond is not favorable. Therefore, any deletions in the neighboring residues could further disfavor the formation of this S-S bond and in turn affect the conformation of the core epitope, the BC loop.

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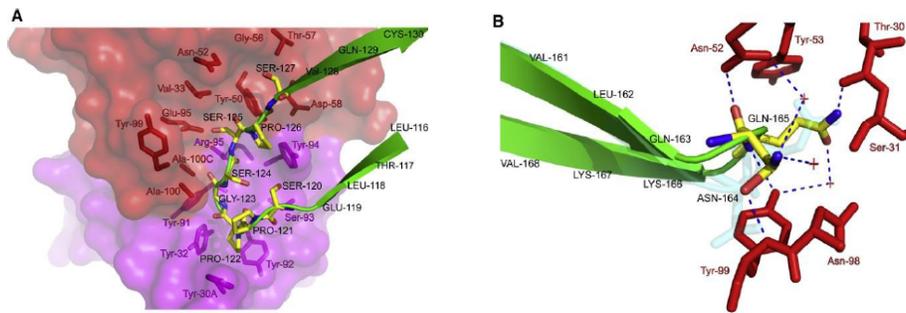


Figure 8: Close-up of major contacts between CD4 and ibalizumab (Figure 4, page 12, TMB-RD-R2017002). (A) Residues making direct contacts between the heavy and light chains of ibalizumab and the BC-loop (residues 121–125) of D2 in CD4. The heavy and light chains of ibalizumab are shown by surface representation in red and magenta, respectively, and the residues that make contacts with CD4 are also shown by stick model in the same color scheme. The BC-loop of CD4 is in green in ribbon diagram and the residues interacting with ibalizumab are shown by stick model with carbon atoms in yellow, nitrogen in blue and oxygen in red. (B) Contacting residues between the FG loop (residues 164, 165) of D2 in CD4 and the ibalizumab heavy chain. The residues that make direct contacts with the FG loop of CD4 in the heavy chain are shown by stick model in red. The FG loop of CD4 is shown in ribbon diagram in green with residues 164 and 165 in stick model in the same color scheme as in (A). The conformation of the two residues in the unbound CD4 is also shown in cyan; a flip of the loop upon binding to ibalizumab is evident.

Based on information contained in the x-ray crystal structure of the complex between ibalizumab and domain 2 of CD4, ibalizumab interacts with CD4 domain 2 residues in the BC-loop (residues 121–125), and also comes into contact with residues between the FG loop (residues 164, 165) of domain 2 in CD4. These positions are in domain 2 of CD4 and are distal to the domain 1 site where MHC-II and HIV-1 gp120 interact with CD4, indicating that ibalizumab would not be in a position to interfere with the adaptive immune response or compete with HIV-1 gp120 (Figure 8). Of note, HIV-1 strains with amino acid changes in the gp120 envelope V5 loop resulting in loss of an N-linked glycan have been associated with reduced susceptibility to ibalizumab ([Toma, et al., 2011](#)). Previous structural analysis indicates that a glycan linked to a position in the V5 loop fills a void between the gp120 V5 loop and the ibalizumab light chain, perhaps causing steric hindrance that disrupts viral entry (Figure 9).

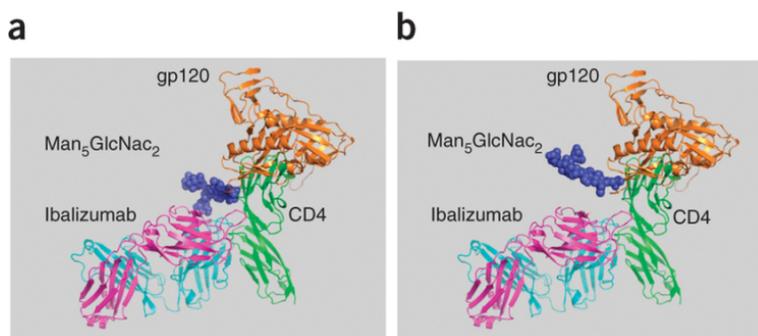


Figure 9: Model of glycosylation in V5 of HIV-1 gp120, in the context of both CD4 and ibalizumab (using PyMOL) (copied from Figure 1, [Song et al., 2013](#)). The complex was modeled by superimposing the structure of D1 and D2 of CD4 in complex with gp120 (Protein Data Bank (PDB) accession number 2NXY) onto the same domains of CD4 in complex with ibalizumab (PDB 3O2D). The glycan (dark blue) was introduced at the relevant asparagine by superimposing the asparagine with that of a glycan-bound asparagine from PDB 3TYG. The H and L chains of ibalizumab are shown as cyan and magenta ribbons, respectively. The first two domains of human CD4 are green, whereas HIV-1 gp120 is orange/brown. (a) Man₅GlcNac₂ at the position of 459 of gp120 in the V5 loop (N terminus). (b) Man₅GlcNac₂ at the position of 463 of gp120 in the V5 loop (C terminus).

In addition to the structural evidence showing that ibalizumab binds to CD4 D2 distal to the HIV-1 gp120 binding epitope, the sponsor provided additional data showing that ibalizumab binding to CD4 does not have a

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noticeable impact on HIV-1 gp120 (C97ZA012 strain) binding using a recombinant gp140 trimer to mimic the biological conformation of the gp120 trimer (Figure 10).

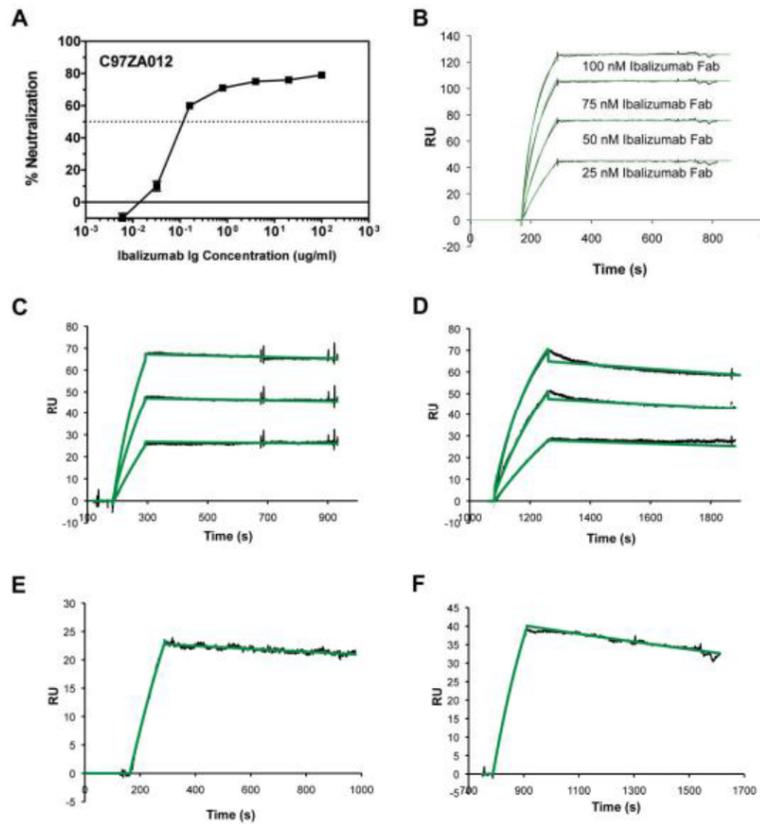


Figure 10: Ibalizumab does not block CD4 binding to a stable, homogenous recombinant HIV-1 gp140 trimer (Figure 5, page 14, TMB-RD-R2017002). (A) Clade C HIV-1 isolate C97ZA012 is sensitive to inhibition by ibalizumab. (B) Ibalizumab Fab binds to soluble CD4 with high affinity. (C) Binding of a stable HIV-1 gp140 trimer derived from C97ZA012 to soluble CD4. (D) Binding of the C97ZA012 gp140 trimer to CD4 in the presence of ibalizumab Fab. (E) Interaction of gp120 derived from the isolate Du156.12 at 100 nM with soluble CD4. (F) Interaction of gp120 derived from the isolate Du156.12 at 200 nM with soluble CD4.

In this study, ibalizumab Fab was tested for its ability to bind soluble CD4 using a surface plasmon resonance binding assay. A soluble recombinant CD4 molecule containing domains 1-4 was immobilized on a CM5 chip and ibalizumab Fab at various concentrations were passed over the surface. The recorded sensorgrams are shown in black and fits to a 1:1 Langmuir binding model in green. Ibalizumab Fab binds to CD4 with high affinity with little dissociation ($k_{on}=2.47 \times 10^5$ (1/Ms); $k_{off}=3.24 \times 10^{-6}$ (1/s); and $K_d=1.31 \times 10^{-11}$ (M) (Figure 10B). The binding of a stable HIV-1 gp140 trimer derived from C97ZA012 was assessed for its affinity for binding to soluble CD4. A stable, homogenous HIV-1 gp140 trimer was produced in insect cells and characterized previously. Soluble CD4 was immobilized on a CM5 chip and solutions of the C97ZA012 gp140 trimer at 75, 150 and 250 nM were passed over the surface with a 2 min association phase. The recorded sensorgrams are in black and fits to a 1:1 Langmuir binding model in green ($k_{on}=3.20 \times 10^4$ (1/Ms); $k_{off}=4.68 \times 10^{-5}$ (1/s); and $K_d=1.46 \times 10^{-9}$ (M) (Figure 10C).

Binding of the C97ZA012 gp140 trimer to CD4 in the presence of ibalizumab Fab. The same CD4 chip used in C was regenerated by injection of 10 mM HCl and 250 mM NaCl or 10 mM NaOH and 1.2 M NaCl. Ibalizumab Fab at 1 μ M was then passed over the surface and unbound Fab was washed off with buffer. The response stayed relatively stable, indicating ibalizumab Fab formed tight complex with immobilized CD4 on the surface. Solutions of the C97ZA012 gp140 trimer at 75, 150, 250 nM were flowed over the surface individually after

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each cycle of regeneration-ibalizumab capturing described above. The recorded sensorgrams are shown in black and fits after subtraction of dissociation of ibalizumab to a 1:1 Langmuir binding model are in green ($k_{on}=2.70 \times 10^4$ (1/Ms); $k_{off}=1.60 \times 10^{-4}$ (1/s); and $K_d=5.92 \times 10^{-9}$ (M)). The binding constants for the CD4-gp140 interaction derived from C and D are similar, indicating that ibalizumab Fab does not block CD4 binding to C97ZA012 gp140 trimer (Figure 10D).

Ibalizumab binding of CD4 did not block or alter the binding of an HIV-1 gp140 trimer derived from Du156.12 (Figure 10E-F). Interaction of gp120 derived from the isolate Du156.12 with CD4. Similar to (C) and (D), Du156.12 gp120 (Immune Technology Corp.) at 100 nM was passed over a CD4 surface (in E) or at 200 nM was flowed over the same CD4 surface after regeneration and ibalizumab Fab capturing (in F). The recorded sensorgrams are in black and fits to a 1:1 Langmuir binding model in green. The binding constants are $k_{on}=2.53 \times 10^4$ (1/Ms); $k_{off}=1.15 \times 10^{-4}$ (1/s); and $K_d=4.54 \times 10^{-9}$ (M) for the gp120-CD4 interaction in absence of ibalizumab and $k_{on}=2.24 \times 10^4$ (1/Ms); $k_{off}=2.92 \times 10^{-4}$ (1/s); and $K_d=1.30 \times 10^{-8}$ (M) in the presence of ibalizumab.

Antiviral Activity in Cell Culture

The inhibitory activity of ibalizumab (Hu5A8) was assessed against 15 primary isolates of HIV-1 group M (Clades A, B, C, D, E, or O) isolates in phytohemagglutinin-stimulated Primary Blood Lymphocytes. According to the sponsor, the HIV-1 strains were isolated from HIV-1 infected individuals in different geographical locations around the globe and they represent different phenotypes, including macrophage-tropic nonsyncytia-inducing (NSI), T cell-tropic syncytia inducing (SI), R5 co-receptor usage, X4 co-receptor usage, and R5/X4 dual-tropic co-receptor usage. The mean EC₅₀ value for ibalizumab against the primary isolates ranged from 0.4 to 600 ng/mL in cell culture, with lower susceptibility observed in macrophage-tropic HIV-1 strains BaL, JR-CSF, YU2, and ADA-M (Table 3).

Table 3. Neutralization of primary isolates of HIV-1 Group M by ibalizumab (Hu5A8)(Table 3, page 4, Section 8 Pharmacology Excerpt).

		Clade B									
		Macrophage Tropic Viruses									
		US1	91/US/056	92/US/717	BAL		JRCSF	YU2	ADA-M	HIV89.6	SHIV89.6PD
		NSI/R5	NSI	NSI	NSI/R5	NSI/R5	NSI/R5	NSI/R5	NSI/R5	SI, R5/X4	SI/R5/X4
[Mab]	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut
µg/ml											
50	99%	99%	96%	74%	78%	94%	-47%	68%	96%	81%	
5	99%	98%	97%	71%	47%	94%	-10%	83%	86%	85%	
1	99%	99%	97%	77%	63%	75%	35%	79%	91%	72%	
0.2	99%	97%	97%	61%	27%	71%	49%	72%	87%	67%	
0.04	95%	95%	83%	46%	-34%	-23%	10%	46%	83%	21%	
0.008	79%	40%	17%	56%	-64%	-4%	1%	32%	25%	21%	
0.0008	44%	18%	-29%	67%	-124%	-3%	54%	6%	39%	17%	
99	1.21	11.99	99.80	-	-	-	-	-	-	-	
90	0.011	0.054	0.26	-	-	4.78	-	-	5.9	-	
50	0.0004	0.001	0.0004	-	0.6	0.152	-	0.027	0.01	0.048	

		Clade A	Clade C	Clade D	Clade E		Clade O
		92/RW/009	ZB20	92/UG/035	CM235	CM246	42368
		SI, R5/X4	NSI	NSI	NSI/R5	NSI/R5	SI, R5/X4
[Mab]	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut	% Neut
µg/ml							
50	99%	98%	98%	96%	94%	99%	98%
5	98%	98%	97%	93%	88%	95%	97%
1	99%	99%	93%	87%	86%	99%	97%
0.2	99%	98%	95%	85%	83%	99%	97%
0.04	93%	98%	79%	70%	50%	84%	86%
0.008	66%	99%	21%	21%	29%	-7%	-52%
0.0008	33%	52%	-67%	43%	32%	-34%	-78%
99	5.19	4.73	83.38	-	-	12.80	31.00
90	0.026	0.001	0.367	1.91	7.23	0.087	0.236
50	0.001	0.0006	0.008	0.005	0.009	0.003	0.008

The ability of ibalizumab to neutralize HIV-1 was assessed using a panel of 116 HIV-1 envelope-pseudotyped viruses that were selected to represent envelope diversity by geography, clade, tropism, and stage of infection.

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Ibalizumab neutralized 92% of the 116 HIV-1 envelope-pseudotyped viruses when using a definition of neutralization as 50% or more inhibition of infection (Table 4). Ibalizumab antiviral activity was compared to several mAbs that target gp120 (Table 4).

Table 4. Median EC₅₀ values against HIV-1 envelope-pseudotyped viruses neutralized at max concentration
(Table 4a, page 7, TMB-RD-R2017008 Study Report).

Clade	b12	2G12	2F5	4E10	Ibalizumab	VRC01	PG9
A	11.85	21.15	4.10	2.00	0.04	0.09	0.16
B	1.90	21.90	1.10	0.80	0.02	0.22	0.43
C	10.40	2.14	14.75	1.90	0.04	0.35	0.22
D	3.90	>50	1.43	2.30	0.10	0.25	0.10
CRF01_AE	26.30	2.05	1.21	0.88	0.03	0.41	0.08
CRF_AG	3.60	12.80	2.60	1.30	0.03	0.70	0.80
G	>50	>50	9.10	4.45	0.10	0.17	0.29
AC	46.10	>50	14.40	15.20	0.23	0.08	-
ACD	34.80	>50	9.10	11.35	0.03	0.50	-
BC	6.00	>50	>50	5.65	0.07	-	-
CD	4.10	25.45	1.70	8.10	0.07	0.04	-
Total	3.60	2.60	2.84	2.34	0.03	0.22	0.22

* >50 µg/mL (white), >20-50 µg/mL (green), >2-20 µg/mL (yellow), >0.2-2 µg/mL (orange), ≤0.2 µg/mL (red)

Median MPI was similar across all of the HIV-1 clades assessed in the HIV-1 envelope-pseudotyped virus assay (Figure 11).

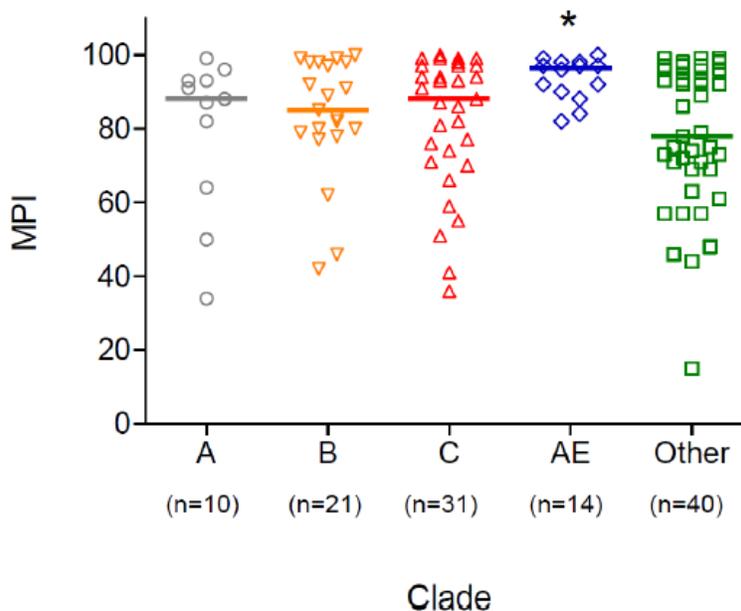


Figure 11. Assessing the MPI of various HIV-1 envelope pseudotypes based on clade (Figure 4b, page 8, TMB-RD-R2017008 Study Report). Other – HIV-1 pseudotypes from clades D, G, AC, AG, ACD, BC, and CD combined.

In addition, the antiviral activity of ibalizumab was assessed against clinical HIV-1 isolates from 17 subjects infected with Clade B with HIV-1 enrolled in clinical trial TNX-355.02. For this assessment, ibalizumab susceptibility testing was performed using the PhenoSense™ HIV Entry Assay, and a single-cycle infectivity assay developed, validated, and performed by (b) (4). The single-cycle infectivity assay used recombinant viruses that express subject-derived HIV-1 envelope proteins to evaluate entry inhibitor drug susceptibility and co-receptor tropism. For the 17 HIV-1 clinical isolates, the median EC₅₀ value at baseline was 12 ng/mL (8.8-16.9 ng/mL; n=17) and the median MPI was 97% (89-99%; n=17)(Table 5).

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Table 5. Antiviral activity of 17 Clade B clinical isolates (DAVP analysis).

Virus	Baseline	
	EC ₅₀ value	MPI
E03-137817	0.0098	97
E03-137819	0.0154	91
E03-137815	0.0114	96
E03-4328	0.0122	99
E03-4329	0.0169	97
E03-4330	0.0114	99
E03-4331	0.0145	94
E03-4332	0.0166	93
E03-4333	0.012	99
E03-4334	0.0169	89
E03-4335	0.0132	99
E03-4514	0.0098	99
E03-4565	0.0096	99
E03-4682	0.0132	96
E03-4684	0.0091	97
E03-4686	0.0101	98
E03-4569	0.0088	99
Mean ± SD	12 ± 3 ng/mL	97 ± 3
Median	12 ng/mL	97
Range	8.8-16.9 ng/mL	89-99

Antiviral Activity Against T Cell Passaged HIV-1 Strains and Primary Patient Isolates

Antiviral activity assessments were also performed to assess for the ability of Mu5A8 to inhibit infectivity of T cell passaged HIV-1 strains and primary patient isolates and the formation of syncytium in CD4⁺ T cells in comparison to other mAbs. For the infectivity assay, T-cell-passaged HIV-1 strains were tested using a microassay. Briefly, purified anti-CD4 mAb and 4x10⁴ C8166 cells were incubated for 30 minutes at 37°C, and then a 100-fold Tissue Culture Infective Dose (TCID) of the HIV strains (HTLV_{IIIB} isolate or C8166-passaged strains CO8 and C17) was added. Wells were scored visually for syncytia under a light microscope. The primary patient isolates (0104B and 0108E derived from clinical blood samples from (b) (4) and cloned patient isolate (JR-CSF from National Institutes of Health AIDS Research and Reagent Program) were propagated in normal human peripheral blood mononuclear cells (PBMCs) activated for 2 to 3 days with phytohemagglutinin (PHA). To assess their infectivity, PHA-blasted PBMC were pretreated with mAb for 30 minutes at 37°C followed by addition of virus and overnight incubation at 37°C. The virus dose chosen was a dilution of virus stock giving a reproducible infection, with p24 detectable within the first week of culture.

H9 cells chronically infected with HIV-1 (HTLV_{IIIB}) were incubated with and without mAb for 30 minutes, followed by incubation with uninfected CD4⁺ C8166 cells for 2 hours. The number of syncytia formed per well were visually scored with a light microscope. The sponsor reported that Mu5A8 blocked free virus infection by the HIV-1 HTLV_{IIIB} strain and two other T cell-line passaged isolates (C08 and C17) into uninfected C8166 cells (ID₁₀₀ range: 0.3 – 5.0 µg/mL). Moreover, Mu5A8 blocked infection by the cloned patient isolate JR-CSF and two other primary patient viruses, 0104B and 0108E (IC₁₀₀ range: 0.08 – 0.6 µg/mL) (Table 6).

Table 6: Mu5A8 blocks infection by diverse HIV-1 isolates (Table 4a, page 7, TMB-RD-R2017005).

mAb	CD4 Domain-Specific	Inhibitory Dose (ID ₁₀₀) (µg/mL)					
		T cell line-passaged virus			Primary patient virus		
		IIIB	C08	C17	JR-CSF	0108E	0104B
Mu5A8	D2	0.3 ^a	0.3	5.0	0.6 ^b	0.08	0.075

ND=Not determined.

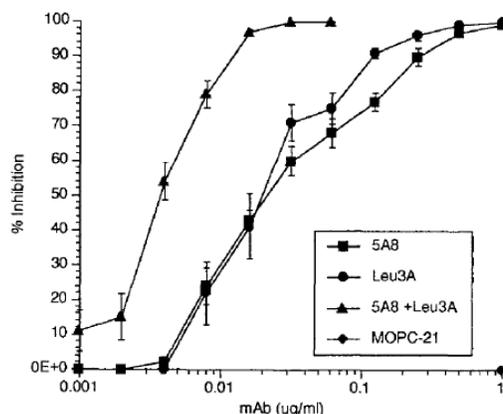
- Concentration of mAb required to completely block infection of C8166 cells as measured by the appearance of syncytia in two experiments (with triplicate wells per experiment) on Days 8 - 10 of culture.
- Concentration of mAb required to completely block infection of human PHA-stimulated PBMCs as measured by appearance of HIV p24 antigen after 2 weeks of culture; results from at least two independent experiments.

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Since HIV-1 transmission could be mediated by fusion (syncytium formation) between HIV-1 infected cells and uninfected CD4⁺ cells, Mu5A8 was tested for its ability to block syncytium formation (Figure 12). In this experiment, Leu3a (an anti-CD4 mAb specific to domain 1) was the positive control, and an irrelevant murine mAb (MOPC21) served as a negative isotype-matched control. According to the sponsor, Mu5A8 inhibited syncytium formation as effectively as Leu3a, and the combination of Mu5A8 with Leu3a showed a synergistic effect. These data support the notion that Mu5A8 inhibits an independent step required for virus infection and therefore, has the potential to act cooperatively with other agents that target the primary interaction between HIV-1 gp120 and CD4.



NOTE: Mu5A8=D2-specific; Leu3a=D1-specific; MOPC-21=IgG1-specific.
Data (mean ± SEM, n=10) represented as percent inhibition relative to the maximum number of syncytia in the absence of mAb.

Figure 12: Inhibition of syncytia formation between HIV-1 HTLV_{III}B-infected H9 cells and uninfected CD4⁺ C8166 cells by CD4-specific monoclonal antibodies (Figure 4a, page 8, TMB-RD-R2017005).

Antiviral Activity Against HIV-1 Viruses Based on Tropism

The activity of ibalizumab was assessed against HIV-1 isolates that use the different chemokine co-receptors, CCR5 and CXCR4, to determine if HIV-1 tropism impacts ibalizumab susceptibility. Using representative viruses from different clades to infect R5-expressing cells, the EC₅₀ value for ibalizumab ranged from 34.8 to 68.2 ng/mL (n=4) for R5-tropic HIV-1 (Table 7). Using representative viruses from different clades to infect X4-expressing cells, the EC₅₀ value for ibalizumab ranged from 33.6 to 59.1 ng/mL (n=3) for X4-tropic HIV-1 (Table 7).

Table 7. Activity of ibalizumab against viruses representing different clades and tropisms (Table 1, page 4, S-1063 Study Report).

Virus	Coreceptor ¹	January 2004		November 2004	
		IC ₅₀ ²	IC ₉₀ ²	IC ₅₀ ²	IC ₉₀ ²
Dual Tanox Control	CCR5	0.0348	0.1426	0.0336	0.1487
JRCSF_CCR5	CCR5	0.0682	0.4557	0.0644	0.5047
Clade B_CCR5	CCR5	0.0490	0.2935	0.0753	0.4639
Clade C_CCR5	CCR5	0.0426	>55	0.0751	>55
Clade D_CCR5	CCR5	0.0482	0.3659	0.0660	0.4432
Dual Tanox Control	CXCR4	0.0430	0.2013	0.0499	0.2052
Clade B_CXCR4	CXCR4	0.0591	0.2066	0.0583	0.2264
Clade C_CXCR4	CXCR4	0.0336	0.1764	0.0547	0.2041
Clade D_CXCR4	CXCR4	0.0485	0.1974	0.0557	0.1972

1. Coreceptor expressed on target cell
2. Values are expressed as µg/mL

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Baseline plasma samples obtained from 78 subjects from clinical trial TNX-355-003 were assessed at baseline to determine co-receptor tropism and ibalizumab susceptibility using the PhenoSense™ Entry assay (b) (4) and the single cell infectivity assay. Of the 78 isolates assessed, 43 were R5-tropic and these isolates had a median EC₅₀ value of 80 ng/mL (20-160 ng/mL; n=43). Only one virus was X4-tropic and it had an EC₅₀ value of 110 ng/mL. A total of 34 viruses were dual-tropic, and these had a median EC₅₀ value of 80 ng/mL (10-140 ng/mL; n=34). Taken together, the antiviral activity data indicate that ibalizumab susceptibility is not associated with tropism as ibalizumab activity is generally the same regardless of HIV-1 tropism.

Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins

Ibalizumab is a monoclonal antibody and as such, will not likely be impacted by serum protein binding.

Cytotoxicity/Therapeutic Index

The sponsor did not provide specific data assessing the cytotoxicity of ibalizumab in cell culture and did not calculate a therapeutic index; however, these are generally not an issue for monoclonal antibodies.

Combination Antiviral Activity in Cell Culture

No drug antagonism was detected using the Prichard and Shipman method to evaluate the efficacy and toxicity of the combination of ibalizumab and the CCR5 co-receptor antagonist maraviroc at or near the EC₅₀ value of each in MAGI-CCR5 cells and PBMCs using HIV-1_{ADA}, HIV-1_{Ba-L}, and HIV-1 JR-CSF (Figure 13).

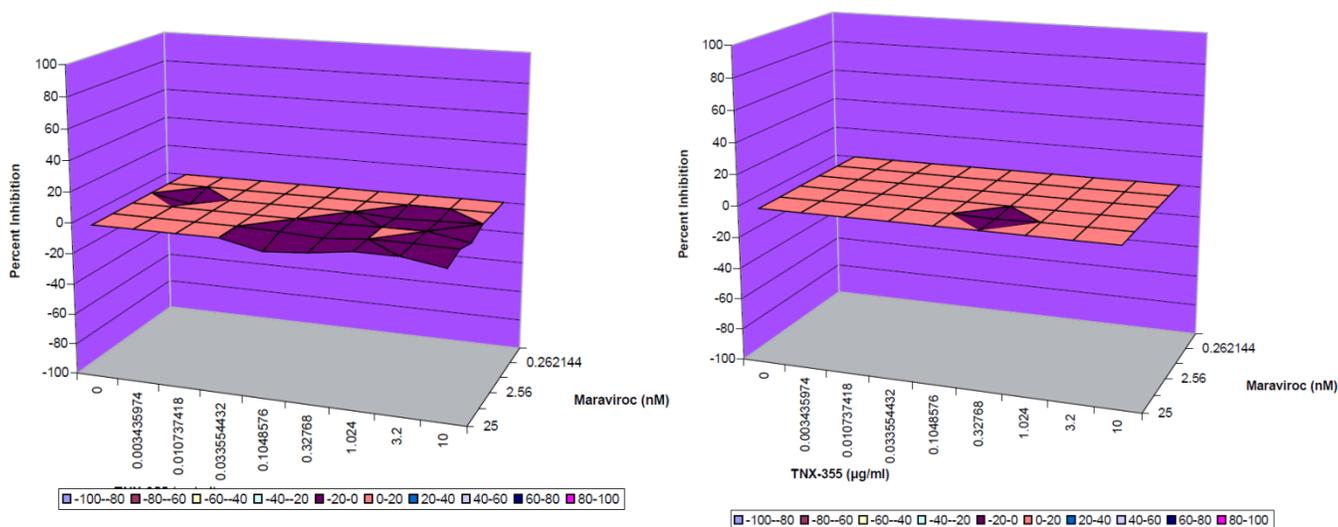


Figure 13. Combination activity and cytotoxicity analyses of ibalizumab+maraviroc in PBMCs (Experiment 7, page 35, TMB-RD-R2017012).

In addition, the sponsor provided MacSynergy™ II graphs showing the results of PBMCs infected with the subtype B HT/92/599 variant of HIV-1 that were incubated at five concentrations spanning the EC₅₀ values of each drug to assess ibalizumab in combination with the gp41 fusion inhibitor enfuvirtide; a nonnucleoside reverse transcriptase inhibitor (efavirenz); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, tenofovir, or zidovudine); or a protease inhibitor (atazanavir). Importantly, the drugs were evaluated at the EC₅₀ value of each drug during review. Statistical evaluations were performed for each combination using the Prichard and Shipman method and no ibalizumab antagonism was observed for any drugs tested (Table 8).

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Table 8. Cell culture combination assessments for ibalizumab in combination with several FDA-approved anti-HIV-1 antiviral drugs (Table 1, page 7, ImQuest-109-02-01 Study Report).

TNX-355 tested in combination with:	Synergy Volume ($\mu\text{M}^2\%$)	Antagonism Volume ($\mu\text{M}^2\%$)	Definition of Interaction
Zidovudine (NRTI)	158.7	0	Slightly synergistic
	34.0	-18.3	Additive
Didanosine (NRTI)	73.9	-10.8	Additive
	53.6	-34.4	Additive
Abacavir (NRTI)	0	-59.4	Additive
	284.6	-0.2	Synergistic
Emtricitabine (NRTI)	75.2	0	Slightly synergistic
	54.6	-10.3	Additive
Tenofovir (NRTI)	122.0	-19.9	Slightly synergistic
	7.3	-47.7	Additive
Efavirenz (NNRTI)	60.8	-16.5	Additive
	56.9	-10.6	Additive
Atazanavir (PI)	5.4	-12.6	Additive
	64.1	-9.3	Slightly synergistic
Enfuvirtide (FI)	151.7	0	Synergistic
	131.2	-12.9	Synergistic
	88.4	-12.8	Synergistic

Resistance Development in Animal Models, Cell Culture, and Cross-Resistance

Resistance to ibalizumab was first shown in two studies where nonhuman primates were infected with Simian Immunodeficiency Virus (SIV) and treated with hu5A8:

- **Study 1:** rhesus macaques infected with SIV were administered single IV injections of 1, 3, or 30 mg/kg of hu5A8. In addition, two SIV-infected monkeys received weekly doses of hu5A8 at 3 mg/kg for 6 weeks.
- **Study 2:** 3 monkeys chronically infected with SIV for 6 to 19 months received 3 mg/kg IV injections of hu5A8; 2 monkeys were dosed on Days 0, 2, 6, and 10, and the remaining monkey continued to receive antibody twice weekly through Day 24.

Overall, plasma SIV RNA levels rapidly declined in all hu5A8-treated SIV-infected monkeys within 2 days of the start of treatment. However, SIV RNA increased prior to the end of treatment while on hu5A8 for most animals, and following treatment with hu5A8, SIV isolates were more resistant to suppression by hu5A8, exhibiting a 5-fold reduction in hu5A8 susceptibility, compared to SIV isolates from naïve animals, in an assay that measured virus replication in PBMC co-cultures treated with various concentrations of hu5A8 (Figure 14).

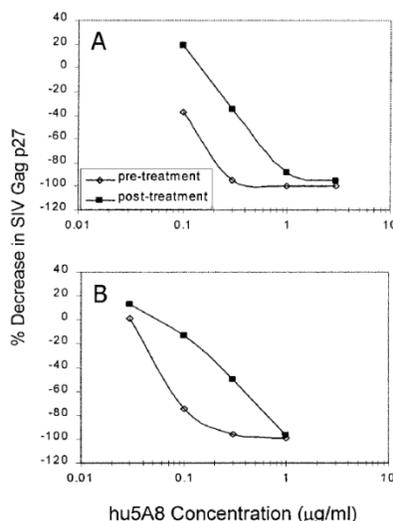


Figure 14. Shift in ibalizumab susceptibility in SIV pre- and post-treatment (Figure 4, page 25, TMB-RD-R2017003 Study Report).

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In addition, ibalizumab resistance was assessed in cell culture using PBMCs harvested from SIV-infected NHPs, comparing ibalizumab susceptibility of SIV prior to treatment with hu5A8 and after a series of 3 mg/kg treatments. Reduced ibalizumab susceptibility, as measured by quantification of SIV Gag p27 in the culture, was observed after 17 days on ibalizumab (Figure 15); however, the viruses were not characterized genotypically in this study.

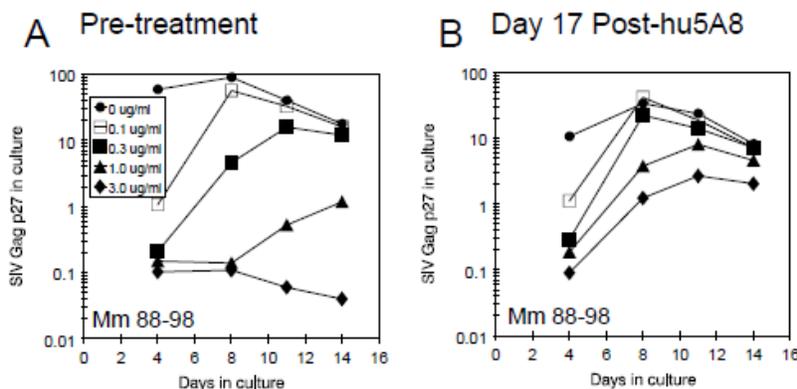


Figure 15. Ibalizumab susceptibility against SIV prior to and after treatment (Figure 1, page 2, TMB-RD-R2017019).

To assess for genotypic determinants of ibalizumab resistance, the HIV-1 envelope sequences derived from the 116 HIV-1 Env-pseudotyped virus assay were sequenced and analyzed based upon ibalizumab susceptibility. In this analysis, a significant association was observed between ibalizumab MPI and the number of V5 PNGSs (Figure 16):

- HIV-1 without V5 PNGSs (~3.4%), exhibited resistance to ibalizumab, with median MPI <50% (n=4, MPI 37.2 ± 16%, $P < 0.001$).
- Viruses with one V5 PNGS were more resistant to ibalizumab compared with those with 2 V5 PNGS (n=59, MPI 77.8 ± 18.3% vs n=51, 89.2 ± 12.5%, $P = 0.001$).
- Viruses with one N-terminal V5 PNGS had higher MPIs compared with viruses with a central or C-terminal V5 PNGS (n = 29, 83.4% ± 18.3% vs n = 30, 72.4% ± 16.8%, $P = 0.02$).

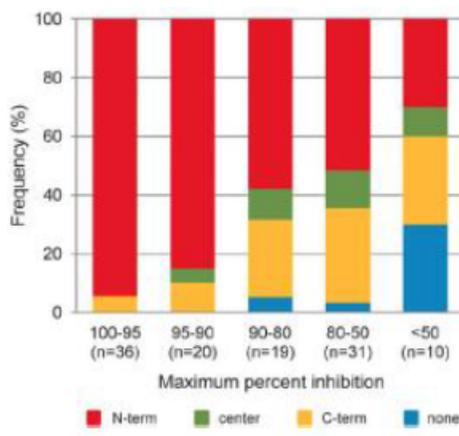


Figure 16. V5 PNGS versus ibalizumab MPI (Figure 4c, page 9, TMB-RD-R2017008 Study Report).

A site-directed mutagenesis study was performed targeting the two naturally occurring PNGSs in the V5 loop

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BLA: [761065](#) SDN: 000 (Original BLA, SDN 012 in DARRTS) REVIEW COMPLETED: 10/03/2017

Clinical Virology Reviewer: Eric F. Donaldson, Ph.D.

of HIV-1 NL4-3 to determine if knocking out each PNGS or both would have an impact on ibalizumab MPI. The results of this study were in agreement with the genotypic data observed in the 116 HIV-1 envelope sequences analyzed. Knocking out both PNGSs had the largest impact on ibalizumab MPI, reducing it to just over 20% (Figure 17). Knocking out the single N-terminal PNGS reduced the ibalizumab MPI to ~60%, whereas knocking out the C-terminal PNGS had no impact on ibalizumab MPI (Figure 17).

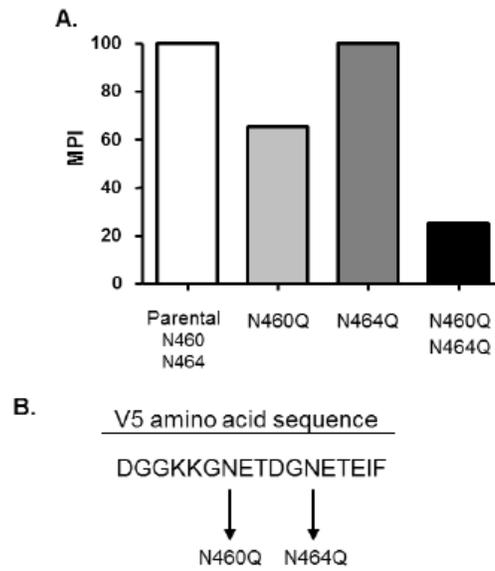


Figure 17. Site-directed mutagenesis of the PNGS sites of HIV-1 NL4-3 (Figure 3, page 12, TNX-355-02 Study Report).

Clinical isolates were used to show that HIV-1 isolates that developed resistance to ibalizumab continued to use CD4 as the primary receptor for entry, and were also used to show that ibalizumab-resistant variants were still as susceptible to maraviroc and enfuvirtide as they were prior to developing resistance to ibalizumab. Please see the clinical resistance in [Section 5](#) below for the details of these analyses.

CD4 Polymorphism Assessments

The presence of genetic polymorphisms within the coding region of the CD4 molecule has been well established (<https://omim.org/entry/186940>). A notable example is the OKT4 deficiency (failure to bind OKT4) in which African American, Caucasian, and Japanese individuals with OKT4 epitope deficiency carry a change at nucleotide position 867 or 868 of the CD4 gene, and this results in an arginine-to-tryptophan change at amino acid 240, R240W ([Hodge et al., 1991](#)). This particular amino acid polymorphism lies in Domain 3 (D3) of CD4, where the OKT4 epitope has also been mapped ([Sattentau et al., 1989](#)).

The potential for any reported CD4 amino acid polymorphism to impact ibalizumab binding can first be evaluated by determining whether or not it alters amino acids that are known to contribute to ibalizumab binding, i.e., the ibalizumab epitope. The ibalizumab epitope on human CD4 has been fine-mapped by extensive site-directed mutagenesis ([Song et al., 2010](#)) and confirmed by X-ray crystallography ([Freeman et al., 2010](#)). The mutagenesis studies determined that CD4 amino acid residues E77, S79, P121, P122, and Q163, are required for ibalizumab binding. Residues E77 and S79 are located near the C-terminal end of Domain 1 while the remaining residues are located in Domain 2.

Crystallographic studies determined that ibalizumab “grips” CD4 mainly by direct contacts between both its heavy and light chains and the BC loop (residues 121–125) in D2 of CD4; additional contacts include an extensive hydrogen bond network formed among residues 120–126 of CD4. The second major contact

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involves the short FG loop in CD4 D2 (residues 164–165) and the ibalizumab H-chain. The third major contact is made by interaction of the tip of CDR L1 with the EF loop in D1 of CD4 (at residues 77 and 79). One additional CD4 residue, L96, at the D1-D2 junction appeared to influence binding in a chimeric mouse-human CD4 construct ([Song et al., 2010](#)) but is not bound by ibalizumab ([Freeman et al., 2010](#)).

A variety of genetic polymorphisms in the CD4 gene can be documented using available online databases. These were surveyed to identify polymorphisms that alter CD4 amino acids known to be involved in ibalizumab binding to CD4. CD4 amino acid polymorphisms in regions outside the ibalizumab epitope would not be expected to impact ibalizumab binding because engineered mutants in these regions have been shown to have no effect on ibalizumab binding to CD4 ([Song et al., 2010](#); [Burkly et al., 1992](#)). Note that amino acid positions are typically listed by their position in the CD4 open reading frame, not the mature CD4 protein. Because CD4 encodes a 25 amino acid signal peptide that is cleaved during membrane translocation, the listed database number for each amino acid position is typically higher by 25 than the amino acid position in mature CD4. For example, the OKT4 deficiency is caused by an Arg(R)-to-Trp(W) change at CD4 amino acid 240 (R240W) and it is listed in the databases as R265W.

UniProtKB is a comprehensive protein sequence database. It identifies 3 natural variants of the CD4 gene – K191E (K166E), F227S (F202S), and R265W (R240W) with numerous independent database entries validating the existence of each polymorphism, along with estimates of frequency in some ethnic groups (<http://www.uniprot.org/uniprot/P01730#sequences>). The K191E (K166E) polymorphism has been estimated to occur in 1.9% of African-Americans but has not been detected in European-Americans. While it lies near the FG loop in CD4 domain 2, this residue does not make contact with ibalizumab in the co-crystal structure ([Freeman et al., 2010](#)) and is not expected to impact binding by ibalizumab. The other two variants impact amino acid residues that lie outside the ibalizumab epitope (F227S and R265W, corresponding to CD4 aa202 and aa240, respectively) and would not be expected to impact ibalizumab binding. Based on Ensemble analyses, polymorphism F227S has a frequency of 7% in the African American population ([Ensemble link](#)) and polymorphism R265W has a frequency of 20% in African Americans, 3% in the east Asian population, 2% in the Ashkenazi Jew population, and 1% in the Latino population ([Ensemble link](#)). In addition, R265W is linked to OKT4 epitope deficiency (<http://www.uniprot.org/uniprot/P01730#sequences>).

The National Heart, Lung, and Blood Institute Exome Variant Server comprises ~13,000 CD4 polymorphisms from European-American and African-American individuals, present in a roughly 2:1 ratio (<http://evs.gs.washington.edu/EVS>). The three common CD4 variants identified in the UniProtKB database (listed above) were also identified in the Exome Variant Server. The Exome Variant Server was further examined to identify additional polymorphisms that might alter the ibalizumab epitope and impact ibalizumab binding of CD4. Only one potential example was found - the Q190R polymorphism in the FG loop of CD4 D2. This residue makes contacts with ibalizumab in the co-crystal structure ([Freeman et al., 2010](#)) but substitution of glutamine with alanine (Q190A) had no impact on binding by ibalizumab ([Song et al., 2010](#)), so it is not clear that this polymorphism would have any impact on ibalizumab binding. The Q190R polymorphism is also quite rare as it occurred in only 1 of 2203 genomes among African-Americans and was not detected in any of 4300 genotypes among European-Americans. No other polymorphisms were identified in the Exome Variant Server that coincide with the ibalizumab epitope.

The National Center for Biotechnology Information (NCBI) maintains the dbSNP Database, an archive of short sequence variations that are considered polymorphic. Not all entries in the dbSNP database are validated by multiple, independent submissions, and few are supported with published reports to confirm phenotypic consequences of the listed polymorphism. The dbSNP identifies a total of 57 single-nucleotide polymorphisms (SNP) in the CD4 gene sequence that result in missense mutations and amino acid substitutions (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?locusId=920). Six of the 57 CD4 SNPs are located within the signal peptide, so only 51 could potentially alter functional interactions of the mature CD4 protein. Of these 51 listed variations, only 2 correspond to amino acid positions involved in ibalizumab binding – S104T (S79T) and

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P147S (P122S). Neither is indicated to have a significant allelic frequency, and only S79T has been validated by a second independent submission to the database, indicating that both are quite rare. Because S79T is a structurally conservative variation, it is not clear that this change should be expected to have an impact on ibalizumab binding to CD4. The P122S change, on the other hand, could have a negative impact on ibalizumab binding.

Similar to the existing dbSNP database, the ExAC (beta version) database is being developed as a large, comprehensive listing of all known nucleotide polymorphisms from various disease-specific and population genetic studies. The ExAC database includes six genetic polymorphisms in CD4 that result in amino acid changes and coincide with elements of the ibalizumab epitope (<http://exac.broadinstitute.org/gene/ENSG00000010610>). Three are within aa120-126 of the BC loop in D2 that mediate binding interactions with ibalizumab – S145N (S120N), P146H (P121H), and G148D (G123D). It is conceivable that any of these three polymorphisms could impact CD4 binding. That being said, all three are extremely rare with overall polymorphic frequencies of 0.00082%, 0.00082%, and 0.0033%, respectively.

The S145N and P146H polymorphisms were each represented by only a single database submission out of >66,700 alleles from non-Finnish European individuals in the database (<0.0015%), and they were not detected in African, East Asian, Finnish, Latino, or any other ethnic group. The G148D polymorphism was represented by four database submissions out of 10,404 sequences from African individuals (0.038%), but it was not detected in any other ethnic group. The other three polymorphisms are within aa163-165 of the FG loop in D2 – Q188K (Q163K), Q188E (Q163E), and Q190R (Q165R). Of these only the Q188K and Q188E polymorphisms might be expected to impact ibalizumab binding as Q190 was not sensitive to substitution in mutagenesis studies ([Song et al., 2010](#)), as described above. While the Q188K and Q188E polymorphisms could potentially impact CD4 binding, they are also extremely rare, with overall allelic frequencies of 0.00083%. The Q188K polymorphism occurred only once in 16,448 genomes from South Asian individuals (0.0061%) but occurred in no other ethnic groups, whereas the Q188E polymorphism occurred only once in 66,426 genomes from non-Finnish Europeans (0.0015%) but occurred in no other ethnic groups.

Because these databases were created to represent the human population distribution, it is reasonable to conclude that the likelihood of a patient carrying a CD4 variant with reduced ibalizumab binding is extremely low. Because of this, existing polymorphisms are unlikely to impact ibalizumab antiviral activity, receptor binding, receptor occupancy, or receptor density.

3. RELEVANT CLINICAL FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Summary of Clinical Efficacy (from the Statistics Review of Dr. Karen Qi)

The applicant submitted TMB-301 to support use of ibalizumab in the treatment of treatment-experienced adult subjects infected with multi-class drug resistant HIV-1. The proposed dosing regimen was administering a single loading dose of 2,000 mg ibalizumab followed by a maintenance dose of 800 mg ibalizumab every two weeks in combination of OBR for 24 weeks.

TMB-301 was a Phase 3 single-arm study that enrolled 40 subjects. There was no untreated control group as each subject's baseline to Day 7 viral load served as their comparator. Based on FDA HIV guidance document and the review team's recommendation, the study should include a short term (7 days – 2 weeks) ibalizumab monotherapy lead-in phase and subjects should be randomized to either continue their failing regimen plus placebo or to receive ibalizumab plus their failing regimen in this lead-in phase. However, due to the concern about the limited patient population of subjects infected with multi-class drug resistant HIV-1, the study instead included a control period from Day 0 to Day 6 where subjects were monitoring on their failing therapy or receiving no therapy. With such a design, the subjects served as their own control, and therefore the sample

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size was smaller than a two-arm, placebo-controlled study.

TMB-301 included two more periods in addition to the control period: 1) an essential monotherapy period from Day 7 to Day 13 where subjects received 2,000 mg loading dose of ibalizumab on Day 7 as well as continued with their failing regimen; and 2) a 23-week maintenance period from Day 14 to Week 25 where the subjects received 800 mg ibalizumab every two weeks in combination of OBR. In the study, the serum HIV-1 RNA level measured prior to the injection of the loading dose of ibalizumab on Day 7 was regarded as baseline, and the value prior to administering OBR on Day 14 was considered as the measurement at the end of the essential monotherapy period. The primary objective demonstrating the antiviral activity of ibalizumab on Day 14 was evaluated by the primary efficacy endpoint of the proportion of subjects achieving a $\geq 0.5 \log_{10}$ decrease from Day 7 to Day 14. However, subjects received both ibalizumab and OBR starting on Day 14 up to Week 25. Therefore, it was impossible to evaluate another primary objective of demonstrating the antiviral activity of ibalizumab at Week 25.

The study results demonstrated that 33 of the 40 (82.5%) subjects achieved a $\geq 0.5 \log_{10}$ decrease from Day 7 to Day 14. By contrast, only one subject (2.5%) achieved a $\geq 0.5 \log_{10}$ decrease from Day 0 to Day 7. Moreover, this subject had a protocol violation of taking OBR on Day 6. The study also showed that 42.5% of the subjects achieved HIV-1 RNA below 50 copies/mL at Week 25.

Finally, there were 18 subjects in TMB-301 receiving additional investigational drug, fostemsavir, as part of their OBR after Day 14. It was of clinical interest to compare efficacy endpoints at Week 25 between the subjects with and without receiving fostemsavir. However, it was difficult to interpret the analysis results since the determination of whether to add fostemsavir in the OBR was after Day 14 and possibly up to the subjects' response to ibalizumab.

The BLA also included TMB-202 which was a supportive Phase 2b trial. The study was a randomized double-blind trial conducted in a similar patient population to TMB-301. TMB-202 compared two ibalizumab dosing regimens, i.e., 800 mg ibalizumab Q2W plus OBR for 24 weeks and 2,000 mg ibalizumab Q4W plus OBR for 24 weeks. The study was not placebo controlled and all subjects received both ibalizumab and OBR throughout the trial. Therefore, the solitary treatment effect of ibalizumab could not be evaluated. The primary efficacy endpoint was the proportion of subjects achieving 50 copies/mL at Week 24. The study resulted in 44.1% of the subjects in the 800 mg ibalizumab Q2W plus OBR group and 27.8% in the 2,000 mg ibalizumab Q4W plus OBR group achieved 50 copies/mL at Week 24.

Based on the results, 800 mg ibalizumab Q2W plus OBR was selected to use in the maintenance period in TMB-301. Based on the results from TMB-301, the reviewer concluded that the proposed ibalizumab regimen was effective in treating the treatment-experienced HIV-1 infected adult subjects who have multi-class drug resistance and limited treatment choices.

3.2 Summary of Clinical Safety (from the Clinical Review of Dr. Virginia Sheikh)

The ibalizumab BLA contains substantial evidence of potency required by law 21 CFR 314.126 to support approval of ibalizumab for the treatment of HIV-1 infection in treatment-experienced adult patients with documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy. Phase 3 Trial TMB-301, performed in heavily treatment-experienced adults with multidrug resistant HIV-1 infection and persistent viremia despite antiretroviral therapy, demonstrated that ibalizumab treatment led to significant reductions in HIV-1 viral load. The majority (83%) of participants achieved a $0.5 \log_{10}$ decrease in HIV-1 RNA after one week of essential ibalizumab monotherapy, compared to only one participant (3%) who achieved the same decrease during the control period. Reductions in HIV-RNA levels are highly predictive of meaningful clinical benefit and analysis of clinical trial data submitted to the FDA demonstrate that a $0.5 \log_{10}$ HIV-RNA reduction in HIV-RNA is associated with a reduction in clinical disease

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progression. The secondary endpoint results, which provide support for the durability of ibalizumab, demonstrated that ibalizumab, in combination with various OBR drugs, led to sustained decreases in HIV-1 RNA.

The safety data submitted with this BLA demonstrate that ibalizumab treatment is associated with a favorable safety profile. The adverse events that occurred, regardless of severity, were generally consistent with events expected in patients with advanced HIV and MDR HIV. The following adverse reactions occurred in at least five percent of participants in the Phase 3 clinical trial (TMB-301); dizziness, diarrhea, rash, and nausea. One serious adverse reaction, immune reconstitution inflammatory syndrome, occurred in TMB-301. Analysis of the supportive Phase 2b trial TMB-202 and review of safety from early phase trials and expanded access studies show similar safety results.

The small size of the ibalizumab safety database and lack of placebo-control are two limitations of the ibalizumab application. Only 40 patients were exposed to the dosage regimen proposed in the label. A total of 303 patients were exposed, including 20 patients who received ibalizumab exclusively through expanded access studies. Only one Phase 2a trial (n=82) included a placebo control and those placebo arm participants were allowed to receive open-label ibalizumab if they experienced virologic failure after trial week 16. The lack of placebo control in the key trials also limited the reviewer's ability to determine if adverse events were the result of drug effect, underlying disease, or chance. The safety database of patients exposed to the intended dosage regimen is small, but sufficient to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need. Post-marketing pharmacovigilance will play an important role in further defining the safety profile of this drug, especially for rare adverse reactions

In conclusion, approval of ibalizumab, in combination with other antiretroviral(s) for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV infection and viremia despite antiretroviral therapy is fully supported by the available evidence of efficacy and safety.

3.3 Summary of Clinical Pharmacology (from Clinical Pharmacology Review of Dr. Qin Sun)

Pharmacodynamics

A clear trend was identified between exposure and response rate for the Phase 2b trial (TMB-202) with two different dose regimens evaluated. The recommended dose regimen would provide a higher probability of clinical success.

Pharmacokinetics

Ibalizumab administered as a single agent exhibits nonlinear pharmacokinetics. Following single-dose administrations of ibalizumab as 0.5 to 1.5-hour infusions, the area under the concentration-time curve increased in a greater than dose-proportional manner, clearance decreased from 9.54 to 0.36 mL/h/kg and elimination half-life increased from 2.7 to 64 hours as the dose increased from 0.3 to 25 mg/kg. The volume of distribution of ibalizumab was approximately that of serum volume, at 4.8 L.

Following the recommended dose regimen (2,000 mg as a loading dose and 800 mg once every 2 weeks as maintenance doses), ibalizumab concentrations reached steady-state levels after the first 800 mg maintenance dose with mean concentrations over 30 mcg/mL throughout the dosing period.

Specific Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates (age, body weight, sex, baseline CD4⁺ cell counts) on ibalizumab pharmacokinetics. The result suggests that body weight was the only statistically significant covariate and ibalizumab concentrations decreased as body weight increased; however, the effect has no clinical relevance and does not warrant dose adjustment.

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Pediatric/Geriatric Patients: Ibalizumab PK have not been evaluated in pediatric/geriatric patients.

Renal/Hepatic Impairment: No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of ibalizumab.

Drug Interaction studies

No drug interaction studies have been conducted with ibalizumab. Based on ibalizumab's mechanism of action and target-mediated drug disposition, drug-drug interactions are not expected.

4. CLINICAL VIROLOGY REVIEW OF EFFICACY

4.1 Summary of Key Efficacy Trials

The sponsor submitted clinical study reports for 5 clinical trials in support of BLA 761065, including two phase 1, two phase 2, and one pivotal phase 3 trial, and these trials are summarized below (Table 9).

Table 9: Clinical trials submitted for review as part of BLA761065 (DAVP analysis).

Protocol Number	Duration	Ibalizumab Dose (IV)	N	OBR	Study Year/Efficacy endpoints
Hu5A8.01 (TNX-355.01) Phase 1a	Single dose	0.3 mg/kg	6	no	2001-2002 HIV-1 RNA CD4 ⁺ cell counts T-lymphocytes
		1.0 mg/kg	6		
		3.0 mg/kg	6		
		10 mg/kg	6		
		25 mg/kg	6		
TNX-355.02 Phase 1b	10-11 W	10 mg/kg, Q1W*10 doses	9	no	2003 HIV-1 RNA CD4 ⁺ cell counts T-lymphocytes
		10 mg/kg loading (1W), 6 mg/kg Q2W*5 doses	10		
		25 mg/kg, Q2W*5 doses	3		
NCT00089700 TNX-355.03 Phase 2a	48W	15 mg/kg Q2W for 48 W	28	yes	2004-2006 HIV-1 RNA CD4 ⁺ cell counts T-lymphocytes
		10 mg/kg Q1W for 9 W, Q2W for 39 W	27		
		Placebo	27		
NCT00784147 TMB-202 (Phase 2b) Supportive	24 W	800 mg Q2W for 24 W	59	yes	2008-2011 HIV-1 RNA CD4 ⁺ cell counts
		2000 mg Q4W for 24 W	54		
NCT02475629 TMB-301 Phase 3 Pivotal	24 W	2000 mg loading (2 W), 800 mg Q2W for 22 W	40	yes	2015-2016 HIV-1 RNA CD4 ⁺ cell counts

Clinical trial TMB-301 is the only clinical trial that enrolled subjects who received doses of ibalizumab that are consistent with the indication being sought, and so this is considered the only pivotal clinical trial for this application. In addition, TMB-202 will be used as a supportive clinical trial given that subjects in this trial received similar doses in one Arm. Many clinical isolates from the earlier trials were characterized in the nonclinical development program for ibalizumab, and these isolates are described in the nonclinical virology section on [resistance](#) above or the [clinical resistance](#) section below.

4.2 TMB-202 (Treatment-experienced subjects infected with multi-drug resistant HIV-1)

Title
A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1 (Amended to 24 Week Study)

Summary of Design and Study Population

This Phase 2b, multicenter, randomized, double-blind study evaluated the effectiveness and safety of ibalizumab in subjects infected with HIV-1. To be considered for participation in the study, subjects had to have

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been receiving treatment with highly active antiretroviral therapy (HAART) for at least 6 months and were to be failing, or were to have recently failed (i.e., in the last 8 weeks) therapy. The two dose regimens of ibalizumab were randomly assigned in a 1:1 ratio to approximately 120 subjects. The random assignment was stratified by (a) use or non-use of a viral entry inhibitor, and (b) use or non-use of an integrase inhibitor in the OBR.

Subjects received one of the following two dose regimens:

- 800 mg of ibalizumab every 2 weeks (Q2W) plus OBR
- 2,000 mg of ibalizumab every 4 weeks (Q4W) and placebo on the intervening 2-week period visit, plus OBR

All subjects were to complete the Week 24/End of Study (EOS) and Week 28 Follow-up Visit procedures.

Beginning at the visit for Week 8, additional blood samples were collected over the following 4 weeks from subjects participating in the Pharmacokinetic Substudy, to further define the pharmacokinetic profile of ibalizumab.

During the study, all subjects received an investigator-selected OBR consisting of two to four antiretroviral agents. The selection of the OBR was aided by results of a screening resistance test and review of the subject's prior antiretroviral therapy. Once the screening resistance data became available and before randomization, the investigator selected an OBR, including at least one agent to which the subject's viral isolate was fully susceptible and which the subject was willing and able to take. After randomization, the OBR was not to be changed until the last infusion of study drug (up to 24 weeks of treatment) with the following exception:

- One OBR substitution was allowed for tolerability reasons provided the subject continued to meet inclusion criteria with the new OBR

Substitutions for intolerance were not required to be "within class". If a subject could not tolerate a minimum of one of the agents to which the virus was susceptible, the subject was not eligible to continue participation in this study.

For this study, prior exposure to integrase strand transfer inhibitors, R5 antagonists, or investigational antiretroviral agents not captured by resistance testing resulted in the subject's viral isolates being considered 'resistant' to those agents; if the subject had no prior exposure to these agents, the isolates were considered susceptible. Note that R4-tropic and dual-tropic virus, as indicated in the results of the Trofile™ assay, was considered "resistant" to R5 inhibitors, regardless of prior exposure.

Subjects who experienced virologic failure were discontinued from this study. Virologic failure was defined as two consecutive measurements (at least 14 days apart) of viral load indicating the following:

- A decrease of $<1.0 \log_{10}$ from Baseline starting at Weeks 12 and 14 (non-response), OR
- A viral load >50 copies/mL starting at Weeks 22 and 24 (suboptimal response or rebound)

Objectives

Primary

The primary objectives of this study were to:

- Evaluate the dose-response effectiveness of antiviral activity of the ibalizumab dose regimens at Week 24 in order to determine the optimal dose and regimen. The primary evaluation of effectiveness was based on the proportion of subjects achieving undetectable viral loads at Week 24 defined as <50 HIV-1 RNA copies/mL

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- Evaluate the safety and tolerability of two dose regimens of ibalizumab for dose selection

Secondary

The secondary objectives of this study were to:

- Evaluate changes from Baseline in viral load, CD4⁺ T-cell counts, and time to loss of virologic response (TLOVR)
- Characterize HIV-1 susceptibility changes associated with ibalizumab administration in combination with OBR
- Determine the presence and significance of anti-ibalizumab antibodies, if any (immunogenicity of ibalizumab)
- Assess CD4 receptor density and occupancy
- Determine the impact of ibalizumab on quality of life as assessed by subject-reported outcomes on questionnaires
- Evaluate the pharmacokinetic profile of two dose regimens of ibalizumab at steady state

FDA Clinical Virology Analysis of Efficacy

An overview of the clinical trial design and the primary and secondary endpoints is shown in Figure 18.

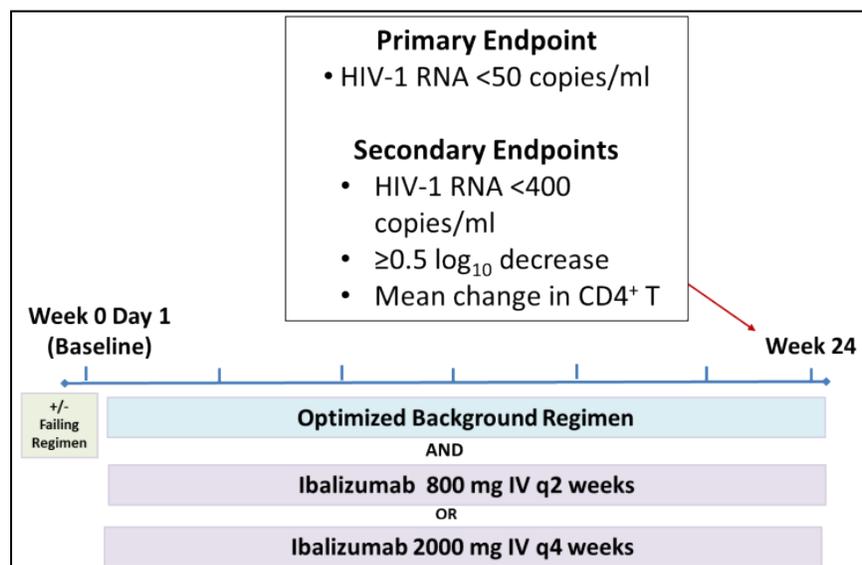


Figure 18: An overview of clinical trial TMB-202 (DAVP analysis).

The sponsor summarized the results for TMB-202 as follows:

1. viral load <50 copies/mL: 44% (26/59) for the 800 mg Q2W arm and 27.8% (15/54) for the 2,000 mg Q4W arm
2. viral load <200 copies/mL: 53% (31/59) for the 800 mg Q2W arm and 43% (23/54) for the 2,000 mg Q4W arm
3. viral load <400 copies/mL: 58% (34/59) for the 800 mg Q2W arm and 46% (25/54) for the 2,000 mg Q4W arm
4. a 1.0 \log_{10} reduction in viral load: 63% (37/59) for the 800 mg Q2W arm and 59% (32/54) for the 2,000 mg Q4W arm
5. a 0.5 \log_{10} reduction in viral load: was 68% (40/59) for the 800 mg Q2W arm and 59% (32/54) for the 2,000 mg Q4W arm

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The clinical virology assessment of efficacy was similar; however, there were small differences that were likely related to the sponsor's censoring of subjects (Table 10).

Table 10: Primary and secondary results for TMB-202 as calculated by Clinical Virology (DAVP analysis).

	<50 c/mL (% subjects)	<200 c/mL (% subjects)	<400 c/mL (% subjects)	Mean Log Reduction (SD)	% subj w/ 1 log reduction	% subj w/ 0.5 log reduction
2000 q4w (n=54)	27.8	46.3	55.6	1.8 (1.2)	72.2	79.6
800 q2w (n=59)	45.8	57.6	62.7	1.9 (1.1)	72.9	83.1

A graph showing the differences in primary and secondary endpoints by Arm is shown in Figure 19. Of note, the 800 Q2W arm performed better in all endpoints than the 2,000 Q4W, which provided evidence for the sponsor's rationale for selecting the 800 mg ibalizumab Q2W for the maintenance dose. The review team discussed the possibility that a 2,000 mg dose Q2W could be better, but ultimately agreed that the dose administration schedule and indication being sought were appropriate for approval.

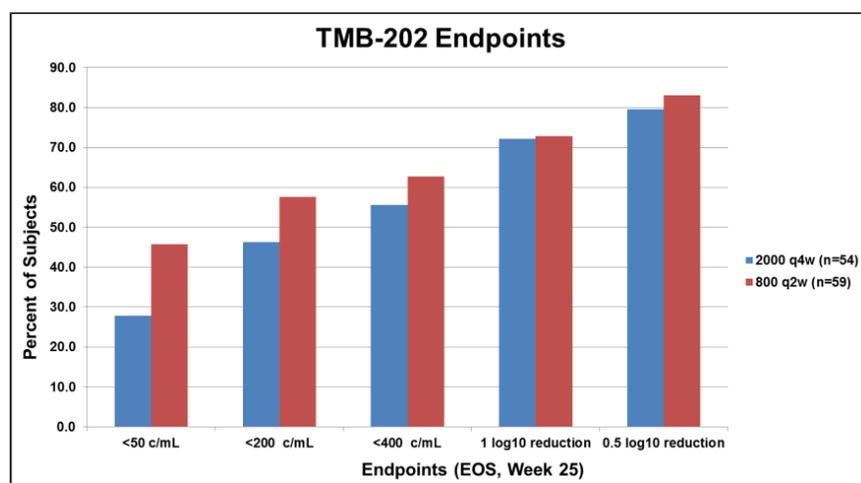


Figure 19: A comparison of endpoints for clinical trial TMB-202 (DAVP analysis).

In general, there was good agreement between the results reported by the sponsor and the results generated by DAVP using the data provided for the study; however, the results appeared to be better using the DAVP analysis due to differences in the subjects used for comparison (Clinical Virology did not censor any subjects). Of note, subgroup analyses performed for TMB-301 (see below) indicated that there might be a difference in efficacy based on HIV-1 tropism at baseline. Based on this observation, a subgroup analysis was performed for all subjects in TMB-202 to see if tropism had an impact on outcome (Table 11, Figure 20).

Table 11: TMB-202 subgroup analysis of efficacy based on tropism and by Arm (DAVP analysis).

ARM	Tropism	<50 c/mL (% subjects)	<200 c/mL (% subjects)	<400 c/mL (% subjects)	Mean Log Reduction (SD)	% subj w/ 1 log reduction	% subj w/ 0.5 log reduction
2000 q4w (n=54)	ALL (n=54)	15 (27.8)	25 (46.3)	30 (55.6)	1.8 (1.2)	39 (72.2)	43 (79.6)
	DM (n=33)	7 (21.2)	14 (42.4)	18 (54.5)	1.6 (1.1)	22 (66.7)	26 (78.8)
	R5 (n=15)	7 (46.7)	9 (60)	10 (66.7)	2.5 (1.1)	14 (93.3)	14 (93.3)
	X4 (n=4)	1 (25)	1 (25)	1 (25)	1.0 (1.7)	2 (50)	2 (50)
	Und (n=2)	1 (50)	1 (50)	1 (50)	1.4 (1.0)	1 (50)	1 (50)
800 q2w (n=59)	ALL (n=59)	27 (45.8)	34 (57.6)	37 (62.7)	1.9 (1.1)	43 (72.9)	49 (83.1)
	DM (n=33)	14 (42.4)	15 (45.5)	17 (51.5)	1.8 (1.2)	23 (69.7)	27 (81.8)
	R5 (n=15)	9 (60.0)	12 (80.0)	12 (80.0)	2.5 (0.9)	13 (86.7)	14 (93.3)
	X4 (n=6)	2 (33.3)	3 (50.0)	4 (66.7)	1.1 (0.9)	4 (66.7)	4 (66.7)
	Und (n=5)	2 (40.0)	4 (80.0)	4 (80.0)	1.8 (1.2)	3 (60.0)	4 (80.0)

Of note, the ten subjects infected with X4-tropic HIV-1 at baseline had worse overall outcomes than those subjects infected with R5-tropic or dual-tropic (also known as dual/mixed and abbreviated DM) virus at baseline (Table 11; tan highlighted rows and Figure 20, green bars). However, there were only 4 subjects (7.4%) in the 2,000 Q4W Arm and 6 subjects (10.2%) in the 800 2qw Arm who were infected with X4-tropic

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HIV-1 at baseline, so the numbers were too small for statistical significance (Figure 21). Looking at virologic failures by viral tropism at baseline combining both arms, 50% (n=30) of subjects infected with R5-tropic virus failed treatment, 70% (n=10) of subjects infected with X4-tropic virus failed treatment, and 68% (n=66) of subjects infected with DM-tropic virus failed treatment.

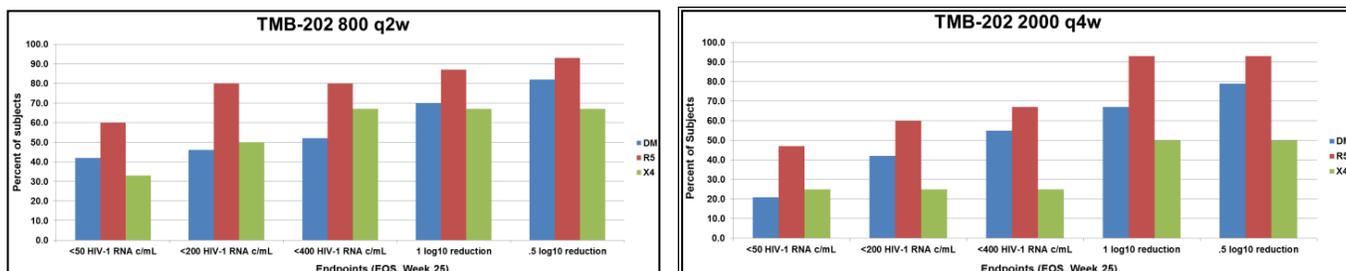
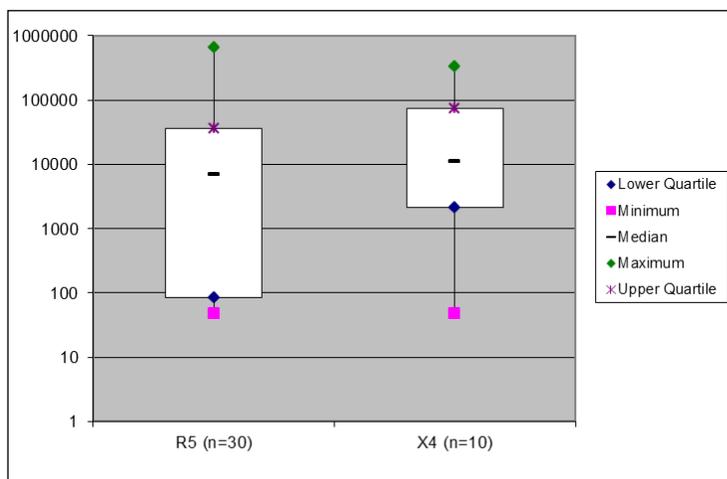


Figure 20: Graphical representation of TMB-202 subgroup analysis of efficacy based on tropism and by Arm (DAVP analysis).

There are at least two possible explanations for this observation. First, subjects with X4-tropic HIV-1 are often in the advanced stages of AIDs, and these subjects generally have worse outcomes. Second, viruses with co-receptor tropism differences have several amino acid differences in gp120 which could have an impact on ibalizumab activity. In particular, amino acid changes in or near the V5 loop could potentially alter the amino acid side chains or glycosylation moieties that project into a structural void between the gp120 V5 loop and the ibalizumab light chain to induce a steric hindrance that reduces the efficiency with which ibalizumab binds CD4.



R5 (n=30)	
Lower Quartile	85.6
Minimum	47
Median	7053.333334
Maximum	657500
Upper Quartile	35658.33334

X4 (n=10)	
Lower Quartile	2162.5
Minimum	47
Median	11113.33334
Maximum	329333.3333
Upper Quartile	73275

Figure 21: Comparison of the overall End of Study HIV-1 RNA copies/mL for subjects infected with X4-tropic versus R5-tropic HIV-1 (DAVP analysis).

Overall, the efficacy results from TMB-202 support approval of ibalizumab, but ibalizumab and the roles of tropism and ibalizumab resistance will be reviewed in detail below.

4.3 TMB-301 (Treatment-experienced subjects infected with multi-drug resistant HIV-1)

Title
A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1

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Summary of Design and Study Population

This study was a Phase 3, single-arm, multicenter study designed to assess the antiviral activity, efficacy, safety, and tolerability of an IV ibalizumab dose regimen in treatment-experienced subjects infected with multi-drug resistant HIV-1. Pharmacokinetics and QoL were also evaluated. Subjects must have been treated with highly active antiretroviral therapy (HAART) for at least 6 months and were failing or had recently failed (i.e., in the last 8 weeks) therapy to determine baseline viral load. All subjects also received a standard-of-care OBR consisting of ARV medications selected by the Investigator on the basis of the subject's treatment history and the results of viral resistance testing. The primary evaluation of efficacy was performed at Day 14. Additional secondary evaluations were conducted at Week 25 (EOS).

The study consisted of three periods: a 6 day control period (Days 0–6), an essential 6 day monotherapy period (Days 7–13), and a 23 week maintenance period (Day 14–Week 25). During the control period (Days 0–6) subjects were monitored on current failing therapy (or no therapy, if the subject had failed and discontinued treatment within the 8 weeks preceding Screening). During the essential monotherapy period (Days 7–13) subjects continued on current failing therapy, receiving one 2,000-mg dose (loading dose) of ibalizumab on Day 7. Day 7 was considered Baseline for the treatment period (Day 7–Week 25).

Day 14 through Week 25 of the study represented the maintenance period. On Day 14 (primary endpoint), the OBR was initiated and must have included at least one agent to which the subject's virus was fully susceptible (as determined at Screening, in combination with historical resistance testing). Beginning at Day 21, 800 mg of ibalizumab was administered every 2 weeks (Q2W) through Week 23. All subjects were to complete the Week 25/EOS Visit and the Week 29/Follow-up Visit procedures. Virologic failure was defined as two consecutive viral load measurements of less $<0.5 \log_{10}$ decline from the baseline viral load beginning at Day 14. Subjects were discontinued from the study at the subject's request or if the subject became pregnant, upon the occurrence of any Grade 3 or 4 treatment-related abnormalities, at Investigator request, for protocol violation, for serious or intolerable AEs, or for toxicity (defined as two consecutive laboratory results, at least 14 days apart, with a CD4⁺ cell count <200 cells/mm³ that also represented a 50% reduction from the baseline CD4⁺ cell count).

FDA Clinical Virology Analysis of Efficacy

TMB-301 was conducted with 40 subjects infected with HIV-1 with documented resistance to at least one drug in three different drug classes. The trial was designed to establish the efficacy of ibalizumab as a monotherapy during the first week of the trial, and then add-on an optimized background regimen (Figure 22).

The sponsor reported that in treatment-experienced subjects infected with multi-drug resistant HIV-1 who received a 2,000-mg loading dose of ibalizumab at Day 7 (Baseline) followed by 800-mg doses of ibalizumab every other week in combination with OBR starting at Day 14, a statistically significant number of subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from Baseline (Day 7) to Day 14 ($n=33$; 82.5%; $p<0.0001$). Other clinically meaningful reductions in viral load observed at Day 14 and Week 25 (EOS) in the ITT population included:

- 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from Baseline (Day 7) to Week 25 (EOS)
- 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at Week 25 (EOS)
- 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at Week 25 (EOS)
- 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from Baseline (Day 7) to Week 25 (EOS)

Of note, breaking down the secondary endpoints by OSS indicated that those with one or more active drugs in the OBR had better outcomes at the EOS than those without an active drug in the OBR. Here are the outcomes based on OSS score:

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1. **OSS = 0 (n=5)**; 20% of subjects achieved HIV-1 RNA <50 copies/mL and 20% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
2. **OSS = 1 (n=12)**; 42% of subjects achieved HIV-1 RNA <50 copies/mL and 50% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
3. **OSS = 2 (n=18)**; 72% of subjects achieved HIV-1 RNA <50 copies/mL and 72% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
4. **OSS = 3 (n=3)**; 33% of subjects achieved HIV-1 RNA <50 copies/mL and 33% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
5. **OSS = 4 (n=2)**; 50% of subjects achieved HIV-1 RNA <50 copies/mL and 50% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)

Of note, it was surprising that subjects with a higher OSS of 3 and 4 did not fare better on the OBR + ibalizumab than subjects with lower OSSs of 1 or 2; however, the number of subjects with higher OSS scores was limited by baseline resistance criteria for the study. In addition, poor adherence to the OBR may have been a factor.

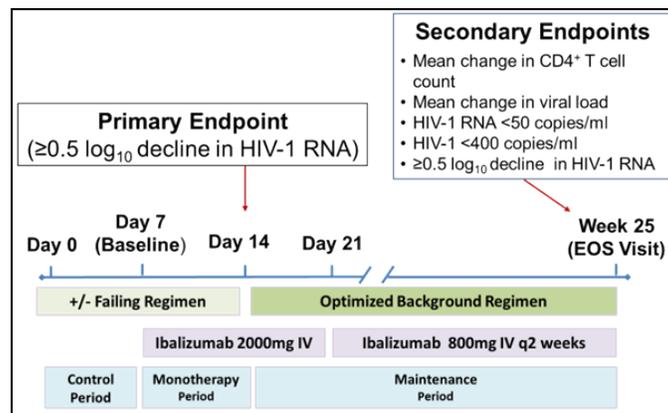


Figure 22: TMB-301 study design and endpoints (DAVP analysis).

Positive responses to treatment with ibalizumab when added to an OBR in treatment-experienced subjects infected with multi-drug resistant HIV-1 were observed with regard to HIV-1 RNA levels and CD4⁺ cell counts for subjects in the ITT population as follows:

- The median change from Day 7 (Baseline) to Day 14 in viral load was a 1.0 log₁₀ reduction (range -0.3 to 2.1 log₁₀ reduction in HIV-1 RNA copies/mL; mean = 1.06±0.61 log₁₀ reduction; n=40)
- The median change from Day 7 (Baseline) to Week 25 EOS in viral load for all subjects who had a Day 7 and Week 25 value was a 2.4 log₁₀ reduction (range -0.1 to 5.3 log₁₀ reduction; n=32). The mean change reported by the sponsor from Day 7 (Baseline) to Week 25 (EOS) in viral load was a 1.64 log₁₀ reduction
- The sponsor reported that the mean increase from Day 7 (Baseline) to Week 25 (EOS) in CD4⁺ cell counts was 62.4 cells/mm³

The sponsor stated that analysis of CD4 receptor occupancy (RO) and CD4 receptor density (RD) indicated that most subjects maintained consistently high levels of CD4 RO. A modest (up to 23%) reduction in CD4 RD was observed over time in response to ibalizumab treatment. The sponsor noted that exploratory analysis of ibalizumab serum concentrations and RO indicated a dose-response relationship. The sponsor also reported that a more sensitive bioanalytical assay was used in this study to measure ibalizumab concentrations in serum. The resulting data support the conclusion that >125 ng/mL ibalizumab in blood is sufficient to saturate

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CD4 receptors on circulating CD4⁺ T cells. The sponsor concluded that robust virologic responses at Week 25 were observed in association with intermediate and high CD4 RO. The sponsor reported that no subjects developed anti-drug antibodies (ADAs) during 24 weeks of treatment with ibalizumab.

Of note, the assays for assessing RO and RD were validated, but the Clinical Pharmacology reviewer informed Clinical Virology that there were no bioanalytic assessments made or reports written or submitted by the sponsor. An Information Request was sent to the sponsor requesting these data, and the FDA was informed that no bioanalytical reports were prepared. Therefore, the data provided for RO and RD assessments are not considered to be robust and reproducible. Therefore, these data will be used to make comparisons, but no conclusions can or will be drawn using these data.

- Day 0-6 (control period). During Days 0 through 6 subjects were monitored on current failing therapy (or no therapy).
- Day 7-13 (essential monotherapy period). During Days 7 through 13 subjects continued on current failing therapy and received one 2,000 mg dose (loading dose) of ibalizumab on Day 7. Day 7 is Baseline for the treatment period (Day 7-Week 25).
- Day 14-Week 25 (maintenance period). On Day 14 (primary endpoint), the optimized background regimen was initiated and was to include at least one agent to which the subject's virus was fully susceptible. Beginning at Day 21, 800 mg of ibalizumab was administered every 2 weeks through Week 23.
- All subjects were to complete the Week 25/EOS Visit and the Week 29/Follow-up Visit procedures.

Virologic failure was defined as 2 consecutive viral load measurements of less than a 0.5 log₁₀ decline from the baseline viral load beginning at Day 14.

Subjects were to be discontinued from the study at the subject's request or if the subject became pregnant, upon the occurrence of any Grade 3 or 4 treatment related abnormalities, at investigator request, for protocol violation, for a serious or intolerable adverse event (AE), or for toxicity (defined as 2 consecutive laboratory results, at least 14 days apart, with a CD4⁺ cell count below 200 cells/mm³ that also represents a 50% reduction from the baseline CD4⁺ cell count).

DAVP Efficacy Results

Primary endpoint. The primary endpoint for TMB-301 was ≥ 0.5 log₁₀ decline in HIV-1 RNA copies/mL from Baseline to Day 14. In agreement with the results provided by the sponsor, Clinical Virology analysis indicated that 82.5% (33/40 subjects) met the primary endpoint. In addition, 52.5% (21/40 subjects) had a ≥ 1.0 log₁₀ reduction on monotherapy with a median 1.0 log₁₀ reduction (range -0.3 to 2.1, n=40) (Figure 23).

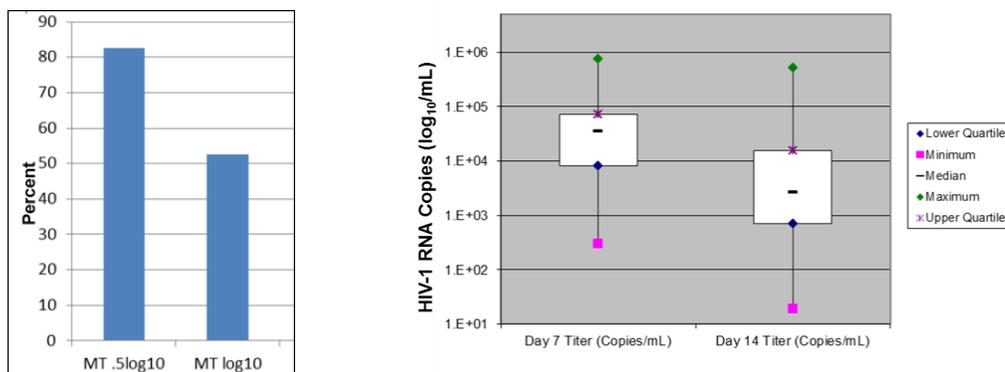


Figure 23: TMB-301 study design and endpoints (DAVP analysis).

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Poor responders to ibalizumab monotherapy. Five subjects did not have a robust response to ibalizumab monotherapy, including subjects 04-001, 05-001, 05-003, 17-003, and 27-001 (Figure 24). Two additional subjects only achieved a 0.3 log₁₀ reduction during ibalizumab monotherapy and these subjects were 08-001 and 21-002 (Figure 24).

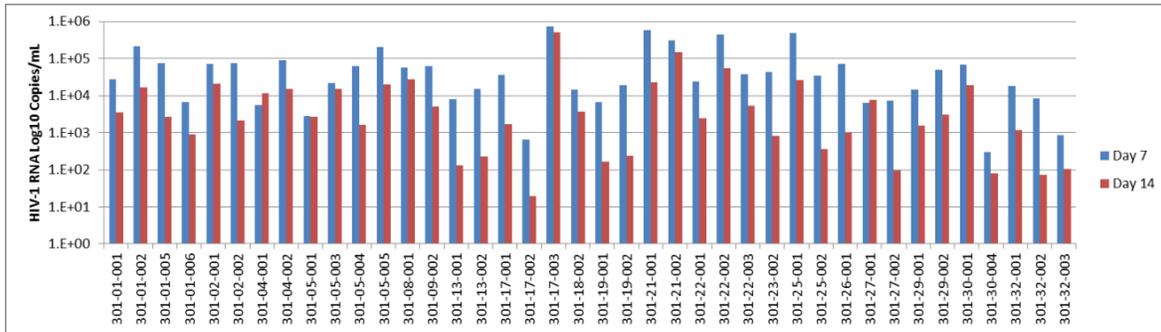


Figure 24: Poor responders to ibalizumab monotherapy (DAVP analysis).

However, despite the poor response during the monotherapy phase of this clinical trial, overall, these subjects fared equal to or better than other subjects in this trial when comparing secondary endpoints (Table 12) indicating that the response was primarily driven by the OBR in these subjects. Of note, only subject 08-001 had an OSS <1, whereas subject 21-002 had an OSS = 1 but discontinued prior to the end of the study and the remaining 5 subjects all had OSS = 2. In addition, 12.5% of subjects (n=5 of 40) had OSS >1 in TMB-301, and the OSS had no impact on the ibalizumab monotherapy outcome (Table 12). Please see the Secondary Endpoints section below for more details.

Table 12: Analysis of subject outcomes based on mean log₁₀ reduction during the ibalizumab monotherapy phase of TMB-301 (Day 7-Day 13)(DAVP analysis).

IBA Monotherapy log ₁₀ reduction	No.	IBA Monotherapy	Primary	EOS				OSS >1 (%)
		HIV-1 RNA Log ₁₀ ↓	MT .5log ₁₀ (%)	<50 (%)	<200 (%)	HIV-1 RNA Log ₁₀ ↓	VF Rate	
<0.5	7	0.1 (0.2)	0.0	42.9	42.9	1.5 (1.1)	57.1	86.0
0.5 to .999	10	0.7 (0.2)	100.0	30.0	50.0	2.4 (1.3)	70.0	90.0
1.0 to 1.499	11	1.2 (0.2)	100.0	27.3	27.3	2.0 (2.0)	72.7	82.0
≥1.5	12	1.8 (0.2)	100.0	66.7	75.0	3.3 (1.4)	33.3	92.0

Secondary endpoints. In addition to the primary endpoint, there were five secondary endpoints assessed for TMB-301 (Table 13).

Table 13: Secondary endpoints assessed for TMB-301 (Day 14-EOS)(DAVP analysis).

- Mean change in CD4⁺ T cell counts
- Mean change in viral load
- HIV-1 RNA <50 copies/ml
- HIV-1 <400 copies/ml
- ≥0.5 log₁₀ decline in HIV-1 RNA

Mean change in CD4⁺ T cell counts. The mean change in CD4⁺ T cells was assessed at various timepoints; however, in several instances data were missing at key timepoints. The Statistical reviewer will perform CD4⁺ T cell analyses using the Last Observation Carried Forward (LOCF) method to account for missing data. For the calculations presented here, samples from n=27 collected at Day 7, samples from n=37 subjects collected at Day 14, and samples from n=27 subjects collected at EOS were evaluated. Of note, the samples were not necessarily collected from the same subjects.

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There was a small difference between CD4⁺ T cells during the monotherapy phase (comparing Day 7 to Day 14) with a Day 7 median of 89.5 cells/mm³ (n=32; range 0-676; mean 161 ± 186 cells/mm³) compared to a Day 14 median of 76 cells/mm³ (n=37; range 0-942; mean 110 ± 124 cells/mm³) representing a decline of 13.5 cells/mm³ (Figure 25). The EOS median of 208 cells/mm³ (n=27; range 2-791; mean 240 ± 206 cells/mm³) representing an increase of 118.5 cells/mm³ (Figure 25). By comparison, the sponsor reported a mean increase from Day 7 (Baseline) to Week 25 (EOS) in CD4⁺ cell counts of 62.4 cells/mm³.

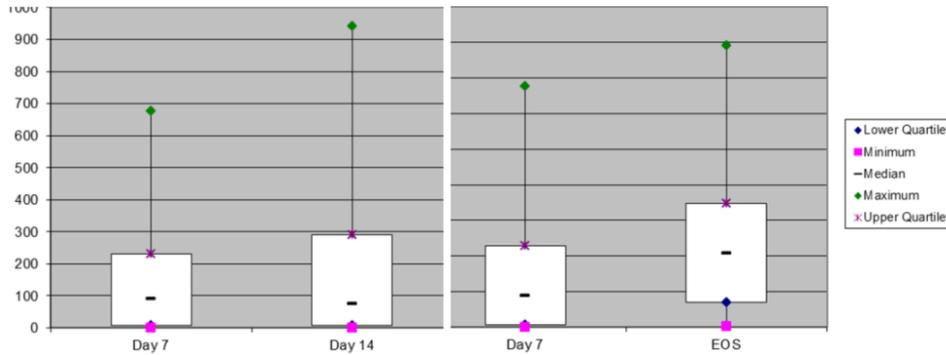


Figure 25: A comparison of CD4⁺ cell counts at Day 7 and Day 14 (Panel 1; monotherapy) and Day 7 and EOS (Panel 2)(DAVP Analysis). The Y-axis represents CD4⁺ T cells in units of cells/mm³.

There were paired Day 7 and EOS CD4⁺ T cell count samples for 21 subjects, and these were also assessed. In this subgroup, the Day 7 median was 189 cells/mm³ (n=21; range 3-676; mean 199 ± 177 cells/mm³) compared to a EOS median of 225 cells/mm³ (n=21; range 2-791; mean 257 ± 211 cells/mm³) representing a median increase of 36 cells/mm³ and a mean increase of 58 cells/mm³ which was similar to the results reported by the sponsor (data not shown).

Mean change in viral load as assessed by HIV-1 RNA copies/mL. The change in viral load was assessed by comparing values observed at Day 7, Day 14, and at EOS. Of note, Clinical Virology calculated means and medians using all of the available data, which included data from n=40 subjects for samples from Day 7 and Day 14, and samples from n=32 subjects taken at baseline. The median viral load at Day 7 was 3.5x10⁴ HIV-1 RNA copies/mL (range 3.0x10² to 7.4x10⁵ HIV-1 RNA copies/mL; n=40; mean was 1x10⁵ ± 1.7x10⁵ HIV-1 RNA copies/mL). At Day 14, the median viral load was 2.7x10³ HIV-1 RNA copies/mL (range 1.9x10¹ to 5.2x10⁵ HIV-1 RNA copies/mL; n=40; mean viral load was 2.4x10⁴ ± 8.3x10⁴ HIV-1 RNA copies/mL) representing a median difference of 1.1 log₁₀ and a mean difference of 0.6 log₁₀ HIV-1 RNA copies/mL. The median viral load at EOS was 2.7x10¹ HIV-1 RNA copies/mL (range 1.0x10⁰ to 2.7x10⁵ HIV-1 RNA copies/mL; n=32; mean viral load at EOS was 1.5x10⁴ ± 4.9x10⁴ HIV-1 RNA copies/mL) representing a median difference of 3.1 log₁₀ HIV-1 RNA copies/mL and a mean 0.8 log₁₀ reduction in HIV-1 RNA copies/mL (Figure 26).

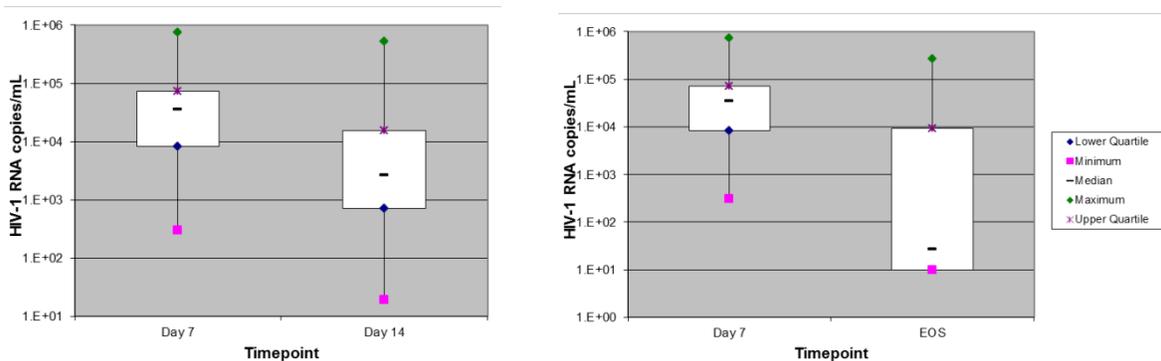


Figure 26: Median reductions in HIV-1 RNA copies/mL from Day 7 to Day 14 and Day 7 to EOS (DAVP Analysis).

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The sponsor reported the mean change from Day 7 (Baseline) to Day 14 in viral load was a 1.07 log₁₀ reduction in HIV-1 RNA copies/mL. The mean change from Day 7 (Baseline) to Week 25 (EOS) in viral load was a 1.64 log₁₀ reduction of HIV-1 RNA copies/mL. The difference in calculations are attributable to the different populations analyzed, as Clinical Virology analyzed data from all 40 subjects whereas the sponsor reported results for the Intent to Treat, Missing Equals Failure (ITT-MEF) population.

Additional secondary endpoints. The percent of subjects who achieved <400 HIV-1 RNA copies/mL, <200 HIV-1 RNA copies/mL, and <50 HIV-1 RNA copies/mL and reductions of 0.5 or 1 log₁₀ are shown in Figure 27.

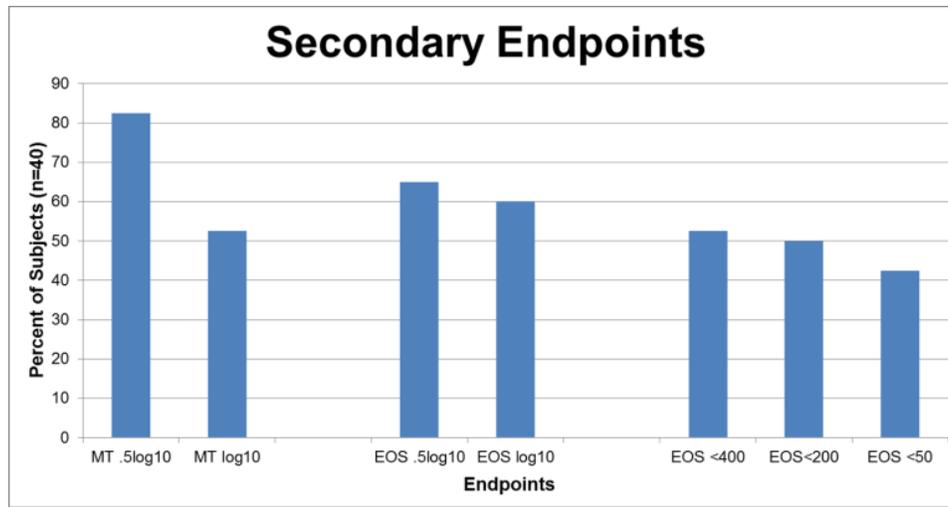


Figure 27: Median reductions in HIV-1 RNA copies/mL from Day to Day 14 and Day 7 to EOS (DAVP Analysis).

Overall, there was good agreement between the results reported by the sponsor and the percentages calculated in Figure 27. In addition, the analyses of the secondary endpoints for TMB-301 provided further support for the approval of BLA 761065.

Subgroup Analysis

Subgroup analyses of subject information from TMB-301 were performed to see if any differences in subgroup efficacy could be attributed to the mechanism of action for ibalizumab (Table 14). Several subgroups were selected for analysis:

1. **Baseline viral load** – was assessed to determine if baseline viral load had an impact on ibalizumab susceptibility.
2. **Baseline HIV-1 resistance status (OSS, GSS, PSS)** – was assessed to determine if HIV-1 strains resistant to several drug classes were less susceptible to ibalizumab.
3. **Tropism** – was assessed to determine if differences in viral tropism at baseline result in differences in ibalizumab susceptibility.
4. **CD4⁺ T cell count** – was assessed to determine if CD4⁺ T cell count correlates with ibalizumab susceptibility.
5. **Receptor occupancy** – was assessed to determine if receptor occupancy correlates with ibalizumab susceptibility.
6. **Other factors** – Several other factors were assessed to see if any subgroup experienced lower efficacy than the norm.

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Table 14: Results of subgroup analysis (DAVP Analysis).

Subgroup		IBA Monotherapy	Primary Endpoint	Subgroup		IBA Monotherapy	Primary Endpoint
N/A	No.	Mean HIV-1 RNA Log10 ↓	Percent	RD Day 7	No.	Mean HIV-1 RNA Log10 ↓	Percent
	40	1.1	82.5				
Viral Load							
>100k	7	0.88 (0.44)	71.4	<10 ⁵	3	0.9 (0.4)	66.7
<100k	33	1.09 (0.64)	84.8	>10 ⁵	29	1.0 (0.6)	82.8
				Und	8	1.2 (0.6)	87.5
OSS				RO Day 7			
0	5	1.1 (0.4)	80	<20%	4	0.7 (0.3)	75
1	12	1.3 (0.5)	91.7	20-100%	13	1.2 (0.6)	92.3
>=2	23	0.9 (0.6)	78.3	>100%	13	1.0 (0.6)	69.2
				Und	10	1.2 (0.6)	90
GSS				RO Day 14			
0	13	1.2 (0.6)	84.6	<20%	1	0.03	0
1	13	1.0 (0.6)	76.9	20-100%	16	1.0 (0.6)	75
>=2	14	1.0 (0.5)	85.7	>100%	20	1.1 (0.6)	90
				Und	3	1.4 (0.3)	33
PSS				Investigational			
0	5	1.4 (0.3)	100	With Fostemsavir	16	1.0 (0.6)	81.3
1	9	1.3 (0.6)	77.8	Without	24	1.1 (0.6)	83.3
>=2	26	0.9 (0.6)	80.8	INSTI			
				Susceptible	13	1.19 (0.53)	92.3
Tropism				Resistant	27	0.99 (0.64)	77.8
DM	28	1.1 (0.6)	85.7	Race			
R5	5	0.8 (0.5)	80	Asia	4	0.8 (0.3)	100
X4	5	0.6 (0.4)	60	Black	22	1.1 (0.5)	84.6
und	2	1.5 (0.3)	100	Latino	1	-0.3	0
				White	13	1.1 (0.6)	81.8
CD4 Cell counts							
<50	18	0.95 (0.55)	77.8				
50-200	11	1.24 (0.75)	81.8				
>200	11	1.05 (0.51)	90.9				

Overall, the subgroups of interest are highlighted in yellow in Table 14 and these included:

- Tropism – subjects infected with the X4-tropic HIV-1 at baseline had worse efficacy outcomes compared with R5- and DM-tropic HIV by the end of treatment. However, only 5 subjects were infected with the X4-tropic HIV-1 at baseline, and there was only one additional subject who met the primary endpoint from the R5-tropic subgroup.
- Receptor Density – subjects with CD4 RD <100,000 Molecules of Equivalent Soluble Fluorochrome (MESF) at baseline (Day 7 post-infusion). However, only 3 subjects had CD4 RD <100,000 MESF at baseline (Day 7 post-infusion).
- Receptor Occupancy – subjects with >100% RO at Day 7 post-infusion and <20% at Day 14 had worse outcomes than subjects with RO between 20-100% at both timepoints; however, overall the numbers were too small to draw conclusions. Only one subject had CD4 RO <20% at Day 14. It is not clear why subjects who had RO >100% at Day 7 post-infusion would have worse outcomes, or why a measurement of greater than 100% was possible. This could represent a problem with the assay. Of note, the sponsor did not provide bioanalytical analysis data for their receptor occupancy data and therefore this information cannot be validated (b) (4).

Overall, the subgroup analysis did not identify any particular subgroup that could be a marker for less ibalizumab susceptibility. This was due in part to the small numbers of subjects in the subgroups, the variable OBR, and potentially confounding factors, such as X4-tropic HIV-1 is more commonly associated with patients who are in the advanced stages of AIDS. However, tropism will be reviewed in more detail below.

Expanded Resistance Assessments

The OBR added onto ibalizumab treatment on Day 7 was assessed by resistance testing to determine which drugs in the OBR the HIV-1 isolate was susceptible to in addition to any activity that ibalizumab might have against the isolate. Fostemsavir, an investigational drug, was given in the OBR of 18 subjects and it was scored based on treatment history and resistance testing. Of the 18 subjects who received fostemsavir, 14/18 (78%) met the primary endpoint and 33% and 44% had <50 and <200 HIV-1 RNA copies/mL at the end of the study, respectively. At the beginning of the study, 35 subjects were determined to be susceptible to fostemsavir, but susceptibility of the investigational product was not assessed at later timepoints. In addition to the resistance assessments looking at the Optimized Susceptibility Score (OSS) ≥2 (see Table 14), we also wanted to assess the OSS at higher values to see if there was a subgroup that may not require the addition of ibalizumab in the OBR. In general, subjects with OSS, ≥3 did not have significantly better outcomes than the

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norm for this trial (Table 15). Some categories that had large differences had small sample sizes.

Table 15: Efficacy assessments for subjects with all OSS, GSS, and PSS scores (DAVP Analysis).

Subgroup	No.	IBA Monotherapy	Primary	EOS		
		HIV-1 RNA Log10 ↓	MT .5log10	<50 (%)	<200 (%)	HIV-1 RNA Log10 ↓
All	40	1.1 (0.6)	82.5	42.5	50.0	2.4 (1.7)
OSS						
0	5	1.1 (0.4)	80.0	20.0	20.0	0.8 (1.1)
1	12	1.3 (0.5)	91.7	41.7	50.0	2.9 (1.7)
2	18	0.9 (0.7)	72.2	50.0	61.1	2.5 (1.3)
3	3	1.2 (0.3)	100.0	33.3	33.3	2.7 (2.6)
4	2	0.9 (0.0)	100.0	50.0	50.0	4.2 (0.0)
GSS						
0	13	1.2 (0.6)	84.6	23.1	38.5	1.7 (1.6)
1	13	1.0 (0.6)	76.9	61.5	61.5	2.9 (1.5)
2	10	1.0 (0.6)	80.0	50.0	60.0	2.7 (1.5)
3	2	1.3 (0.3)	100.0	0.0	0.0	0.1 (0.0)
4	2	0.9 (0.0)	100.0	50.0	50.0	4.2 (0.0)
PSS						
0	5	1.4 (0.3)	100.0	40.0	40.0	1.6 (1.5)
1	9	1.3 (0.6)	77.8	22.2	33.3	1.9 (1.8)
2	10	1.1 (0.6)	90.0	60.0	70.0	2.6 (1.3)
3	10	0.9 (0.5)	80.0	40.0	50.0	2.6 (1.6)
4	4	0.9 (0.5)	75.0	50.0	50.0	3.2 (1.9)
5	1	-0.3 (0.0)	0.0	0.0	0.0	1.0 (0.0)
und	1	1.9 (0.0)	100.0	100.0	100.0	4.3 (0.0)

Note: The GSS, PSS, and OSS evaluations provided by the sponsor were independently assessed by Clinical Virology, and our independent OSS calculations were in agreement with those provided by the sponsor.

Tropism and Impact on Ibalizumab Efficacy

As noted in the TMB-202 section on tropism, subjects infected with X4-tropic HIV-1 at baseline had worse overall outcomes than subjects infected with HIV-1 that were R5-tropic or DM. This trend was also observed in TMB-301 (Table 16).

Table 16: Efficacy assessments for HIV-1 with different tropisms derived from subjects at baseline (DAVP Analysis).

ARM	Tropism	<50 c/mL (% subjects)	<200 c/mL (% subjects)	<400 c/mL (% subjects)	Mean Log Reduction (SD)	% subj w/ 1 log reduction	% subj w/ 0.5 log reduction
2000 LD, 800 q2w (n=40)	ALL	17 (42.5)	20 (50)	21 (52.5)	1.1 (0.6)	24 (60)	26 (65)
	DM (n=28)	11 (39.3)	14 (50.0)	15 (53.6)	2.5 (1.6)	16 (57.1)	24 (85.7)
	R5 (n=5)	4 (80.0)	4 (80.0)	4 (80.0)	3.7 (1.1)	2 (40.0)	4 (80.0)
	X4 (n=5)	1 (20.0)	1 (20.0)	1 (20.0)	0.8 (1.3)	1 (20.0)	3 (60.0)
	Und (n=2)	1 (50.0)	1 (50.0)	1 (50.0)	2.2 (1.7)	2 (100.0)	2 (100.0)

Of the five subjects in TMB-301 who were infected with X-4 tropic HIV-1 at baseline, only one subject achieved <50 copies/mL, <200 copies/mL, or <400 copies/mL of HIV RNA by EOS (Figure 28). These results were similar to those observed in TMB-202.

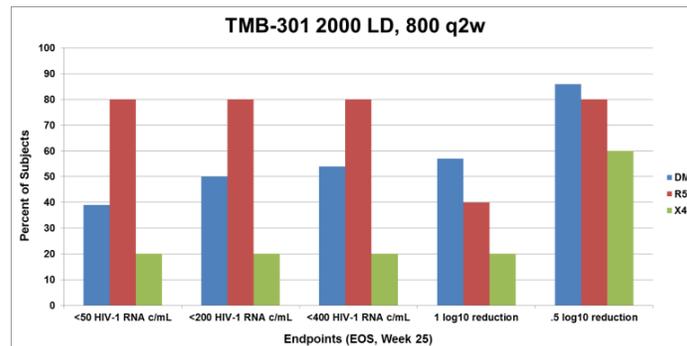


Figure 28: Efficacy assessments of TMB-301 secondary endpoints for HIV-1 with different tropisms derived from subjects at baseline (DAVP Analysis).

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4.4 Pooled Efficacy Success and Virologic Failure Rates

Table 17 provides a pooled summary of efficacy and virologic failure results for 153 subjects from TMB-202 and TMB-301. For all HTE subjects who received ibalizumab in the various doses and time periods assessed in these clinical trials, 37.9% (59/153) achieved <50 HIV-1 RNA copies/mL at the end of treatment, 52.3% of these subjects had <400 HIV-1 RNA copies/mL, and a combined virologic failure rate of 15.7%. Of note, the failure rate was based on the protocol defined virologic failure definition for each clinical trial.

Table 17: Pooled efficacy endpoints and virologic failure rates (DAVP Analysis).

Endpoints	TMB-202		TMB-301	ALL
	800 mg q2wk	2000 mg q4wk	2000 mg LD; 800 mg q2wk	n/a
≥0.5 log ₁₀ decline in HIV-1 RNA (MT)	n/a	n/a	82.5% (34/40)	82.5% (34/40)
HIV-1 RNA <50 copies/ml	44% (26/59)	27.8% (15/54)	42.5% (17/40)	37.9% (58/153)
HIV-1 RNA <400 copies/ml	58% (34/59)	46% (25/54)	52.5% (21/40)	52.3% (80/153)
≥0.5 log ₁₀ decrease	68% (40/59)	59% (32/54)	65% (25/40)	63.4% (97/153)
Mean change in CD4 ⁺ T	37 ± 63	40 ± 80	62 ± 106 cells	45 cells
Mean change in viral load	1.6 ± 1.3 log ₁₀	1.5 ± 1.4 log ₁₀	1.6 ± 1.5 log ₁₀	1.6 log ₁₀
VF Rate*	15.3 (n=9)	14.8 (n=8)	17.5 (n=7)	15.7 (n=34)

MT=ibalizumab monotherapy; n/a=not applicable; *=virologic failure rate was based on the number of subjects who met the protocol defined definition of virologic failure

Of note, given that ibalizumab was dosed in conjunction with an OBR, it is nearly impossible to determine the number of subjects who experienced treatment failure with ibalizumab alone. Therefore, these virologic failure rates reflect subjects who failed the OBR. The ibalizumab failure rate is likely higher but masked by components of the OBR that retained activity against HIV-1.

4.5 Durability of Efficacy Success

The durability of ibalizumab is difficult to assess directly because of the addition of an OBR that was added-on after 1 week of essential monotherapy with ibalizumab. However, comparing the secondary endpoint of percent of subjects with <50 HIV-1 RNA copies/mL at the end of the study, which was 42.5%, to the same endpoint that was the primary endpoint at the end of ibalizumab monotherapy and was reached by 82.5% of subjects, it is clear that ibalizumab (and probably other drugs in the OBR) was not durable in this population.

In addition, given that ibalizumab exhibited a low barrier to resistance during nonclinical development and in clinical trials that explored the use of ibalizumab as a monotherapy, it appears that ibalizumab rapidly selects for variants of HIV-1 that are less susceptible to this drug, and therefore, this drug should not be used as a monotherapy under any circumstances.

5. IBALIZUMAB RESISTANCE IN CLINICAL TRIALS

5.1 Overview of Available Data and Resistance Analysis Methods

A decrease in susceptibility to ibalizumab, as determined by a shift in EC₅₀ value and a decrease in MPI, has been associated with the loss or shifting of PNGS in the V5 loop of the envelope gp120. Presumably, the alteration of PNGS in this region impacts the carbohydrate moieties that can attach to the amino acids in this region, and these moieties may play a role in the anti-HIV-1 activity of ibalizumab. Hypothetically, the presence of multiple glycans in the V5 loop or glycans in the N-terminal region of the V5 loop in particular contribute to the steric hindrance that prevents the HIV-1 envelope protein to interact with the co-receptor. Shifting the PNGS toward the C-terminal region of the V5 loop or eliminating it all together would likely allow HIV-1 to engage with the co-receptor while ibalizumab is still bound to domain 2 of CD4.

The sponsor used next generation sequencing of the envelope gene to determine what changes occurred in

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the HIV-1 of subjects who met the criteria of protocol defined virologic failure, by comparing the V5 loop region at baseline to that at the time of failure in clinical trials TMB-202 and TMB-301. Despite our requests to the sponsor for the raw NGS sequence reads for the entire envelope sequence, the sponsor only submitted NGS files that were limited to sequence fragments that contained the V5 loop. They also provided a resistance table wherein the envelope sequences, as determined by Sanger sequencing, were populated, but many of the amino acid positions were marked with an 'X' indicating a lack of consensus or a problem with the nucleotides in the codon. Resistance analysis was performed by the sponsor by looking at the number and positions of the PNGS in the V5 loop, comparing the genotype and baseline to the genotype from the sample collected close to the time of failure. In addition, DAVP looked at substitutions across the envelope gene and were detected in the Sanger sequencing data at the time of failure, but not at baseline, that occurred in 2 or more subjects. Hypothetically, amino acid changes elsewhere in the envelope protein could allow for HIV-1 to interact with the co-receptor in the presence of ibalizumab.

5.2 HIV-1 Resistance Analyses

Antiretroviral resistance testing was performed by [REDACTED] (b) (4) as described previously, to determine the susceptibility of HIV-1 isolates to drugs in the OBR. Ibalizumab resistance was assessed for clinical trials TMB-202 and TMB-301 by sequencing the V5 loop of the gp120 envelope at baseline and collected at the time of confirmed virologic failure while the subject was still on treatment with the prescribed study drug regimen and assessing the genotypic data for changes in PNGS. Viral resistance monitoring included: collecting blood samples at time points before treatment, at regular intervals during treatment, and then at the end of study. Two sets of samples were collected at each timepoint: one for viral load and one for susceptibility testing. Samples selected for ibalizumab resistance analysis were collected at the time of confirmed virologic failure while the subject was still on treatment with the prescribed study drug regimen. Protocol-defined virologic failure:

TMB-202: two consecutive viral load measurements with $<1 \log_{10}$ reduction from Baseline

TMB-301: two consecutive viral load measurements with $<0.5 \log_{10}$ reduction from Baseline viral load

5.3 Other Exploratory Resistance Analyses

In addition to the genotypic analyses performed by the sponsor when assessing the differences in PNGS in the V5 loop region, DAVP also compared envelope amino acid sequences derived at baseline and at the time of failure from subjects who met protocol defined virologic failure to determine if amino acids that evolved over the course of treatment could be associated with ibalizumab resistance.

6. EFFICACY AND RESISTANCE ANALYSES

6.1 TMB-202 Efficacy Analyses

Title
A Phase 2b, Randomized, Double-Blinded, 48-Week, Multicenter, Dose-Response Study of Ibalizumab plus an Optimized Background Regimen in Treatment-Experienced Patients Infected with HIV-1 (Amended to 24 Week Study)

Summary of Design and Study Population

A total of 113 subjects were enrolled and randomized into two arms: 1) 59 subjects in the 800 mg ibalizumab every 2 week arm, and 2) 54 subjects in the 2,000 mg ibalizumab every 4 week arm.

In addition, all subjects received an investigator-selected OBR consisting of two to four antiretroviral agents. The selection of the OBR was aided by results of a screening resistance test and review of the subject's prior antiretroviral therapy and included at least one agent to which the subject's viral isolate demonstrated full susceptibility and which the subject was willing and able to take. After randomization, the OBR was not to be

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changed until the last infusion of study drug (up to 24 weeks of treatment) with the following exception:

- One OBR substitution was allowed for tolerability reasons provided the subject continued to meet inclusion criteria with the new OBR

Subjects who experienced virologic failure were discontinued from this study. Virologic failure was defined as two consecutive measurements (at least 14 days apart) of viral load indicating the following:

- A decrease of $<1.0 \log_{10}$ from Baseline starting at Weeks 12 and 14 (non-response), OR
- A viral load >50 copies/mL starting at Weeks 22 and 24 (suboptimal response or rebound)

FDA Clinical Virology Analysis of Efficacy

The efficacy assessments performed by the sponsor were generally in agreement with the results determined by Clinical Virology. The sponsor summarized the results for TMB-202 as follows:

1. viral load <50 copies/mL: 44% (26/59) for the 800 mg Q2W arm and 27.8% (15/54) for the 2,000 mg Q4W arm
2. viral load <200 copies/mL: 53% (31/59) for the 800 mg Q2W arm and 43% (23/54) for the 2,000 mg Q4W arm
3. viral load <400 copies/mL: 58% (34/59) for the 800 mg Q2W arm and 46% (25/54) for the 2,000 mg Q4W arm
4. a $1.0 \log_{10}$ reduction in viral load: 63% (37/59) for the 800 mg Q2W arm and 59% (32/54) for the 2,000 mg Q4W arm
5. a $0.5 \log_{10}$ reduction in viral load: was 68% (40/59) for the 800 mg Q2W arm and 59% (32/54) for the 2,000 mg Q4W arm

6.2 TMB-202 Resistance Analyses

Baseline Resistance Characteristics

Baseline resistance-associated substitutions could not be assessed because the sponsor did not provide the baseline gp120 sequences for all subjects who were enrolled in TMB-202. In addition, in this clinical trial there was no monotherapy treatment phase, making it nearly impossible to determine baseline substitutions associated with a lower susceptibility specifically to ibalizumab. However, the EC_{50} values assessed at baseline did not show any appreciable changes in ibalizumab susceptibility to HIV-1 strains with 1 PNGS site in the gp120 V5 loop at baseline versus those with 2 PNGS sites in the V5 loop (Table 18).

Table 18. Baseline EC_{50} values for subsets of subjects in TMB-202 (DAVP Analysis). EC_{50} values are shown in $\mu\text{m/mL}$.

	ALL	EFF=Yes	EFF=No	RESIST	2 PNGS	1 PNGS
N	104	37	67	17	9	8
Mean	0.032	0.035	0.031	0.034	0.044	0.022
SD	0.031	0.031	0.030	0.032	0.041	0.006
Median	0.025	0.027	0.023	0.024	0.026	0.022
Min	0.009	0.014	0.009	0.015	0.016	0.015
Max	0.218	0.188	0.218	0.150	0.150	0.033

ALL is all subjects in TMB-202, **EFF=Yes** represents subjects who were determined to be treatment successes, **EFF=No** represents subjects who failed treatment, **RESIST** represents subjects for whom resistance analysis was performed, **2 PNGS** represents subject from the RESIST subgroup whose virus had two PNGS at baseline, and **1 PNGS** represents subjects from the RESIST subgroup whose virus had one PNGS at baseline.

Treatment-Emergent Resistance

A decrease in susceptibility to ibalizumab, as determined by a shift in EC_{50} value and a decrease in MPI, has been associated with the loss of PNGS in the V5 loop of the envelope gp120. Presumably, the alteration of

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PNGS in this region impacts the carbohydrate moieties that can attach to the amino acids in this region, and these moieties may play a role in the anti-HIV-1 activity of ibalizumab.

Discussion of treatment recommendations

Given that ibalizumab exhibited a low barrier to resistance during nonclinical development and in clinical trials that explored the use of ibalizumab as a monotherapy, it appears that ibalizumab rapidly selects for variants of HIV-1 that are less susceptible to this drug, and therefore, this drug should not be used as a monotherapy.

6.3 TMB-301 Efficacy Analyses

Title

A Phase 3, Single Arm, 24-Week, Multicenter Study of Ibalizumab plus an Optimized Background Regimen (OBR) in Treatment-Experienced Patients Infected with Multi-Drug Resistant HIV-1

Summary of Design and Study Population

This study was a Phase 3, single-arm, multicenter study designed to assess the antiviral activity, efficacy, safety, and tolerability of an IV ibalizumab dose regimen in treatment-experienced subjects infected with multi-drug resistant HIV-1. Subjects must have been treated with HAART for at least 6 months and were failing or had recently failed (i.e., in the last 8 weeks) therapy to determine baseline viral load. All subjects also received a standard-of-care OBR consisting of ARV medications selected by the Investigator on the basis of the subject's treatment history and the results of viral resistance testing. The primary evaluation of efficacy was performed at Day 14. Additional secondary evaluations were conducted at Week 25 (EOS).

The study consisted of three periods: a control period (Days 0–6), an essential monotherapy period (Days 7–13), and a maintenance period (Day 14–Week 25). During the control period (Days 0–6) subjects were monitored on current failing therapy (or no therapy, if the subject had failed and discontinued treatment within the 8 weeks preceding Screening). During the essential monotherapy period (Days 7–13) subjects continued on current failing therapy, receiving one 2000-mg dose (loading dose) of ibalizumab on Day 7. Day 7 was considered Baseline for the treatment period (Day 7–Week 25).

FDA Clinical Virology Analysis of Efficacy

TMB-301 was conducted with 40 subjects infected with HIV-1 with documented resistance to at least one drug in three different drug classes. The trial was designed to establish the efficacy of ibalizumab as a monotherapy during the first week of the trial, and then add-on an optimized background regimen (Figure 22).

The sponsor reported that in treatment-experienced subjects infected with multi-drug resistant HIV-1 who received a 2000-mg loading dose of ibalizumab at Day 7 (Baseline) followed by 800-mg doses of ibalizumab every other week in combination with OBR starting at Day 14, a statistically significant number of subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from Baseline (Day 7) to Day 14 (82.5%; $p < 0.0001$). Other clinically meaningful reductions in viral load observed at Day 14 and Week 25 (EOS) in the ITT population included:

- 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from Baseline (Day 7) to Week 25 (EOS)
- 17 (42.5%) subjects achieved an HIV-1 RNA level < 50 copies/mL at Week 25 (EOS)
- 21 (52.5%) subjects achieved an HIV-1 RNA level < 400 copies/mL at Week 25 (EOS)
- 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from Baseline (Day 7) to Week 25 (EOS)

Of note, breaking down the secondary endpoints by OSS indicated that those with one or more active drugs in the OBR had better outcomes at the EOS than those without an active drug in the OBR. Here are the outcomes based on OSS score:

1. **OSS = 0 (n=5)**; 20% of subjects achieved HIV-1 RNA < 50 copies/mL and 20% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)

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2. **OSS = 1 (n=12)**; 42% of subjects achieved HIV-1 RNA <50 copies/mL and 50% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
3. **OSS = 2 (n=18)**; 72% of subjects achieved HIV-1 RNA <50 copies/mL and 72% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
4. **OSS = 3 (n=3)**; 33% of subjects achieved HIV-1 RNA <50 copies/mL and 33% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)
5. **OSS = 4 (n=2)**; 50% of subjects achieved HIV-1 RNA <50 copies/mL and 50% of subjects achieved $\geq 1.0 \log_{10}$ reduction at Week 25 (EOS)

6.4 TMB-301 Resistance Analyses

Baseline Resistance Characteristics

Baseline resistance-associated substitutions could not be assessed because the sponsor did not provide the gp120 sequence for all subjects who were enrolled in TMB-301.

Treatment-Emergent Resistance

Ibalizumab administered in clinical trial TMB-301 at a loading dose of 2,000 mg followed with 800 mg Q2W resulted in a statistically significant number of subjects achieving $\geq 0.5 \log_{10}$ reduction in HIV-1 RNA copies/mL from BL (Day 7) to Day 14 (n=33; 82.5%; p<0.0001) during the essential monotherapy treatment phase. When ibalizumab was combined with an OBR, 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from BL to EOS, 17 (42.5%) subjects achieved an HIV-1 RNA level <50 copies/mL at EOS, 21 (52.5%) subjects achieved an HIV-1 RNA level <400 copies/mL at EOS and 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from BL to EOS. The seven subjects who failed to meet the primary endpoint did not fare any better or worse by EOS than those who achieved the primary endpoint in this study. Resistance analyses were performed on samples collected from 10 subjects who failed treatment with ibalizumab + OBR, and the predominant ibalizumab resistance pathway was associated with altered potential N-link glycosylation sites (PNGS) in the V5 loop of the HIV-1 envelope.

An independent assessment of the NGS data provided for the HIV-1 from the 10 subjects from TMB-301 who were assessed for the development of resistant indicated that the results reported by the sponsor were in agreement with the results observed by DAVP. The predominant changes occurred in the V5 loop and resulted in altered PNGS in this region. However, there were a couple of additional HIV-1 gp160 amino acid substitutions that emerged on treatment in at least two subjects that were noted in different regions of the gp160 protein sequence (Table 19). Phenotyping these substitutions will be recommended as a PMR/PMC.

Table 19: Potential resistance-associated substitutions that emerged in 2 or more subjects who failed treatment in TMB-301 (DAVP analysis).

Substitution	No	Ratio	Subjects	CDS
V75I	2	2-0	17001, 18002	C1cons
E229G/Q229P/R	2	1-1	22001, 17001	gp41cons
L274V/A274T	2	1-1	21001, 32001	gp41cons
N12K	2	2-0	17001, 21001	V1V2
N14D,V14M/deletion	2	1-1	18002, 22001	V1V2
T23N/deletion	2	1-1	4001, 9002	V4

Discussion of treatment recommendations

Given that ibalizumab exhibited a low barrier to resistance during nonclinical development and in clinical trials that explored the use of ibalizumab as a monotherapy, it appears that ibalizumab rapidly selects for variants of HIV-1 that are less susceptible to this drug, and therefore, this drug should not be used as a monotherapy.

6.5 Combined Analysis of Efficacy

The combined analysis of efficacy for TMB-301 and TMB-202 is shown in Table 20. Overall, there was good

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agreement between these two clinical trials, particularly when comparing the 800 mg Q2W Arm from TMB-202 to the 2000 mg LD, 800 mg Q2W of TMB-301 (Table 20).

Table 20: A comparison of endpoints between TMB-301 and TMB-202 (DAVP Analysis).

Endpoints	TMB-202		TMB-301
	800 mg q2wk	2000 mg q4wk	2000 mg LD; 800 mg q2wk
≥0.5 log ₁₀ decline in HIV-1 RNA (MT)	n/a	n/a	82.5% (34/40)
HIV-1 RNA <50 copies/ml	44% (26/59)	27.8% (15/54)	42.5% (17/40)
HIV-1 RNA <400 copies/ml	58% (34/59)	46% (25/54)	52.5% (21/40)
≥0.5 log ₁₀ decrease	68% (40/59)	59% (32/54)	65% (25/40)
Mean change in CD4 ⁺ T	37 ± 63	40 ± 80	62 ± 106 cells
Mean change in viral load	1.6 ± 1.3 log ₁₀	1.5 ± 1.4 log ₁₀	1.6 ± 1.5 log ₁₀

A comparison of the major endpoints of percentage of subjects with ≥0.5 log₁₀ reduction, subjects with <400 HIV-1 RNA copies/mL, or subjects with <50 HIV-1 RNA copies/mL showed that the 800 mg Q2W dose was comparable across clinical trials (Figure 29).

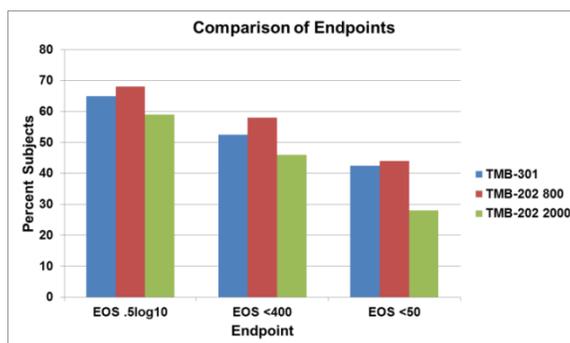


Figure 29: A comparison of the major endpoint results from clinical trials TMB-301 and TMB-202 (DAVP Analysis).

Those infected with X4-tropic HIV-1 strains had worse overall outcomes at the end of the study (secondary endpoints but not primary) in all arms of TMB-202 and TMB-301 (Table 21); however, it is also possible that subjects infected with R5-tropic HIV-1 at baseline had better outcomes than average. A comparison of tropism across the different endpoints showed that subjects infected with R5-tropic HIV-1 at baseline had above average outcomes and those infected with X4-tropic HIV-1 at baseline had below average outcomes (Figure 30).

Table 21: Comparison of efficacy endpoints from TMB-202 and TMB-301 by tropism (DAVP Analysis).

ARM	Tropism	<50 c/mL (% subjects)	<200 c/mL (% subjects)	<400 c/mL (% subjects)	Mean Log Reduction (SD)	% subj w/ 1 log reduction	% subj w/ 0.5 log reduction
2000 q4w (n 54)	ALL (n 54)	15 (27.8)	25 (46.3)	30 (55.6)	1.8 (1.2)	39 (72.2)	43 (79.6)
	DM (n 33)	7 (21.2)	14 (42.4)	18 (54.5)	1.6 (1.1)	22 (66.7)	26 (78.8)
	R5 (n 15)	7 (46.7)	9 (60)	10 (66.7)	2.5 (1.1)	14 (93.3)	14 (93.3)
	X4 (n 4)	1 (25)	1 (25)	1 (25)	1.0 (1.7)	2 (50)	2 (50)
	Und (n 2)	1 (50)	1 (50)	1 (50)	1.4 (1.0)	1 (50)	1 (50)
	800 q2w (n 59)	ALL (n 59)	27 (45.8)	34 (57.6)	37 (62.7)	1.9 (1.1)	43 (72.9)
DM (n 33)	14 (42.4)	15 (45.5)	17 (51.5)	1.8 (1.2)	23 (69.7)	27 (81.8)	
R5 (n 15)	9 (60.0)	12 (80.0)	12 (80.0)	2.5 (0.9)	13 (86.7)	14 (93.3)	
X4 (n 6)	2 (33.3)	3 (50.0)	4 (66.7)	1.1 (0.9)	4 (66.7)	4 (66.7)	
Und (n 5)	2 (40.0)	4 (80.0)	4 (80.0)	1.8 (1.2)	3 (60.0)	4 (80.0)	
2000 LD, 800 q2w (n 40)	ALL (n 40)	17 (42.5)	20 (50)	21 (52.5)	1.1 (0.6)	24 (60)	26 (65)
	DM (n 28)	11 (39.3)	14 (50.0)	15 (53.6)	2.5 (1.6)	16 (57.1)	24 (85.7)
	R5 (n 5)	4 (80.0)	4 (80.0)	4 (80.0)	3.7 (1.1)	2 (40.0)	4 (80.0)
	X4 (n 5)	1 (20.0)	1 (20.0)	1 (20.0)	0.8 (1.3)	1 (20.0)	3 (60.0)
	Und (n 2)	1 (50.0)	1 (50.0)	1 (50.0)	2.2 (1.7)	2 (100.0)	2 (100.0)

There could be two explanations for this observation. First, subjects with X4-tropic HIV-1 are often in the advanced stages of AIDs, and these subjects generally have worse outcomes.

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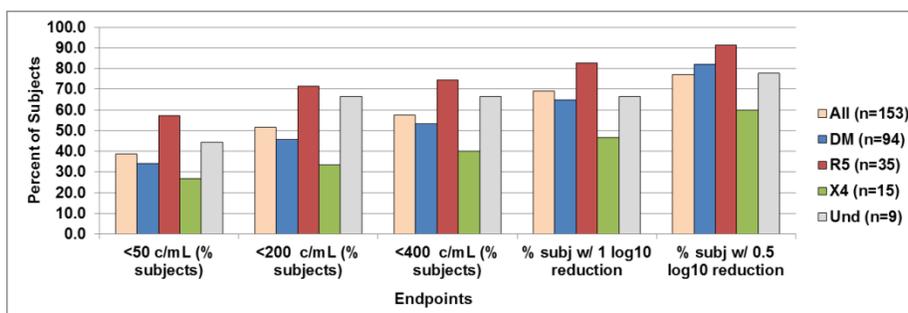


Figure 30: Comparison of efficacy endpoints from TMB-202 and TMB-301 by tropism (DAVP Analysis).

Second, viruses with co-receptor tropism differences have several amino acid differences in gp120 that reportedly alter the net charge and composition of glycosylation sites in gp120 (Figure 31) which could have an impact on ibalizumab activity. In particular, changes in or near the V5 loop could potentially alter the amino acid side chains or glycosylation moieties that project into a structural void between the gp120 V5 loop and the ibalizumab light chain to induce a steric hindrance that reduces the efficiency with which ibalizumab binds CD4.

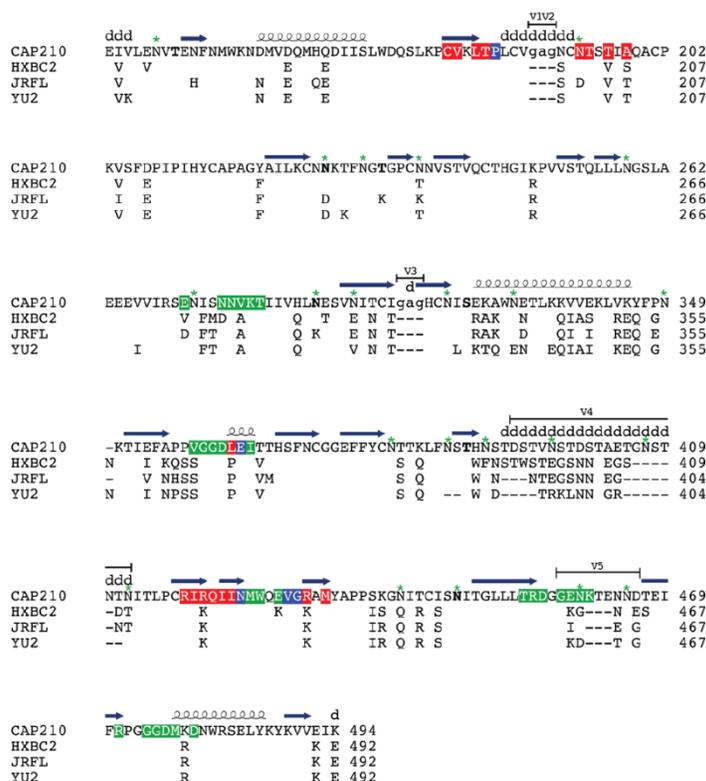


Figure 31: Structure-based sequence alignment of CAP210 and clade B gp120s with known 3-D structures (copied from Supplemental Figure 1, from the [Supplemental Material](#) from [Diskin et al., 2010](#)). The CAP210 sequence is presented with differences in the other gp120 sequences shown below. Gaps are designated with a dash. Locations of the V1-V5 variable loops are indicated above the sequence. Deletions to remove the V1V2 and V3 loops are denoted with lowercase letters. α -helices and β -strands are denoted with spirals and arrows, respectively. Regions that are disordered in the CAP210 structure are indicated above its sequence with the letter "d". CAP210 residues that contact both sCD4 and 21c are shown in blue, residues that contact only sCD4 are in green, and residues that contact only 21c are in red. Potential N-linked glycosylation sites in CAP210 are indicated with a green asterisk above the asparagine in the Asn-X-Ser/Thr motif. Residues that were mutated in CAP210 to eliminate N-linked carbohydrate sites are bold. CAP210, mutated strain generated in the paper referenced; HXBC2, prototypical X4 strain; JRFL, uses the CCR5 co-receptor; YU2, uses the CCR5 co-receptor.

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Combined Analysis of Resistance

- 25 subjects in TMB-202 and 7 in TMB-301 experienced protocol-defined virologic failure
- 5 additional subjects in TMB-202 and 3 in TMB-301 experienced virologic rebound or breakthrough, defined as 1 log₁₀ increase in viral load or increase from below to above 200 copies/mL
- Genotypic analysis demonstrated the absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab MPI
- Phenotypic test results demonstrated the loss of susceptibility to one or more agents of the OBR and to ibalizumab at the time of virologic failure
- There was no evidence in either study that changes in ibalizumab susceptibility impact susceptibility to maraviroc or enfuvirtide

The development of resistance to ibalizumab was evident when comparing baseline MPI scores to the MPI scores of ibalizumab at the time of virologic failure (Figure 32). A more than 20% decrease in MPI was observed for each of the three doses studied in clinical trials TMB-202 and TMB-301.

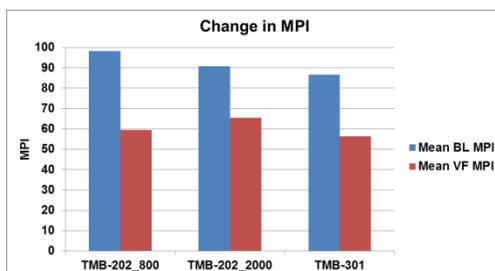


Figure 32: Changes in MPI from baseline to time of virologic failure (DAVP Analysis).

Change in OSS

Changes in HIV-1 susceptibility to OBR agents were monitored at VF to determine changes in susceptibility associated with the loss of antiviral activity (Table 22). The sponsor reported that the phenotypic assessment of fostemsavir could not be performed in TMB-301 due to unavailability of the drug for testing.

Table 22: Changes in OSS from baseline to VF (Table 15, page 23, TMB-202-TMB-301 Viral Resistance Report).

PID	OBR	Baseline	Virologic Failure
		OSS	OSS
TMB-202 800 mg			
16003	RAL, DRV, TFV, FTC	3	4
17003	RAL, ABC, TFV	2	0
32002	RAL, ENF, FTC, TFV	2	2
42017	ENF, DRV, TFV, FTC	1	1
45002	MVC, RAL, DRV, TFV, FTC	1	0
51003	RAL, DRV, ETR, TFV, FTC	0	0
51006	MVC, RAL, DRV	1	0
51008	RAL, SQV, ABC, EFV	1	0
52001	IDV, ABC, AZT, 3TC	0	nd ^b
TMB-202 2000 mg			
14004	RAL, DRV, ETR, 3TC, AZT	1	0
15005	MVC, ENF, DRV, TFV, FTC	2	0
25004	DRV, ETR, TFV	1	0
28003	LPV, SQV, TFV	0	0
32007	ETR, TPV, TFV, FTC	2	0
33003	ENF, ETR, TFV, FTC	2	0
48007	ENF, TPV	0	0
51004	ETR, LPV	0	0
TMB-301			
01-001	DTG, DRV, FTC, TFV	4	3
04-001	DRV, FTC, TFV, DTG, FSV, ENF	3	3
08-001	TPV, FTC, TFV, FSV	1	1
09-002	DTG, FTC, TFV	3	nd ^b
17-001	FSV, DTG, DRV, FTC, TFV	0	0
18-002	ABC, FSV, DRV, FTC, TFV	2	3
21-001	DRV, MVC, FTC, TFV	1	0
22-001	FTC, TFV, DRV	3	3
27-002	DRV, DTG, FTC, TFV	0	0
29-002	DRV, 3TC, RAL, TFV	2	1
32-001	FTC, TFV, FSV	0	0

^a RAL, raltegravir; DRV, darunavir; TFV, tenofovir; FTC, emtricitabine; ABC, abacavir; ETR, etravirine; 3TC, lamivudine; AZT, azidothymidine; SQV, saquinavir; EFV, efavirenz; ENF, enfuvirtide; TPV, tipranavir; MVC, maraviroc; LPV, lopinavir; IDV, indinavir.
^b Not determined due to failed PSQT test at virologic failure

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There were a total of 25 subjects in TMB-202 and 7 in TMB-301 who experienced protocol-defined VF. In addition, 5 subjects in TMB-202 and 3 in TMB-301 experienced virologic rebound or breakthrough, defined as 1 log₁₀ increase in viral load or increase from below to above 200 copies/mL. The sponsor performed resistance analysis for 17 subjects from TMB-202 and 10 subjects in TMB-301, looking primarily at the absence or loss of a PNGS in the V5 loop of HIV-1 gp120. The sponsor concluded that genotypic analysis demonstrated the absence or loss of a PNGS in the V5 loop of HIV-1 gp120 is the primary genetic determinant associated with reduced ibalizumab MPI.

For the 10 subjects from TMB-301 who were analyzed for resistance, the virus of five subjects started with two V5 PNGS in the V5 loop of the HIV-1 gp120 and each lost one PNGS over the course of treatment. Of the remaining 5 subjects, 4 had one V5 PNGS in their HIV-1 at baseline and 1 of these subjects lost the V5 PNGS in their HIV-1 at the time of failure, and 1 subject had no V5 PNGS in their HIV-1 at baseline but had one PNGS at the time of failure (Table 23).

Table 23: TMB-301 PNGS among VF at baseline and failure (Table 15, page 22, TMB-301 Virology Report).

Subject ID	Baseline				Virologic Failure				VF/BL IC _{HalfMax} FC
	MPI	# V5 PNGS motif, %			MPI	# V5 PNGS motif, %			
		0	1	2		0	1	2	
Majority V5 2 PNGS at Baseline									
01-001	72	0	4	96	48	1	87	12	0.4
08-001	99	0	1	98	63	25	75	0	1.9
17-001	98	0	2	97	72	1	98	0	2.0
21-001	94	0	2	98	63	8	78	14	0.7
32-001	95	0	2	98	43	1	99	0	1.5
Majority 1 PNGS at Baseline									
04-001	55	6	64	30	55	1	58	41	2.5
09-002	99	1	99	0	60	100	0	0	1.9
18-002	67	3	97	0	52	84	16	0	0.3
27-002	96	2	98	0	55	99	1	0	2.8
Majority 0 PNGS at Baseline									
22-001	91	97	1	2	52	3	97	0	1.7

By comparison, in TMB-202, 9 subjects started with two V5 PNGS in their HIV-1 at baseline and six of these had only one V5 PNGS in their HIV-1 at VF (Table 24). Eight subjects had one V5 PNGS in their HIV-1 at baseline and half of these had no V5 PNGS in their HIV-1 at the time of failure.

Table 24: TMB-202 PNGS among VF at baseline and failure (Table 14, page 26, TMB-202 Virology Report).

Subject ID	Baseline				Virologic Failure				VF/BL IC _{HalfMax} FC
	MPI	# V5 PNGS motif, %			MPI	# V5 PNGS motif, %			
		0	1	2		0	1	2	
Majority V5 2 PNGS at Baseline									
32007	96	0	2	97	94	0	8	92	0.4
14004	97	5	2	93	92	7	29	64	1.9
51003*	98	0	12	88	81	1	92	7	2.0
51006*	98	0	28	72	76	26	56	18	0.7
32002	99	0	8	92	65	1	88	10	1.5
42017	97	2	1	96	61	0	2	98	1.1
17003	100	0	27	73	49	34	66	0	3.2
33003	99	0	2	98	44	2	95	3	1.3
51008*	99	0	5	95	38	2	97	1	3.4
Majority 1 PNGS at Baseline									
28003	94	1	99	0	72	30	70	0	1.9
25004*	78	0	100	0	61	0	100	0	0.3
45002	96	1	99	0	61	0	86	14	2.8
15005	89	1	99	0	58	100	0	0	2.5
51004	88	1	78	22	55	42	58	0	1.7
16003*	99	0	99	0	54	96	4	0	2.8
52001*	99	2	88	10	51	100	0	0	1.8
48007*	86	27	73	0	47	99	1	0	1.3

* Experienced viral load rebound with high mean receptor occupancy

In addition, tropism change at the EOS did not appear to correlate with treatment failure supporting the observation that ibalizumab has antiviral activity against HIV-1 regardless of tropism.

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7. CONCLUSIONS

In conclusion, ibalizumab administered in clinical trial TMB-301 at a loading dose of 2,000 mg followed with 800 mg Q2W resulted in a statistically significant number of subjects achieving $\geq 0.5 \log_{10}$ reduction in HIV-1 RNA copies/mL from BL (Day 7) to Day 14 (n=33; 82.5%; $p < 0.0001$) during the essential monotherapy treatment phase. When ibalizumab was combined with an OBR, 25 (62.5%) subjects achieved $\geq 0.5 \log_{10}$ reduction in viral load from BL to EOS, 17 (42.5%) subjects achieved an HIV-1 RNA level < 50 copies/mL at EOS, 21 (52.5%) subjects achieved an HIV-1 RNA level < 400 copies/mL at EOS and 22 (55%) subjects achieved $\geq 1.0 \log_{10}$ reduction in viral load from BL to EOS. The seven subjects who failed to meet the primary endpoint did not fare any better or worse by EOS than those who achieved the primary endpoint in this study.

Mechanism of action studies support the class designation for this drug as a CD4 post-attachment HIV-1 inhibitor.

Antiviral activity assessments performed with clinical isolates support ibalizumab activity against clade B HIV-1. In addition, ibalizumab is active against R5-tropic, dual-tropic, and X4-tropic HIV-1.

Resistance analyses were performed on samples collected from 10 subjects who failed treatment with ibalizumab + OBR, and the predominant ibalizumab resistance pathway was associated with altered potential N-link glycosylation sites (PNGS) in the V5 loop of the HIV-1 envelope. Experiments performed during nonclinical development combined with susceptibility testing performed before and after treatment in TMB-301 indicated that the emergence of ibalizumab resistance did not have an impact on the antiviral activity of the CCR5 co-receptor antagonist, maraviroc, or with the gp41 fusion inhibitor, enfuvirtide.

This Original BLA is approvable from a Clinical Virology perspective, pending final agreement on the prescribing information.

8. PRESCRIBING INFORMATION (LABEL)

~~Strikethrough font~~ represents the sponsor's original text that will be deleted

Red font represents changes made by the FDA

8.1 Proposed Prescribing Information (with initial Reviewer-recommended changes)

INDICATIONS AND USAGE

TROGARZO, (b) (4) a CD4 post-attachment HIV-1 inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection (b) (4) failing current antiretroviral therapy. (b) (4)
(1)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4) Ibalizumab-xxxx is an HIV-1 antiretroviral drug [see (b) (4) Microbiology (12.4)]

12.4 Microbiology

Mechanism of Action

(b) (4) Ibalizumab-xxxx, a recombinant humanized mouse monoclonal antibody, blocks HIV-1 from infecting CD4⁺ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

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Ibalizumab-xxxx Does Not Impact CD4 Function

The binding specificity of ibalizumab-xxxx to CD4 allows ibalizumab-xxxx to block viral entry into host cells without causing immunosuppression. Epitope mapping studies (b) (4) indicate that (b) (4) ibalizumab-xxxx binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope (b) (4) is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and therefore does not interfere with CD4-mediated immune functions. (b) (4)

Additionally, (b) (4) ibalizumab-xxxx does not interfere with gp120 attachment to CD4. (b) (4)

Antiviral Activity (b) (4)

Ibalizumab-xxxx inhibits the replication of CCR5- and CXCR4-tropic laboratory strains and primary isolates of HIV-1 in phytohemagglutinin stimulated peripheral blood lymphocytes. The median EC₅₀ value (50% effective concentration) for ibalizumab-xxxx against HIV-1 group M isolates (subtypes A, B, C, D, E, or O) was 8 ng/mL (n=15, range of 0.4 to 600 ng/mL) in cell culture, with lower susceptibility observed in macrophage-tropic HIV-1 strains (BaL, JR-CSF, YU2, and ADA-M). In a single-cycle infection assay, (b) (4) ibalizumab-xxxx inhibited 17 clinical isolates of subtype B with a median EC₅₀ (b) (4) value of 12 ng/mL (range of 8.8 to 16.9 ng/mL; mean 12 ± 3 ng/mL) and a median maximum percentage inhibition (MPI) of 97% (range of 89 to 99%; mean 97 ± 3%). (b) (4)

Three CCR5-tropic clinical isolates from (b) (4) subtypes B, C, and D, were inhibited with EC₅₀ values ranging from 59-66 ng/mL and 3 CXCR4-tropic clinical isolates from subtypes (b) (4) B, C, and D, with EC₅₀ values ranging from 44-59 ng/mL (b) (4)

Antiviral Activity in Combination with Other Antiviral Agents

(b) (4) No antagonism was observed when PBMCs or MAGI-CCR5 cells infected with the subtype B Ba-L or ADA variants of HIV-1 were incubated with ibalizumab-xxxx in combination with the CCR5 co-receptor antagonist, maraviroc, or when PBMCs infected with the subtype B HT/92/599 variant of HIV-1 were incubated with (b) (4) ibalizumab-xxxx in combination with the gp41 fusion inhibitor, enfuvirtide; a nonnucleoside reverse transcriptase inhibitor (efavirenz); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, (b) (4) emtricitabine, tenofovir, or zidovudine); (b) (4) or a protease inhibitor (b) (4) (atazanavir). (b) (4)

Antiviral Activity in (b) (4) **Antiretroviral-Resistant Virus**

(b) (4) Subjects enrolled in (b) (4) TMB-301 had HIV-1 with documented triple-class resistance. TROGARZO Ibalizumab-xxxx inhibited 38 baseline isolates at (b) (4) -a median EC₅₀ value of 31 ng/mL (range of 13 to 212 ng/mL; mean value of 39 ± 36 ng/mL) (b) (4) with a median MPI of 97% (range of 41-100%; mean 91 ± 14%) (b) (4) For 10 subjects in TMB-301 who failed treatment, at the time of failure the median ibalizumab-xxxx EC₅₀ value was 566 ng/mL (range of 148 to >54,900 ng/mL; mean 11,768±21,650 ng/mL) representing an EC₅₀ value shift of >18-fold. For the HIV-1 derived from the same subjects, the median MPI was 55% (range of 43-72%; mean 56 ± 8%) representing a 42

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percentage point reduction.

Decreased Susceptibility

Decreased susceptibility to (b) (4) ibalizumab-xxxx, as defined by a decrease in MPI, has been observed in (b) (4) subjects experiencing virologic failure and may be associated with genotypic changes in the HIV-1 envelope coding sequence that results in the loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120.

The (b) (4) clinical significance of decreased susceptibility to (b) (4) ibalizumab-xxxx has not been established.

Cross-Resistance

Phenotypic and genotypic test results revealed no evidence of cross-resistance between (b) (4) ibalizumab-xxxx and all approved classes of anti-retroviral drugs (b) (4) co-receptor antagonists, gp41 (b) (4) fusion inhibitors (b) (4), INSTIs, NNRTIs, NRTIs, and PIs). Ibalizumab-xxxx is active against HIV-1 resistant to all approved antiretroviral agents and (b) (4) (b) (4) exhibits antiretroviral activity against R5-tropic, X4-tropic, and dual-tropic HIV-1.

(b) (4)
Decreased susceptibility to (b) (4) ibalizumab-xxxx following multiple dose administrations of (b) (4) ibalizumab-xxxx has been observed in some subjects (b) (4). Cell culture studies performed with HIV-1 variants with reduced susceptibility to ibalizumab-xxxx indicate that phenotypic changes associated with resistance to ibalizumab-xxxx do not alter susceptibility to other approved agents and do not result in the selection of CD4-independent viral isolates.

CD4 Polymorphisms and Ibalizumab-xxxx Activity

CD4 polymorphisms reported in public databases were analyzed to determine if any naturally occurring amino acid substitutions in the CD4 molecule from different human populations would potentially impact the antiviral activity of ibalizumab-xxxx. None of the known CD4 polymorphisms are likely to have an impact on ibalizumab-xxxx binding to CD4.

8.2 Reviewer's Proposed Prescribing Information (clean)

INDICATIONS AND USAGE

TROGARZO, a CD4 post-attachment HIV-1 inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing current antiretroviral therapy. (1)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibalizumab is an HIV-1 antiretroviral drug [see Microbiology (12.4)].

12.4 Microbiology

Mechanism of Action

Ibalizumab-xxxx, a recombinant humanized mouse monoclonal antibody, blocks HIV-1 from infecting CD4⁺ T

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cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

Ibalizumab-xxxx Does Not Impact CD4 Function

The binding specificity of ibalizumab-xxxx to domain 2 of CD4 allows ibalizumab-xxxx to block viral entry into host cells without causing immunosuppression. Epitope mapping studies indicate that ibalizumab-xxxx binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and therefore does not interfere with CD4-mediated immune functions. Additionally, ibalizumab-xxxx does not interfere with gp120 attachment to CD4.

Antiviral Activity

Ibalizumab-xxxx inhibits the replication of CCR5- and CXCR4-tropic laboratory strains and primary isolates of HIV-1 in phytohemagglutinin stimulated peripheral blood lymphocytes. The median EC₅₀ value (50% effective concentration) for ibalizumab-xxxx against HIV-1 group M isolates (subtypes A, B, C, D, E, or O) was 8 ng/mL (n=15, range of 0.4 to 600 ng/mL) in cell culture, with lower susceptibility observed in macrophage-tropic HIV-1 strains (BaL, JR-CSF, YU2, and ADA-M). In a single-cycle infection assay, ibalizumab-xxxx inhibited 17 clinical isolates of subtype B with a median EC₅₀ value of 12 ng/mL (range of 8.8 to 16.9 ng/mL; mean 12 ± 3 ng/mL) and a median maximum percentage inhibition (MPI) of 97% (range of 89 to 99%; mean 97 ± 3%). Three CCR5-tropic clinical isolates from subtypes B, C, and D, were inhibited with EC₅₀ values ranging from 59-66 ng/mL and 3 CXCR4-tropic clinical isolates from subtypes B, C, and D, with EC₅₀ values ranging from 44-59 ng/mL.

Antiviral Activity in Combination with Other Antiviral Agents

No antagonism was observed when PBMCs or MAGI-CCR5 cells infected with the subtype B Ba-L or ADA variants of HIV-1 were incubated with ibalizumab-xxxx in combination with the CCR5 co-receptor antagonist maraviroc or when PBMCs infected with the subtype B HT/92/599 variant of HIV-1 were incubated with ibalizumab-xxxx in combination with the gp41 fusion inhibitor enfuvirtide; a nonnucleoside reverse transcriptase inhibitor (efavirenz); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, tenofovir, or zidovudine); or a protease inhibitor (atazanavir).

Antiviral Activity in Antiretroviral-Resistant Virus

Subjects enrolled in TMB-301 had HIV-1 with documented triple-class resistance. Ibalizumab-xxxx inhibited 38 baseline isolates at a median EC₅₀ value of 31 ng/mL (range of 13 to 212 ng/mL; mean 39 ± 35 ng/mL) with a median MPI of 97% (range of 41-100%; mean 91 ± 14%). For 10 subjects in TMB-301 who failed treatment, at the time of failure the median ibalizumab-xxxx EC₅₀ value was 566 ng/mL (range of 148 to >54,900 ng/mL; mean 11,768±21,650 ng/mL) representing an EC₅₀ value shift of >18-fold. For the HIV-1 derived from the same subjects, the median MPI was 55% (range of 43-72%; mean 56 ± 8%) representing a 42 percentage point reduction.

Decreased Susceptibility

Decreased susceptibility to ibalizumab-xxxx, as defined by a decrease in MPI, has been observed in subjects experiencing virologic failure and may be associated with genotypic changes in the HIV-1 envelope coding sequence that results in the loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120. The clinical significance of decreased susceptibility to ibalizumab-xxxx has not been established.

Cross-Resistance

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Phenotypic and genotypic test results revealed no evidence of cross-resistance between ibalizumab-xxxx and all approved classes of anti-retroviral drugs (CCR5 co-receptor antagonists, gp41 fusion inhibitors, INSTIs, NNRTIs, NRTIs, and PIs). Ibalizumab-xxxx is active against HIV-1 resistant to all approved antiretroviral agents and exhibits antiretroviral activity against R5-tropic, X4-tropic, and dual-tropic HIV-1.

Decreased susceptibility to ibalizumab-xxxx following multiple dose administrations of ibalizumab-xxxx has been observed in some subjects. Cell culture studies performed with HIV-1 variants with reduced susceptibility to ibalizumab-xxxx indicate that phenotypic changes associated with resistance to ibalizumab-xxxx do not alter susceptibility to other approved agents and do not result in the selection of CD4-independent viral isolates.

CD4 Polymorphisms and Ibalizumab-xxxx Activity

CD4 polymorphisms reported in public databases were analyzed to determine if any naturally occurring amino acid substitutions in the CD4 molecule from different human populations would potentially impact the antiviral activity of ibalizumab-xxxx. None of the known CD4 polymorphisms are likely to have an impact on ibalizumab-xxxx binding to CD4.

8.3 Final Approved Package Insert

Due to the timing of NDA milestones and PDUFA goal deadlines, the final approved package insert was not available at the time of finalization of this review.

9. RECOMMENDATIONS

This reviewer recommends the following post-marketing commitments or requirements (as appropriate):

1. Conduct a phenotypic study to determine the impact of the following gp120 amino acid substitutions on ibalizumab susceptibility: P236E, K303R, P367L, I369V, R474K, K615R/N, N649I/R, L774S, and L831V. In addition, determine the phenotypes of the substitutions observed in the various coding sequences noted: C1cons_V75I; gp41cons_E229G/Q229P/R and gp41cons_L274V/A274T; V1V2_N12K and V1V2_N14D/V14M/deletion; V4_T23N/deletion.
2. Provide the fastq envelope sequences from the next generation sequencing of samples collected from subjects who failed treatment to better characterize the HIV-1 gp120 sequence at the time of failure. (We note that the Sanger sequencing data contained a lot of positions that could not be adequately called.)

10. REFERENCES (describing studies with ibalizumab)

1. Song R, Pace C, Seaman MS, Fang Q, Sun M, et al. Distinct HIV-1 Neutralization Potency Profiles of Ibalizumab-Based Bispecific Antibodies. *J Acquir Immune Defic Syndr*. 2016 Dec 1;73(4):365-373. PubMed PMID: 27792681; NIHMSID: NIHMS796582; PubMed Central PMCID: PMC5123706.
2. Pace C, Markowitz M. Monoclonal antibodies to host cellular receptors for the treatment and prevention of HIV-1 infection. *Curr Opin HIV AIDS*. 2015 May;10(3):144-50. PubMed PMID: 25700204.
3. Mazor Y, Hansen A, Yang C, Chowdhury PS, Wang J, et al. Insights into the molecular basis of a bispecific antibody's target selectivity. *MAbs*. 2015;7(3):461-9. PubMed PMID: 25730144; PubMed Central PMCID: PMC4622944.
4. Wang YT, Chuang LY. Insight into the modified Ibalizumab-human CD4 receptor interactions: using a computational binding free energy approach. *J Comput Aided Mol Des*. 2015 Jan;29(1):69-78. PubMed PMID: 25342515.
5. Su ZY. Ibalizumab-human CD4 receptor interaction: computational alanine scanning molecular dynamics studies.

**DIVISION OF ANTIVIRAL PRODUCTS
CLINICAL VIROLOGY REVIEW**

BLA: [761065](#) SDN: 000 (Original BLA, SDN 012 in DARRTS) REVIEW COMPLETED: 10/03/2017

Clinical Virology Reviewer: Eric F. Donaldson, Ph.D.

Curr Comput Aided Drug Des. 2014;10(3):217-25. PubMed PMID: 25756667.

6. Song R, Oren DA, Franco D, Seaman MS, Ho DD. Strategic addition of an N-linked glycan to a monoclonal antibody improves its HIV-1-neutralizing activity. *Nat Biotechnol.* 2013 Nov;31(11):1047-52. PubMed PMID: 24097413; NIHMSID: NIHMS511374; PubMed Central PMCID: PMC3825789.
7. Pace CS, Song R, Ochsenbauer C, Andrews CD, Franco D, et al. Bispecific antibodies directed to CD4 domain 2 and HIV envelope exhibit exceptional breadth and picomolar potency against HIV-1. *Proc Natl Acad Sci U S A.* 2013 Aug 13;110(33):13540-5. PubMed PMID: 23878231; PubMed Central PMCID: PMC3746901.
8. Pace CS, Fordyce MW, Franco D, Kao CY, Seaman MS, et al. Anti-CD4 monoclonal antibody ibalizumab exhibits breadth and potency against HIV-1, with natural resistance mediated by the loss of a V5 glycan in envelope. *J Acquir Immune Defic Syndr.* 2013 Jan 1;62(1):1-9. PubMed PMID: 23023102.
9. Guo D, Shi X, Arledge KC, Song D, Jiang L, et al. A single residue within the V5 region of HIV-1 envelope facilitates viral escape from the broadly neutralizing monoclonal antibody VRC01. *J Biol Chem.* 2012 Dec 14;287(51):43170-9. PubMed PMID: 23100255; PubMed Central PMCID: PMC3522310.
10. Fessel WJ, Anderson B, Follansbee SE, Winters MA, Lewis ST, et al. The efficacy of an anti-CD4 monoclonal antibody for HIV-1 treatment. *Antiviral Res.* 2011 Dec;92(3):484-7. PubMed PMID: 22001594; NIHMSID: NIHMS335419; PubMed Central PMCID: PMC4388049.
11. Toma J, Weinheimer SP, Stawiski E, Whitcomb JM, Lewis ST, et al. Loss of asparagine-linked glycosylation sites in variable region 5 of human immunodeficiency virus type 1 envelope is associated with resistance to CD4 antibody ibalizumab. *J Virol.* 2011 Apr;85(8):3872-80. PubMed PMID: 21289125; PubMed Central PMCID: PMC3126132.
12. Freeman MM, Seaman MS, Rits-Volloch S, Hong X, Kao CY, et al. Crystal structure of HIV-1 primary receptor CD4 in complex with a potent antiviral antibody. *Structure.* 2010 Dec 8;18(12):1632-41. PubMed PMID: 21134642; NIHMSID: NIHMS250919; PubMed Central PMCID: PMC3005625.
13. Bruno CJ, Jacobson JM. Ibalizumab: an anti-CD4 monoclonal antibody for the treatment of HIV-1 infection. *J Antimicrob Chemother.* 2010 Sep;65(9):1839-41. PubMed PMID: 20639524.
14. Song R, Franco D, Kao CY, Yu F, Huang Y, et al. Epitope mapping of ibalizumab, a humanized anti-CD4 monoclonal antibody with anti-HIV-1 activity in infected patients. *J Virol.* 2010 Jul;84(14):6935-42. PubMed PMID: 20463063; PubMed Central PMCID: PMC2898252.
15. Jacobson JM, Kuritzkes DR, Godofsky E, DeJesus E, Larson JA, et al. Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. *Antimicrob Agents Chemother.* 2009 Feb;53(2):450-7. PubMed PMID: 19015347; PubMed Central PMCID: PMC2630626.
16. Dimitrov A. Ibalizumab, a CD4-specific mAb to inhibit HIV-1 infection. *Curr Opin Investig Drugs.* 2007 Aug;8(8):653-61. PubMed PMID: 17668367.
17. Zhang XQ, Sorensen M, Fung M, Schooley RT. Synergistic in vitro antiretroviral activity of a humanized monoclonal anti-CD4 antibody (TNX-355) and enfuvirtide (T-20). *Antimicrob Agents Chemother.* 2006 Jun;50(6):2231-3. PubMed PMID: 16723592; PubMed Central PMCID: PMC1479151.
18. Kuritzkes DR, Jacobson J, Powderly WG, Godofsky E, DeJesus E, et al. Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. *J Infect Dis.* 2004 Jan 15;189(2):286-91. PubMed PMID: 14722894.
19. Reimann KA, Khunkhun R, Lin W, Gordon W, Fung M. A humanized, nondepleting anti-CD4 antibody that blocks virus entry inhibits virus replication in rhesus monkeys chronically infected with simian immunodeficiency virus. *AIDS Res Hum Retroviruses.* 2002 Jul 20;18(11):747-55. PubMed PMID: 12167266.
20. Boon L, Holland B, Gordon W, Liu P, Shiao F, et al. Development of anti-CD4 MAb hu5A8 for treatment of HIV-1 infection: preclinical assessment in non-human primates. *Toxicology.* 2002 Apr 2;172(3):191-203. PubMed PMID: 11893418.
21. Reimann KA, Lin W, Bixler S, Browning B, Ehrenfels BN, et al. A humanized form of a CD4-specific monoclonal antibody exhibits decreased antigenicity and prolonged plasma half-life in rhesus monkeys while retaining its unique biological and antiviral properties. *AIDS Res Hum Retroviruses.* 1997 Jul 20;13(11):933-43. PubMed PMID: 9223409.

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/s/

ERIC F DONALDSON
10/03/2017

JULIAN J O REAR
10/03/2017

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

BLA Number: 761065 **Applicant:** TaiMed Biologics **Stamp Date:** 05/03/2017
Drug Name: Ibalizumab **BLA/NDA Type:** Original-1

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X		
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	N/A		
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
9	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		Draft labelling was submitted but the Microbiology section will require significant rewriting to add in important details and to be consistent with the format of other labels.

File name: 5_Microbiology Filing Checklist for a NDA or Supplement 010908

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
10	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		Annotated microbiology draft labelling was submitted but will require significant rewriting to add in important details and to be consistent with the format of other labels.
11	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Eric F. Donaldson, Ph.D. 5/25/2017

 Reviewing Virologist Date

Jules O’Rear, Ph. D. 5/25/2017

 Supervisory Microbiologist Date

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/s/

ERIC F DONALDSON
05/25/2017

JULIAN J O REAR
05/25/2017