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Efficacy, Pharmacokinetics, and Safety Over 48 Weeks With Ibalizumab-Based Therapy in Treatment-Experienced Adults Infected With HIV-1: A Phase 2a Study

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Abstract: Ibalizumab, a humanized monoclonal antibody targeting CD4, blocks HIV-1 entry into cells and is the first Food and Drug Adminstration-approved long-acting agent for HIV-1 treatment. In this phase 2a study, 82 HIV-infected adults failing antiretroviral therapy were assigned an individually optimized background regimen (OBR) and randomized 1:1:1 to arm A (15 mg/kg ibalizumab q2wk), arm B (10 mg/kg weekly for 9 weeks, then q2wk), or placebo. Subjects with an inadequate response at week 16 were permitted to cross over to a new OBR plus 15 mg/kg ibalizumab q2wk. At week 16, viral load (VL) reduction was significantly greater than placebo (0.26 $\log_{10}$) in arms A (1.07 $\log_{10}$; $P = 0.002$) and B (1.33 $\log_{10}$; $P < 0.001$); $CD4^+$ T cell counts increased significantly in arm A. After week 16, 11/27 (arm B) and 19/27 (placebo) subjects crossed over to OBR plus 15 mg/kg ibalizumab; 8/28 in arm A initiated a new OBR. Ibalizumab treatment resulted in VL reduction at week 24 (-0.77 and -1.19 $\log_{10}$ for arms A and B, respectively, versus -0.32 $\log_{10}$ for placebo) and 48 weeks (-0.54 and -0.77 versus -0.22 $\log_{10}$). Compared with placebo, VL differences were statistically significant for arm B at week 24 ($P = 0.001$) and week 48 ($P = 0.027$). $CD4^+$ T cell counts increased significantly by week 48 in both arm A and arm B, relative to placebo. No ibalizumab-related serious adverse events were reported. The durable antiviral activity and tolerability of ibalizumab support its use in treating individuals harboring multidrug-resistant HIV-1.

Key Words: ibalizumab, HIV-1, antiretroviral therapy, treatment-experienced, multidrug resistance

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INTRODUCTION

Treatment with effective combination antiretroviral therapy (cART) has significantly decreased mortality and morbidity from HIV in the modern era.[1] However, some patients treated with cART fail to achieve or maintain control of viremia for a variety of reasons, including previous exposure to serial monotherapy, dual-therapy, and other suboptimal combination therapies, as well as nonadherence to prescribed cART. Because development of multiclass ART resistance greatly reduces available options, novel treatments are urgently needed for such subjects.[2,3] Ideally, new options should be safe, simply dosed, and with novel mechanisms of action, thus minimizing the likelihood of non-adherence, drug-drug interactions and inherent cross-resistance.

Ibalizumab, a humanized IgG4 monoclonal antibody, binds domain 2 of the CD4 receptor, a mechanism distinct from other antiretroviral agents (ARVs), including the entry inhibitors enfuvirtide or maraviroc.[4–8] Ibalizumab binding to CD4 blocks post-attachment conformational changes in the viral envelope gp120-CD4 cell receptor complex that are required for viral entry.[5] Because inhibition occurs before coreceptor engagement, ibalizumab is active against both CCR5-tropic and CXCR4-tropic viruses. Furthermore, because ibalizumab binds to CD4 at a site distinct from that of major histocompatibility complex class II molecule interactions,[9] ibalizumab does not interfere with antigen presentation or $CD4^+$ T cell function.[10,11] Ibalizumab's potency was previously demonstrated in a phase 1b monotherapy trial.[12] Its efficacy in combination with an optimized background regimen (OBR) has also been studied in a phase 2b study[13] and a recently published phase 3 study.[14] Food and Drug Adminstration approval of ibalizumab in combination with other ARVs for subjects with multidrug-resistant HIV-1 infection was based on phase 2 as well as phase 3 clinical data.

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This 48-week phase 2a study compared the safety, antiviral activity, and immunologic effects of 2 different weight-based dose regimens of ibalizumab versus placebo in combination with OBR in triple class treatment-experienced, HIV-1-infected individuals who were failing or had recently failed a cART regimen.

METHODS

Study Design

TNX-355.03 (ClinicalTrials.gov number NCT00089700) was a randomized, double-blind, placebo-controlled, 3-arm phase 2a study in treatment-experienced subjects infected with HIV-1. The study was conducted at 20 sites in the United States, Canada, and Puerto Rico from March 2004 to March 2008 and was approved by institutional review boards at all sites.

OBRs for each subject were selected by the principal investigator before randomization, based on the medication history and the results of viral resistance testing (PhenoSense GT [PSGT] assay, Monogram Biosciences, Inc. South San Francisco, CA). Individuals were randomized 1:1:1 to 1 of 3 study arms: arm A (alternating weekly 15 mg/kg ibalizumab IV infusions and placebo for the first 9 doses [up to week 8], followed by 15 mg/kg infusions q2wk), arm B (weekly 10 mg/kg ibalizumab IV infusions for the first 9 doses, followed by 10 mg/kg infusions q2wk) or a placebo arm (weekly placebo IV infusions for the first 9 doses, followed by placebo infusions q2wk).

Subjects received blinded therapy for a minimum of 16 weeks to a maximum of 48 weeks, or until virologic failure, defined as 2 consecutive assessments in which viral load (VL) reduction was less than 0.5 $\log_{10}$, relative to baseline, after week 12. Subjects who experienced virologic failure after week 16 (the earliest point at which virologic failure could be confirmed after week 12) were given the option to receive open-label 15 mg/kg ibalizumab q2wk plus a new OBR based on resistance testing. Subjects who experienced a second virologic failure were discontinued from the study.

Randomized subjects were assessed at screening, day 1 (before the start of therapy), weekly through week 4, and then q2wk through week 48. VL and $CD4^+$ T cell counts were assessed at each visit. Samples to assess $CD4^+$ T cell coating and trough pharmacokinetics (PK) were collected at all visits starting at day 1. Immunogenicity to ibalizumab was determined from the serum levels of antidrug antibodies at screening, day 1, weeks 16, 24, and 48. Adverse events were assessed at every visit.

Study Population

Eligibility criteria included: HIV-1-infected adults ($\geq$18 years) who were failing their current cART regimen or who had discontinued a failing cART regimen within 8 weeks before screening, $\geq$6 months of cumulative cART with triple-class experience [nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor and protease inhibitor], viral susceptibility to $\geq$1 ARV in their selected OBR, HIV-1 RNA load $\geq$10,000 copies/mL, and $CD4^+$ T cell count $\geq$50 cells/μL. Stable VL was required, with $\leq$0.5 $\log_{10}$ difference between 2 measurements within the study screening period. Exclusion criteria included: significant comorbidities, including life expectancy less than 6 months or illness that would preclude adherence to the study protocol, any investigational drug use within 30 days before randomization, prior participation in an HIV vaccine study, and prior exposure to ibalizumab or to any other virus fusion/entry inhibitors. Women were excluded if they were pregnant or breast-feeding.

Assessments and Assays

The primary efficacy endpoint was change from baseline VL at week 24, determined using the Amplicor HIV Monitor Assay (version 1.5; Roche Molecular Systems, Branchburg, NJ). Secondary efficacy endpoints included the proportion achieving a VL decrease $\geq$0.5 $\log_{10}$ and $\geq$1.0 $\log_{10}$ at weeks 24 and 48, and the change from baseline $CD4^+$ T cell count at each time point.

Exploratory efficacy endpoints included achievement of VL $\leq$400/mL by Week 48, change in VL from baseline to week 48, and time to loss of virologic response (TLOVR) up to week 48. Virologic and immunologic responses at week 16, the last time point before any treatment crossover, were also examined as exploratory endpoints. Other analyses examined the relationships between ibalizumab coating of $CD4^+$ T cells and virologic response and between serum concentrations of ibalizumab and ibalizumab coating of $CD4^+$ T cells.

Ibalizumab serum concentrations were measured using a validated competitive enzyme-linked immunosorbent assay using an antihuman IgG4 antibody. The lower limit of quantitation was 0.100 μg/mL. Screening for antiibalizumab antibodies was performed at Tanox, Inc (Houston, TX) by enzyme-linked immunosorbent assay. $CD4^+$ T-cell counts and the extent of cell coating by ibalizumab were analyzed by flow cytometry on whole blood specimens (ICON Laboratories, Farmingdale, NY).

Statistical Methods

Primary efficacy data were analyzed from the modified intent-to-treat population, which included all randomized subjects in the safety population (individuals receiving any study drug, including OBR) who had at least one VL measurement and one $CD4^+$ T-cell count after treatment initiation. In assessing changes in VL and in $CD4^+$ T-cell count, the zero-change imputation method was used for missing values. There was no imputation for subjects with virologic failure after a switch to open-label ibalizumab. Changes in VL, $CD4^+$ T-cell count, and proportion achieving threshold decreases from baseline VLs were compared using Dunnett's 2-sided multiple comparison procedure, 2-sample Wilcoxon rank sum test, and Fisher's exact test, respectively.

The distribution of values for TLOVR through week 48 was estimated by Kaplan–Meier analysis, and the

treatment arms were compared using log-rank tests. Individuals who never achieved a virologic response on their randomized treatment (a VL decrease of $\geq$0.5 $\log_{10}$ before death, introduction of a new ART, or last visit) were retroactively censored from the analysis at day 0.

RESULTS

Subject Disposition and Baseline Characteristics

Eighty-two triple class-experienced individuals underwent randomization (arm A: ibalizumab 15 mg/kg, n = 28; arm B: ibalizumab 10 mg/kg, n = 27, placebo arm, n = 27) (see Fig. 1, Supplemental Digital Content, http://links.lww.com/QAI/B589). All were included in the safety and modified intent-to-treat populations. By week 24, 26 (93%), 25 (93%), and 25 (93%), subjects remained in study arms A, B, and placebo, respectively. By week 48, 8 (29%) in arm A had transitioned to a new OBR; 11 (41%), and 19 (70%) subjects in arms B and placebo, respectively, had switched to open-label ibalizumab 15 mg/kg dosing. Sixteen (57%), 17 (63%), and 13 (48%) subjects, respectively, completed the 48-week double-blind portion of the study. Discontinuations were due to virologic failure (18 subjects), adverse events (6 subjects), loss to follow-up (2 subjects), withdrawn consent (6 subjects), death (1 subject), or others (reduced $CD4^+$ cell count). Overall, 37 (45%) of the patients opted to enroll in an open-label extension trial of 15 mg/kg ibalizumab.

Median ages across the 3 study arms were 44.0–46.0 years, and most subjects (87%) were men. Approximately half were White. Of 82 subjects, 32 (39%) had baseline VL >100,000/mL, and 37 (45%) had <200 $CD4^+$ T cells/μL. Baseline demographic and disease characteristics were generally similar between the arms (Table 1), although arm A included more subjects of the African origin and exhibited a higher median VL, lower median $CD4^+$ T-cell count, and higher proportion of subjects with <200 $CD4^+$ T cells/μL than the other arms. Subjects were heavily treatment-experienced, having used a median of 10.5–12.0 prior HIV medications. Consistent with this long treatment history, a limited number of fully active agents were available for the OBR for many subjects. The median number of susceptible ARV components of the OBR was similar among treatment arms (1in arm A, 2 in arm B, and 2 in the placebo arm). Initial OBRs included ARVs from the 3 older classes (NRTI, non-NRTI, and protease inhibitor). After week 16, 32 (38%) patients switched their OBR, including 5 (6%) who switched to a then-experimental enfuvirtide-containing regimen (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B594).

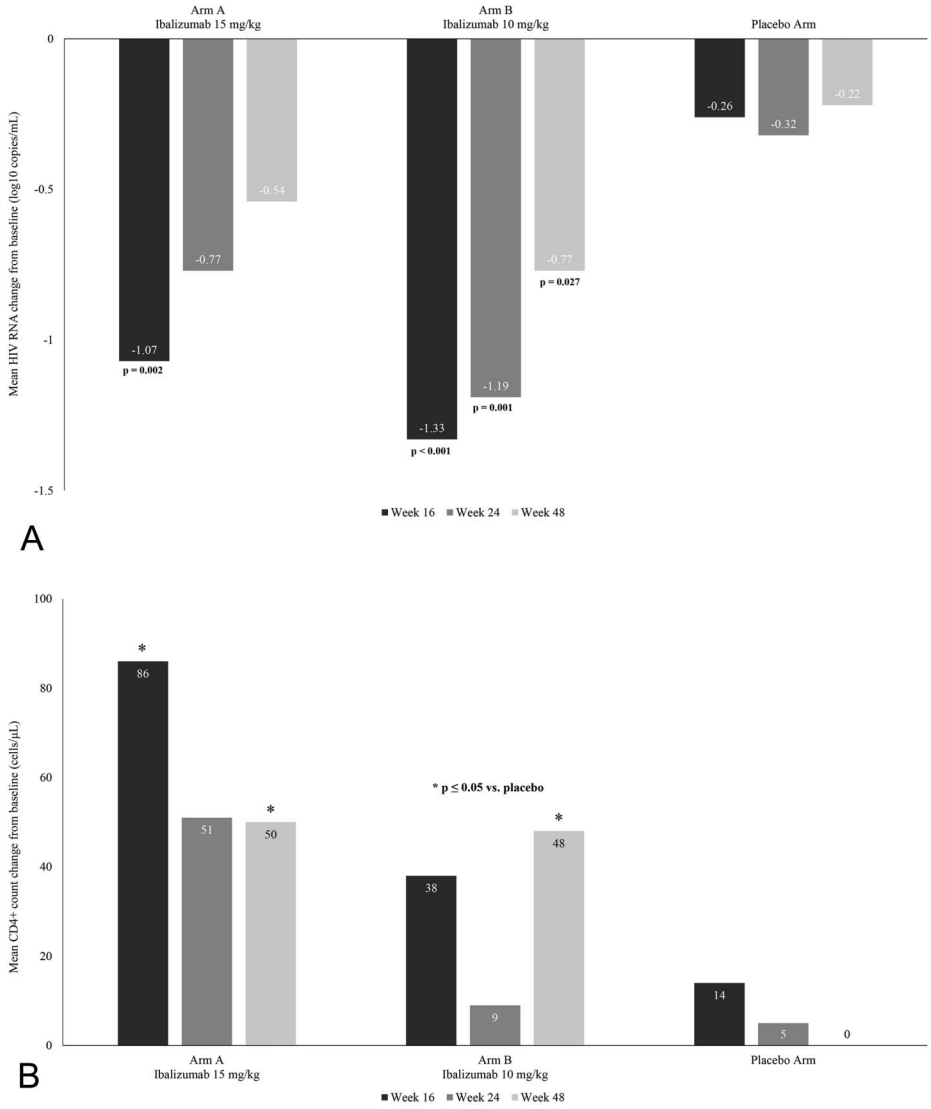
Virologic Response

Ibalizumab at both doses led to statistically significant reductions in mean VL compared with placebo at week 16—a decrease of 1.07 $\log_{10}$ for arm A and 1.33 $\log_{10}$ for arm B versus 0.26 $\log_{10}$ for the placebo arm (Fig. 1A). For the primary endpoint of VL reduction at week 24, the VL load reduction seen in arm A subjects was not statistically significant compared with placebo (reduction of 0.77 $\log_{10}$ versus 0.32 $\log_{10}$ HIV-1 RNA/mL, respectively; $P = 0.13$), whereas reduction in arm B was significant (1.19 $\log_{10}$; $P = 0.001$). Similarly, compared with placebo, VL reductions at week 48 (0.54 and 0.77 $\log_{10}$ HIV-1 RNA/mL for arms A and B, respectively, versus 0.22 for placebo) were significant for arm B ($P = 0.027$) but not for arm A ($P = 0.26$). Relative to placebo, more subjects in the ibalizumab arms

TABLE 1. Patient Characteristics and Disposition

Baseline Demographic and Disease Characteristics	Arm A Ibalizumab 15 mg/kg (n = 28)	Arm B Ibalizumab 10 mg/kg (n = 27)	Placebo Arm (n = 27)
Median age, yr (range)	44 (28–59)	46 (18–75)	44 (31–66)
Male, n (%)	26 (93)	21 (78)	24 (88)
Race, n (%)			
White	12 (43)	14 (52)	12 (44)
Hispanic	7 (25)	8 (30)	12 (44)
Black	8 (29)	4 (15)	3 (11)
Median weight, kg (range)	72 (51–101)	73 (54–101)	73 (61–124)
Median $CD4^+$ Count/μL (range)	178 (38–532)	263 (47–721)	241 (48–715)
$CD4^+$ cell count [N (%)]			
<200 cells/μL	17 (61)	7 (26)	13 (48)
200–300 cells/μL	6 (21)	12 (44)	10 (37)
>300 cells/μL	5 (18)	8 (30)	4 (15)
Median HIV-1 RNA $\log_{10}$ copies/mL (range)	5.2 (4.2–5.9)	4.8 (4.0–5.5)	4.8 (3.9–5.8)
HIV-1 RNA load [N (%)]			
$<40 \times 10^3$ copies/mL	9 (32)	8 (30)	9 (33)
$40–100 \times 10^3$ copies/mL	3 (11)	12 (44)	9 (33)
$>100 \times 10^3$ copies/mL	16 (57)	7 (26)	9 (33)
Median number of prior HIV medications (range)	10.5 (3–19)	11.0 (3–17)	12.0 (4–16)
Median number of prior protease inhibitors (range)	4.0 (1–7)	4.0 (1–8)	4.0 (1–7)
Median number of active agents in baseline OBR (range)	1.0 (1–3)	2.0 (0–4)	2.0 (0–4)
Patients remaining on-study [N(%)]			
Through week 16	27 (96)	25 (93)	27 (100)
Through week 24	26 (93)	25 (93)	25 (93)
Through week 48	16 (57)	17 (63)	13 (48)
Enrolled in open-label extension	14 (50)	14 (52)	9 (33)
Patients with no OBR change throughout the study [N(%)]	20 (71)	15 (56)	15 (56)
Patients maintaining blinded dosing throughout the study*	NA	16 (59)	8 (30)

*After week 16, patients randomized to arms B and C were permitted to transition to 15 mg/mL twice-weekly ibalizumab on an open-label basis.
OBR, optimized background regimen.



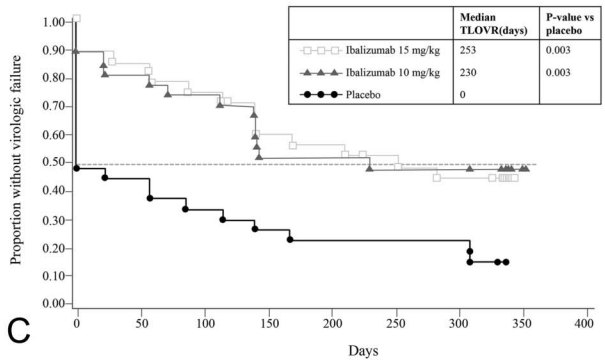


FIGURE 1. Mean antiviral (A) and immunological responses (B) at week 24 and 48 and Kaplan–Meier estimates of TLOVR (C). Missing data were imputed using the last observation carried forward (LOCF). *P*-values are in comparison with the placebo arm at the same time point. For TLOVR analysis, individuals who never showed a virologic response (≥0.5 $\log_{10}$ reduction in HIV-1 RNA) were considered to have failed at t = 0. The dashed line indicates 50%.

achieved thresholds for viral response (0.5 or 1.0 $\log_{10}$ decrease). By week 48, 25% of patients in arm A (P = 0.50), 52% in arm B (P = 0.008), and 15% in the placebo arm achieved HIV-1 RNA ≤400 copies/mL.

Immunologic Response

At week 16, $CD4^+$ T-cell count was significantly increased in arm A (+86/μL; P = 0.05) and numerically increased in arm B (+38/μL; P = 0.13), relative to placebo

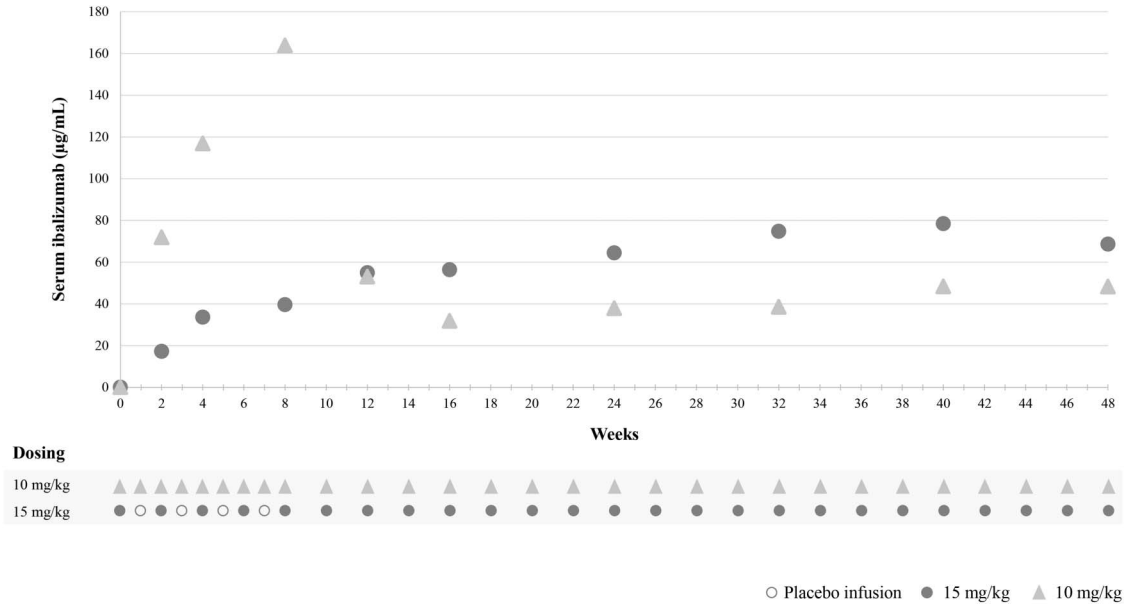


FIGURE 2. Serum ibalizumab trough concentration over time in arms A and B. Note that during the initial weeks of the study, dosing with ibalizumab was more frequent in arm B (solid triangles) than in arm A (solid circles).

(+14/μL). The differences between ibalizumab arms and placebo at week 24 were not statistically significant, but by week 48, both ibalizumab doses resulted in significant increases in mean $CD4^+$ T-cell count, relative to changes seen in the placebo arm (+50/μL ($P = 0.020$) and +48/μL ($P = 0.028$) for arms A and B, respectively, versus 0 cells/μL for the placebo arm) (Fig. 1B).

Virologic Failure and Loss of Virologic Response

For individuals who demonstrated a virologic response ($\geq$0.5 $\log_{10}$ reduction from baseline), TLOVR was calculated from the earliest of the following events: death, introduction of a new ARV, last visit before loss to follow-up, and time of confirmed virologic failure (VL reduced by $<$0.5 $\log_{10}$ copies/mL from baseline). Overall, fewer subjects experienced virologic failure in the ibalizumab arms than placebo, and the median time TLOVR was longer in the ibalizumab arms than placebo (Fig. 1C). The proportion maintaining virologic response by week 48 was 44.5% in arm A, 48.1% in arm B, and 14.8% in the placebo arm. The median TLOVR was 253 days in arm A, 230 days in arm B, and 0.0 days in the placebo arm (log-rank $P = 0.003$ for both ibalizumab arms versus placebo). The difference in TLOVR was driven primarily by the significantly greater proportion of individuals in the ibalizumab arms who achieved a virologic response at any time up to week 24, relative to the placebo arm.

PK and $CD4^+$ Cell Coating

Ibalizumab trough concentrations were initially greater in arm B compared with arm A, as expected, given the more frequent ibalizumab dosing during the 8-week loading phase in arm B (Fig. 2). In arm A, where no loading regimen was applied, ibalizumab accumulated over time. By week 16 and thereafter, subjects in arm A experienced $\geq$42% greater overall exposure, compared with arm B.

The extent of $CD4^+$ T-cell coating with ibalizumab was evaluated throughout the study. Both ibalizumab dosages resulted in complete $CD4^+$ T-cell coating for most subjects early in the study (data not shown). Thus, by week 2, 88.5% of subjects in arm A and 95.8% of subjects in arm B had complete cell coating; all subjects in the placebo arm had uncoated CD4 receptors. However, from week 24–48, $CD4^+$ cell coating was more consistent in arm A than in arm B. Regression analysis (data not shown) indicated that complete $CD4^+$ T-cell coating was associated with increased probability of improved virologic outcomes.

Safety

Both doses of ibalizumab in combination with OBR were generally well tolerated. The incidence, frequency, and intensity of treatment–emergent adverse events (TEAEs) were similar in the active treatment and placebo arms (Table 2). Sixteen serious adverse events (SAEs) were reported by 11 subjects (10 subjects reported nonfatal SAEs and 1 died); none were considered to be related to ibalizumab. There was one death reported through week 48 in arm B in a subject with a history of cardiovascular disease (prior myocardial infarction, stroke, and heart catheterization). The subject experienced a fatal myocardial infarction after 262 days on the study; this event was deemed unrelated to the study drug.

The most frequently reported treatment-related AEs were headache (17.9 and 22.2% for the ibalizumab arms versus 18.5% for placebo), diarrhea (7.4 and 17.8% versus 7.4%), nausea (3.7 and 10.7% versus 3.7%), fatigue (10.7 and 11.1% versus 22.2%), somnolence (0 and 14.3% versus 0%), and rash (10.7 and 14.8% versus 0%) (Table 3). No other

treatment-related AEs were reported by ≥10% of subjects in either active arm. One grade 3 and one grade 4 maculopapular rash event was reported in arms A and B, respectively. These events were not deemed by investigators to be ibalizumab-related; other rash events were of mild or moderate intensity. The number of individuals reporting hepatotoxicity-related TEAE was small (2 in arm A and 1 in the placebo arm). Likewise, the total number of subjects reporting an event of benign, malignant, or unspecified neoplasm was small (3 in arm A and 2 in the placebo arm). None of the hepatotoxicity or neoplasm events were judged to be related to ibalizumab exposure.

Infusion site reactions were assessed each week during the infusion period. Only one infusion site reaction was reported, by a subject in the placebo arm. No subjects showed evidence of clinically significant ibalizumab immunogenicity.

TABLE 2. Treatment-Emergent Adverse Events (TEAEs) Through Week 48 (Safety Population)

n (%)	Arm A Ibalizumab 15 mg/kg (n = 28)	Arm B Ibalizumab 10 mg/kg (n = 27)	Placebo Arm (n = 27)
Any TEAE	26 (93)	24 (89)	24 (89)
Treatment-related*	14 (50)	14 (52)	14 (52)
Resulting in study discontinuation	3 (11)	1 (4)	2 (7)
Potentially life-threatening	2 (7)	1 (4)	3 (11)
Any nonfatal SAE	3 (11)	3 (11)	4 (15)
Treatment-related	0 (0)	1 (4)	0 (0)
Causing discontinuation of study drug	1 (4)	1 (4)	1 4)
Potentially life-threatening	1 (4)	0 (0)	2 (7)
Death	0 (0)	1 (4)	0 (0)
Maximum severity† of any TEAE			
Mild	3 (11)	2 (7)	4 (15)
Moderate	16 (57)	15 (56)	12 (44)
Severe	5 (18)	6 (22)	5 (19)
Potentially life threatening	2 (7)	1 (4)	3 (11)
Maximum severity of treatment-related TEAE			
Mild	5 (18)	3 (11)	3 (11)
Moderate	9 (32)	9 (33)	7 (26)
Severe	0 (0)	2 (7)	4 (15)
Potentially life-threatening	0 (0)	0 (0)	0 (0)
Any dose-limiting toxicity	0 (0)	2 (7)	4 (15)

*Treatment-related events are those with a definite, possible, probable, or unknown relation to the study drug.

†For the same TEAE within a subject, the event with the highest severity was selected for analysis.

DISCUSSION

In this study, triple class-experienced individuals received an OBR and were randomized to receive IV ibalizumab (arm A: 15 mg/kg q2wk; arm B: 10 mg/kg weekly for 9 weeks followed by 10 mg/kg q2wk) or placebo. The inclusion of a placebo arm in this study is unique in the literature describing the clinical development of ibalizumab in the treatment of MDR HIV-1. More frequent ibalizumab infusions led to greater serum ibalizumab trough levels in arm B in the early weeks of the study. However, the data presented here were insufficient to optimize a weight-based ibalizumab regimen—an approach that was not pursued in later research. Rather, fixed doses of 800 mg Q2W and 2000 mg Q4W were investigated in a subsequent phase 2b study, to optimize the ibalizumab treatment interval.[13]

Here, both active treatment regimens exhibited antiviral activity, as demonstrated by decreased VL at weeks 24 and 48 in comparison with placebo. Furthermore, significantly more subjects in the ibalizumab arms achieved a virologic response at some point, up to week 48. Consistent with greater antiviral activity, both doses of ibalizumab resulted in significantly extended TLOVR through week 48 and higher percentages of individuals achieving a reduction of ≥0.5 and ≥1.0 $\log_{10}$ HIV-1 RNA copies/mL, compared with placebo. Statistically significant increases in $CD4^+$ T-cell counts at week 48 were associated with ibalizumab administration, in comparison with placebo.

The sustained antiviral and immunological responses through week 48 seen in this study are consistent with subsequent studies where most subjects treated with ibalizumab plus OBR achieved virologic responses comparable with the standard applied here (≥0.5 log10 reduction relative to baseline) at the end of the observation period.[13,14]

At week 16, the last time point before crossover was permitted, both ibalizumab doses were associated with substantial virologic suppression (average reduction from baseline >1 $\log_{10}$ copies/mL) that was statistically superior to placebo, but only arm A showed statistically significant increase in $CD4^+$ T cells. Conversely, arm B yielded greater VL reductions at both week 24 and week 48 compared with arm A. These virologic and immunologic responses should be interpreted cautiously, in light of baseline differences between arms A and B in VL and median $CD4^+$ T-cell count.

Pharmacodynamic data indicated a more consistent coating of CD4 with ibalizumab from week 24 to 48 in the 15 mg/kg dosing every 2 weeks in arm A versus 10 mg/kg every 2 weeks in arm B. Evidence of drug accumulation (during the loading phase for arm B and up to week 24 for arm A) and the rapid decline in serum ibalizumab after the end of weekly loading doses for arm B support previously reported features of ibalizumab PK.[12,15] Namely, these findings are consistent with dose-dependent, saturable elimination of ibalizumab by target-mediated drug distribution by the CD4 receptor,[15,16] rather than by normal clearance of IgG4, which occurs with a half-life of 3 weeks.[17]

Both doses of ibalizumab in combination with OBR were generally well tolerated, with mostly mild or moderate TEAEs identified. Most individuals in each treatment arm reported at least one TEAE. Because of the wide range of ARVs used in subjects' OBRs, many of the TEAEs are likely

TABLE 3. Treatment-Related Adverse Events Reported by at Least 10% of Subjects in Either Ibalizumab Arm Through Week 48 (Safety Population)

Adverse Event, No. (%)	Arm A Ibalizumab 15 mg/kg (n = 28)	Arm B Ibalizumab 10 mg/kg (n = 27)	Placebo Arm (n = 27)
Any treatment-related adverse events	14 (50.0)	14 (51.9)	14 (51.9)
General disorders			
Fatigue	3 (10.7)	3 (11.1)	6 (22.2)
Gastrointestinal disorders			
Diarrhea	5 (17.9)	2 (7.4)	2 (7.4)
Nausea	3 (10.7)	1 (3.7)	1 (3.7)
Nervous system disorders			
Headache	5 (17.9)	6 (22.2)	5 (18.5)
Somnolence	4 (14.3)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders			
Rash	3 (10.7)	4 (14.8)	0 (0.0)

attributable to concomitant use of cART, as well as to the underlying disease, as study subjects were clinically advanced.

Rashes appeared more frequently (18.5 and 25.0% in ibalizumab arms versus 7.4% in placebo arm) and were more frequently judged treatment-related among subjects in the ibalizumab arms, relative to the placebo arm. Most rashes were grade 1 or 2, but there was 1 grade 3 rash event in arm B and 1 grade 4 event in arm A; for both events, treatment was discontinued, although the rash was judged not to be ibalizumab-related. In the phase 3 study of ibalizumab plus OBR, where rash was deemed an AE of special interest, 5 of 40 subjects experienced rashes over 25 weeks. Most of these events were mild, although 1 subject experienced multiple rash AEs, including one SAE. This subject was able to continue ibalizumab treatment after completing the study.[14] Thus, although it seems that this adverse event is rarely treatment-limiting, incidence of rash should be monitored in patients on ibalizumab.

ARVs and underlying immunosuppression have been associated with hepatotoxicity and neoplasm.[18] In this study, the frequency of TEAEs suggestive of either hepatoxicity or neoplasm was small, and none of these events were considered related to ibalizumab. Overall, there were no severe adverse events and no incidents of injection site reaction related to ibalizumab. In addition, no clinically significant ibalizumab immunogenicity was observed.

One limitation of this study relates to differences in baseline characteristics across treatment arms, including higher VL, lower $CD4^+$ T-cell count, and fewer ARV options in arm A; these differences may have confounded comparisons of the 2 weight-based doses, but they do not detract from the significant virologic and immunologic responses seen in both arms, relative to placebo. The cell coating assay used in this study was investigational and may not have been optimal for detecting a correlation with antiviral response. Subsequent studies used improved methods to evaluate relationships of virologic response to pharmacokinetic and pharmacodynamic parameters. Finally, the results of weight-based dosing, described here, required additional insights from a later, fixed-dose study[13] to establish the ibalizumab infusion regimen now approved for clinical use.

Conversely, the inclusion of a placebo arm in this phase 2a study represents a substantial methodologic strength and clearly establishes the high potency of ibalizumab, allowing for clear attribution of positive clinical outcomes to the presence of ibalizumab in the treatment regimen. Likewise, the week 16 analysis provided here is important because it represents the last time point at which subjects' clinical outcomes reflect their randomization group, uncomplicated by crossover to active treatment.

In this highly treatment-experienced population, ibalizumab administered q2wk at 15 mg/kg or at 10 mg/kg (with weekly dosing during the 9-week loading period) was safe and well tolerated and resulted in sustained antiviral and immunological response over 48 weeks. With proven activity against multiple drug-resistant strains regardless of viral tropism, ibalizumab is a valuable addition to the treatment armamentarium.[4,13,14] Because of its effective inhibition of HIV entry, tolerability, and long-acting dosing, ibalizumab is an attractive drug for use in individuals with limited treatment options because of multidrug resistance.

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