Safety, Efficacy, and Pharmacokinetics of TBR-652, a CCR5/CCR2 Antagonist, in HIV-1–Infected, Treatment-Experienced, CCR5 Antagonist–Naive Subjects

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Objectives: To determine the antiviral activity, pharmacokinetics, pharmacodynamics, safety, and tolerability of several dose levels of oral TBR-652 monotherapy in HIV-1–infected, antiretroviral experienced, CCR5 antagonist–naive subjects.

Design: Double-blind placebo-controlled study in the United States and Argentina.

Methods: Subjects were randomized in a ratio of 4:1 per dose level to TBR-652 (25, 50, 75, 100, or 150 mg) or placebo, taken once daily for 10 days. Changes from baseline in HIV-1 RNA and $CD4^+$ cell counts were measured through day 40 and for monocyte chemotactic protein-1 (MCP-1), high-sensitivity C-reactive protein (hs-CRP), and IL-6 at day 10. Pharmacokinetic data were analyzed using noncompartmental statistics. Laboratory and clinical adverse events (AEs) and electrocardiogram changes were recorded.

Results: Maximum median reductions in HIV-1 RNA values for the 25, 50, 75, and 150 mg doses were −0.7, −1.6, −1.8, and −1.7 $\log_{10}$ copies per milliliter, respectively. All changes were significant. Median time to nadir was 10–11 days. Suppression persisted well into the posttreatment period. Mean MCP-1 increased significantly by day 10 in the 50-mg and 150-mg dose groups. Effects on $CD4^+$ cell counts, hs-CRP, and IL-6 levels were negligible. TBR-652 was generally safe and well tolerated, with no withdrawals due to AEs.

Conclusions: TBR-652 caused significant reductions in HIV-1 RNA at all doses. Significant increases in MCP-1 levels suggested a strong CCR2 blockade. TBR-652 was generally well tolerated with no dose-limiting AEs. Pharmacodynamics indicate that TBR-652 warrants further investigation as an unboosted once-daily oral CCR5 antagonist with potentially important CCR2-mediated anti-inflammatory effects.

Key Words: TBR-652, receptors, CCR5/antagonists and inhibitors, antiretroviral therapy, clinical trial, phase II, CCR2/antagonists and inhibitors

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INTRODUCTION

TBR-652 (formerly known as TAK-652) is a novel potent oral inhibitor of ligand binding to CC chemokine receptor 5 (CCR5) and is currently being developed for the treatment of HIV-1 infection. Tests of TBR-652 in clinical isolates show a protein binding–adjusted 50% inhibitory concentration (IC_{50}) of 0.29 nM against CCR5. In addition, TBR-652 has the unique property in vitro of being a CCR2 antagonist with an IC_{50} of 5.9 nM. The CCR2/MCP-1 pathway seems to be active in a number of diseases, including atherosclerosis, metabolic syndrome, and insulin resistance.[1] Studies in healthy volunteers have shown TBR-652 to be generally safe, with a mean half-life of 35 to 40 hours, supporting once daily dosing.[2,3] This is the first evaluation of the antiviral activity and safety of TBR-652 in HIV-infected antiretroviral treatment–experienced subjects.

METHODS

Study Design

This was a double-blind, randomized, placebo-controlled, dose-escalating study assessing the antiviral activity, pharmacokinetics/pharmacodynamics (PK/PD), and safety and tolerability of oral once-daily TBR-652 monotherapy for 10 days in HIV-1–infected, antiretroviral treatment–experienced, CCR5 antagonist–naive subjects. The primary objectives were to evaluate the antiviral activity and safety of

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TBR-652 at doses of 25, 50, 75, and 150 mg versus placebo. TBR-652 PK and PD were secondary objectives. A 100-mg dose in a different formulation was tested in the same study. Because PK results indicated bioavailability that was not dose proportional,[4] being closer to the 75-mg dose, this formulation is no longer under development and is not reported in the efficacy data below. It is included with the safety results to provide a complete assessment of TBR-652 safety.

Study Population

HIV-positive men and women aged 18 through 65 years were eligible provided they had confirmed HIV-1 RNA levels of at least 5000 copies per milliliter and $CD4^+$ cell counts of at least 250 cells per cubic millimeter. Virus must have been CCR5 tropic by the enhanced Trofile assay (Monogram Biosciences, South San Francisco, CA) at screening. Subjects had to have discontinued prior antiretroviral therapy at least 6 weeks before study entry. Subjects were excluded if they had CXCR4 or dual/mixed tropic virus; active Centers for Disease Control and Prevention AIDS-defining illness other than cutaneous Kaposi sarcoma that did not require treatment; history of hepatitis B or C or other active or chronic liver disease, including cirrhosis; elevated alanine aminotransferase or aspartate aminotransferase levels; recent clinically significant infection; treatment with any immunomodulator (including vaccines) or agents with anti-HIV effects within 30 days of dosing; treatment with prescription drugs, over-the-counter drugs, or supplements that could interfere with CYP 3A4 or CYP 2C8 enzymes or P-glycoprotein transporter activity within 30 days of dosing; or a history of clinically significant hepatic, metabolic, endocrine, renal, hematologic, pulmonary, gastrointestinal, or cardiovascular disorders [including electrocardiogram (ECG) abnormalities]. Women were excluded if they were pregnant or breast-feeding. All subjects of reproductive potential were required to use barrier contraception. Persons who did not meet entry criteria at screening could have been rescreened only once for eligibility. All subjects were screened for alcohol abuse or illicit drug use before dosing.

Ethics

The trial was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent before participating. Institutional review boards and independent ethics committees approved the informed consent, the protocol, and all protocol amendments before and during the trial.

Assessments and Monitoring

HIV-1 RNA levels were measured twice during screening, once at baseline, and on days 2, 3, 4, 7, 8, 10, 11, 15, 24, and 40. Samples were tested with the COBAS Amplicor polymerase chain reaction (PCR) assay (Roche Diagnostics, Branchburg, NJ); if levels were below the lower limit of quantitation (<400 copies/mL), the sample was evaluated with the ultrasensitive COBAS PCR assay (lower limit of quantitation <50 copies/mL). Viral coreceptor tropism was measured by the enhanced Trofile assay at screening and baseline, and on days 10, 24, and 40 if HIV-1 RNA levels permitted. $CD4^+$ cell counts were evaluated at screening, baseline, and days 4, 7, 10, 15, 24, and 40.

Plasma PK was measured predose on days 1-10; then at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours postdose on days 1 and 10; and at hours 96 and 120 hours after the day 10 dose. MCP-1, hs-CRP, and IL-6 levels were measured at baseline and day 10. MCP-1 levels were measured at the central laboratory using the BD cytometric bead array (BD Biosciences, Sparks, MD).

Safety assessments included a physical examination at screening, baseline, and days 10 and 24; vital signs at screening and baseline, then daily except weekends and holidays; clinical safety laboratory evaluations (chemistry, hematology, and coagulation profile) at screening, baseline, and days 2, 4, 7, 8, 10, 24, and 40 (ICON Central Laboratories, Farmingdale, NY and CIBC, Rosario, Argentina); urinalysis at screening, baseline, and days 10 and 24; and assessment of adverse events (AEs) and concomitant medications daily except weekends and holidays, when such information was gathered retrospectively. ECG tracings were obtained at screening, baseline, and days 7, 10, and 24 and were read locally and at a central processing site (eResearch Technology, Inc, Philadelphia, PA). Women had a serum pregnancy test at screening and urine pregnancy tests at baseline and days 10 and 24. Treatment compliance was assured by direct observation of subjects each time a dose was taken, except on weekends and holidays.

Statistical Analyses

Efficacy analyses included all subjects randomized to the study who took at least 1 dose of study drug and provided at least 1 valid HIV-1 RNA assessment after the first dose of study drug. Safety analyses included all subjects randomized into the study who took at least 1 dose of study drug. PK analyses included all subjects who provided adequate plasma PK samples. Subjects randomly assigned to placebo were analyzed as one group.

Demographics and baseline characteristics, including gender, age, race, height, weight, and body mass index, were summarized using descriptive statistics for each treatment group and for all randomized subjects. Plasma HIV-1 RNA level (in $\log_{10}$ copies/mL) at day 1 predose (baseline) and mean change from baseline thereafter were summarized and analyzed, as were plasma HIV-1 RNA level changes from baseline to nadir. At baseline, an analysis of variance model was used to compare each dose with placebo. For each change from baseline, an analysis of covariance model was used to compare each dose with placebo using the baseline value as a covariate. Subjects achieving HIV-1 RNA levels <400 copies per milliliter or <50 copies per milliliter were summarized and analyzed using a logistic regression model to compare each dose with placebo using the baseline value as a covariate. HIV-1 RNA values outside the limits of quantification were assigned the upper or lower quantitative value. All statistical tests were 1 sided, and a P value of 0.05 or less was considered statistically significant.

PK parameters were calculated using noncompartmental analysis. Differences in trough concentrations of TBR-652 on days 8, 9, and 10 were assessed using Helmert contrasts from a repeated measurement analysis of variance model to

determine the time to steady state. Steady state was concluded if Helmert contrasts were not statistically significant at a 2-sided alpha level of 5%. PD analyses included nadir HIV-1 RNA change from baseline using an analysis of covariance model including baseline value as a covariate.

Treatment-emergent AEs were defined as any AEs that occurred during treatment and follow-up and were classified by the investigator as to seriousness, intensity, and relationship to study drug. Clinically notable abnormalities were defined in the statistical analysis plan as any grade 1–4 alanine aminotransferase or aspartate aminotransferase level and any other grade 3 or 4 laboratory value, vital sign, or ECG event, based on the Division of AIDS (DAIDS) toxicity grading criteria.

RESULTS

Subject Demographics and Baseline Characteristics

Fifty-four subjects were enrolled—52 at 9 sites in the United States and 2 at 1 site in Argentina. All patients had clade B HIV-1. The 100-mg dose group, which is excluded from the efficacy presentation but included in the safety presentation, included the 2 patients from Argentina. All subjects completed dosing except 1 subject in the 75-mg dose group who was lost to follow-up after 1 dose of TBR-652. One subject each in the other cohorts was lost to follow-up or left the study early after completing dosing. No one discontinued because of an AE. The study population was predominantly men and white, with median HIV-1 RNA levels of 4.0 to 4.6 $\log_{10}$ copies per milliliter and median $CD4^+$ cell counts of 402 to 508 cells per cubic millimeter (Table 1). One subject assigned to the 50 mg/d dose group was inadvertently dosed with 25 mg/d and was therefore analyzed in the 25-mg dose group. One subject in the 150 mg/d dose group was excluded from the efficacy analysis because of dual/mixed tropic virus present at baseline. The subject in the 75 mg/d dose group who took only 1 dose was excluded from the efficacy and PK analyses.

The 10 subjects who received the 100-mg dose had significantly different PK results,[4] and although the safety profile at this dose was similar to the 25-mg dose group,[5] the formulation is no longer under development. These subjects are excluded from the efficacy presentation but included in the safety data.

HIV-1 RNA Changes

TBR-652 showed a potent dose–response effect on HIV-1 RNA levels, as measured by PCR, which persisted well after discontinuation of treatment (Fig. 1). The mean HIV-1 RNA reductions from baseline achieved statistical significance by day 4 for all doses, and by day 7, it reached $P = 0.002$ for the 25-mg one-daily (QD) dose and $P < 0.001$ the 50-mg, 75-mg, and 150-mg QD doses. The mean HIV-1 RNA reductions remained significant through day 15 for all TBR-652 dose groups. HIV-1 RNA reductions were still significant at day 24 in 150-mg dose group ($P = 0.03$). Mean changes from baseline to nadir viral load were also statistically significant for all TBR-652 dose groups and resulted in median decreases of up to 1.8 $\log_{10}$ copies per milliliter in the 75-mg dose group. At the 25-, 50-, 75-, and 150-mg doses, 33%, 71%, 100%, and 75% of subjects, respectively, achieved HIV-1 RNA reductions of at least 1 $\log_{10}$ copies per milliliter. One subject in the 25-mg dose group, 2 in the 50-mg dose group, and 3 in the 150-mg dose group achieved HIV-1 RNA levels below 400 copies per milliliter. Two subjects in the 150-mg dose group achieved levels below 50 copies per milliliter in this short-duration monotherapy study.

$CD4^+$ Cell Counts

Mean and median changes in $CD4^+$ cell counts were mixed (Fig. 2A). Least square mean values were significantly increased only at the 50-mg QD level on day 7 (+116 cell/mm^3; $P = 0.036$) and day 10 (+97 cells/mm^3; $P = 0.020$).

TABLE 1. Baseline Characteristics and Demographics of Subjects

Characteristic	Placebo (n = 10)	TBR-652, 25 mg (n = 8)	TBR-652, 50 mg (n = 8)	TBR-652, 75 mg (n = 9)	TBR-652, 150 mg (n = 9)
Male gender, n (%)	9 (90.0)	8 (100)	7 (87.5)	9 (100)	6 (66.7)
Mean age (range), yr	33.9 (24–44)	41.0 (24–47)	40.8 (24–47)	41.0 (33–50)	40.0 (26–56)
Race, n (%)					
African American	4 (40.0)	0	2 (25.0)	1 (11.1)	3 (33.3)
White	4 (40.0)	7 (87.5)	4 (50.0)	6 (66.7)	3 (33.3)
Hispanic	2 (20.0)	1 (12.5)	2 (25.0)	1 (11.1)	1 (11.1)
Other	0	0	0	1 (11.1)	2 (22.2)
Mean BMI (SD), kg/m^2	25.39 (3.27)	26.50 (3.00)	30.51 (11.04)	24.84 (2.61)	23.52 (2.73)
Missing	0	1	1	0	0
Median HIV-1 RNA (range), $\log_{10}$ copies/mL	4.20 (3.23–5.10)	4.20 (3.10–6.00)	4.50 (3.90–4.70)	4.60 (4.30–5.30)	4.00 (3.60–4.90)
Median $CD4^+$ cell count (range), cells/mm^3	417.5 (294–867)	402.0 (211–557)	460.0 (227–704)	436.0 (216–837)	508.0 (199–793)
Mean MCP-1 (range), pg/mL	22.4 (6–50)	20.0 (7–44)	12.6 (5–37)	26.6 (5–92)	31.6 (8–82)

BMI, body mass index; MCP, monocyte chemotactic protein.

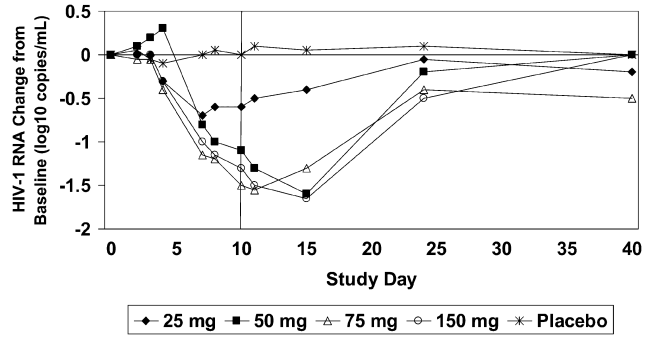

FIGURE 1. Median HIV-1 response to TBR-652. Data to the left of the vertical line show the changes in HIV-1 levels during the 10-day TBR-652 treatment period. Data to the right of the vertical line show the gradual loss of viral suppression off treatment during the 30-day follow-up period.

PK/PD Results

Maximum plasma concentrations of TBR-652 were achieved in 3–4 hours at all doses (Table 2). Helmert contrasts showed that steady-state concentrations (C_{ss}) were achieved by day 8. Log-normal (ln) transformed 24-hour area-under-the concentration–time curve (AUC_{0-24}) and maximum plasma concentrations (C_{max}) suggested a greater than dose-dependent increase in these parameters.

Inflammatory Marker Changes

A unique feature of TBR-652 as a CCR5 inhibitor is its CCR2 antagonism. Exploratory assessment of MCP-1, hs-CRP, and IL-6 levels found significant dose-dependent increases in MCP-1 (Fig. 2B). On day 10, least square mean MCP-1 levels obtained by flow cytometry were 56.3, 94.2, 34.4, and 334.3 pg per milliliter higher than at baseline in the 25, 50, 75, and 150-mg dose groups, respectively, compared with a slight decline in the placebo group. At the 50 and 150-mg doses, these results were statistically significant ($P = 0.024$ and $P < 0.001$, respectively). TBR-652 had minimal effect on hs-CRP, for which there were nonsignificant declines by day 10 (Fig. 2C). There were no changes in IL-6 levels at day 10 compared with baseline in any of the dose groups (data not shown).

Safety

TBR-652 was generally safe and well tolerated at the doses studied. The most commonly encountered treatment-emergent AEs for the subjects on active drug were gastrointestinal disorders (n = 19, 43%); general disorders (n = 11, 25%); nervous system disorders (n = 10, 23%); respiratory, thoracic, and mediastinal disorders (n = 10, 23%); infections and infestations (n = 7, 16%); and psychiatric disorders (n = 5, 11%). Most AEs in subjects on TBR-652 were mild (n = 24) or moderate (n = 5) in intensity. There was only 1 severe AE in a TBR-652–treated subject, an abscess on the shoulder, which was judged as nonserious and unrelated to study drug by the investigator, did not require treatment, and resolved without sequelae. There were no life-threatening AEs, no discontinuations because of an AE, and no deaths. No AEs were judged to be definitely related to study drug. AEs reported as possibly or probably related to study drug are listed

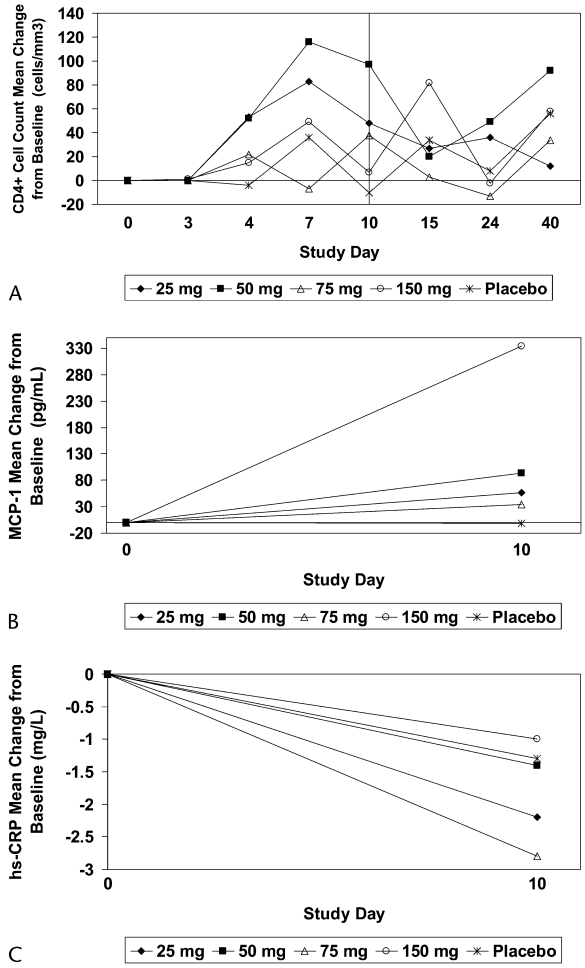

FIGURE 2. Least square mean changes in immune parameters during treatment with TBR-652. A, Data to the left of the vertical line show the changes in $CD4^+$ cell counts during the 10-day TBR-652 treatment period. Data to the right of the vertical line show the 30-day follow-up period. B, C, MCP-1 and hs-CRP were measured at baseline and day 10 only.

in Table 3. Most AEs resolved without intervention. Only 4 subjects on TBR-652 required concomitant medication for an AE assessed as possibly related to study drug. These were hydrocodone plus paracetamol for abdominal pain in the 25-mg dose group, paracetamol for headache in the 50-mg dose group, ondansetron for nausea in the 100-mg dose group, and ibuprofen for a subject with headache and nausea in the 150-mg dose group. No AEs requiring treatment were considered probably related to study drug.

The only clinically notable laboratory events were a grade 3 hypophosphatemia in the 25-mg dose group that was present before dosing, a grade 4 elevated triglyceride in the 50-mg dose group in a patient who had a grade 3 triglyceride at baseline, and grades 3 and 4 amylase and lipase elevations, respectively, in a patient in the 25-mg dose group who had a history of pancreatitis (Table 3). All cases were asymptomatic except the last; this patient was diagnosed with grade 2 pancreatitis and was subsequently found to have a history of

TABLE 2. Mean (CV%) PK Parameters of TBR-652 at Day 10

PK Parameter	Placebo (n = 10)	TBR-652, 25 mg (n = 9)	TBR-652, 50 mg (n = 7)	TBR-652, 75 mg (n = 8)	TBR-652, 150 mg (n = 9)
AUC_{τ} (ng·h/mL)	—	382.0 (52.8,)	1245 (40.4	1916 (30.6)	7272 (36.8)
$AUC_{0\text{-last}}$ (ng·h/mL)	—	611.7 (70.3)	2650 (40.7)	3625 (29.9)	15390 (32.8)
C_{max} (ng/mL)	—	35.11 (46.9)	102.4 (41.9)	157.0 (41.0)	508.1 (34.9)
C_{min} (ng/mL)	—	6.88 (55.7)	21.5 (44.9)	30.1 (36.7)	128.0 (40.4)
C_{ss} (ng/mL)	—	15.9 (52.8)	51.9 (40.4)	79.8 (30.6)	303 (36.8)
T_{max} (h)*	—	2.98 (1.00–4.03)	4.00 (2.00–6.00)	3.50 (2.00–6.17)	4.00 (3.00–8.00)
$t_{1/2}$ (h)	—	22.50 (42.7)	47.62 (44.5)	29.78 (12.4)	41.26 (42.1)
CL_{ss}/F (L/h)	—	81.31 (45.3)	49.26 (55.3)	42.17 (27.8)	22.95 (32.3)
V_{ss}/F (L)	—	2106 (54.7)	2400 (69.5)	1424 (42.3)	910.3 (49.0)
MRT (h)	—	26.81 (34.3)	47.45 (37.2)	33.03 (18.8)	38.66 (22.6)

*Median (minimum–maximum).

AUC, area-under-the concentration–time curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{ss}, steady-state concentration; $t_{1/2}$, apparent plasma terminal phase half-life; CL_{ss}/F, apparent oral clearance at steady-state; V_{ss}/F, apparent volume of distribution at steady-state; MRT, mean residence time.

pancreatitis and alcohol consumption before initial dosing. There were no changes in vital signs, physical examinations, or ECGs at any doses that were deemed to be clinically relevant.

DISCUSSION

TBR-652 showed potent antiviral activity after 10 days of once-daily monotherapy. Nadir changes ranged from −0.7 to −1.8 $\log_{10}$ copies per milliliter and were greatest in the 50-, 75-, and 150-mg dose groups at −1.6, −1.8, and −1.7 $\log_{10}$ copies per milliliter, respectively. The fact that the median time to achieve nadir was 10–11 days indicates that a true nadir may not have been reached in the 10-day treatment. Nadir and day 11 HIV-1 RNA changes from baseline were significant at all dose levels. In addition, the antiviral effect persisted well into the posttreatment period, with HIV-1 RNA levels still significantly lower for all TBR-652 dose groups 5 days after the treatment was discontinued and significantly lower than baseline in the 150-mg dose group 2 weeks after treatment discontinuation. The numbers of subjects who achieved HIV-1 RNA reductions of at least 1 $\log_{10}$ copies per milliliter compare favorably with the 10-day treatment studies of maraviroc. Maraviroc doses of 50, 100, and 150 mg twice daily resulted in HIV-1 RNA declines of greater than 1 $\log_{10}$ copies per milliliter in 50%, 88%, and 88% of subjects at day 11, respectively,[6] compared with 71%, 100%, and 75% of patients, respectively, on once-daily TBR-652. In addition, 33% of patients on 25 mg of TBR-652 also achieved a decline of at least 1 $\log_{10}$ copies per milliliter. The C_{ss} of TBR-652 associated with the 50% inhibitory concentration was 13.1 ng/mL, indicating that TBR-652 at doses of 50, 75, and 150 mg QD should provide strong antiviral activity in longer-duration studies.

AEs were reported in 34 subjects overall, 30 of whom were on TBR-652. Most AEs were mild, and there were no indications of a dose relationship through the 100-mg dose. The reported AEs and laboratory abnormalities did not show a dose-effect pattern. Given the generally mild AEs and the few laboratory abnormalities, no toxicity signal for TBR-652 could be found in this HIV-1–infected population, and there was no evidence of having reached a maximum-tolerated dose.

Exploratory assessments of MCP-1, hs-CRP, and IL-6 were undertaken because CCR2 antagonism with elevated MCP-1 was seen in binding studies of TBR-652 in Chinese hamster ovary cells.[7] The roles of various biomarkers of inflammation, including hs-CRP and IL-6, in the inflammation processes mediated by CCR2 and its MCP-1 ligand have been investigated in the aging HIV-1–infected population, and much research is currently looking at the interrelationships of inflammation and aging with HIV infection and antiretroviral therapy.[8–12] Elevations in these biomarkers have been associated with a number of inflammatory and aging-related diseases/conditions. This study found significant increases in MCP-1 at the 50- and 150-mg dose levels from 10 days of TBR-652 monotherapy; TBR-652 had little or no effect on the other measured immune parameters, including $CD4^+$ cell counts, which was not unexpected given that this was a monotherapy trial of short duration in a generally healthy HIV-1–infected population that would be expected to have low levels of inflammation. Although the combination of CCR5 and CCR2 antagonism is unique among currently published studies for CCR5 antagonists in clinical development, there was no discernable adverse interaction of this combination receptor blockade. Both hs-CRP and IL-6 were significantly elevated in patients who died from non-AIDS causes in the Strategies for Management of Anti-Retroviral Therapy (SMART) study.[9] The areas that would warrant observation in longer-duration controlled studies are potential changes in incidence of atherosclerosis,[13–16] measures of weight gain and insulin resistance,[17–19] rate of disease progression (especially if there are tropism shifts from CCR5 to CXCR4 virus during treatment),[20] incidence of other infections,[21–23] and incidence of neurologic changes in HIV-1–infected subjects.[24,25] Observations of demographic effects, particularly gender and race, on aging and inflammation in HIV-positive patients also warrant study.[26–28]

Overall, this proof-of-concept study showed TBR-652 to be a potent, well-tolerated anti-HIV drug with potential for additional benefit through a CCR2-mediated anti-inflammatory

TABLE 3. Summary of Treatment-Emergent Drug-Related AEs and Clinically Significant Laboratory Events

System Organ Class Preferred Term	Number of Subjects (%)					
	Placebo (n = 10)	TBR-652, 25 mg (n = 9)	TBR-652, 50 mg (n = 7)	TBR-652, 75 mg (n = 9)	TBR-652, 100 mg (n = 10)	TBR-652, 150 mg (n = 9)
Any SAE	0	0	0	0	0	0
Any treatment-emergent drug-related AE*	3 (30)	4 (44)	3 (43)	0	5 (50)	8 (89)
Gastrointestinal disorders	3 (30)	2 (22)	2 (29)	0	4 (40)	5 (56)
Nausea	1 (10)	1 (11)	1 (14)	0	1 (10)	3 (33)
Diarrhea	0	0	0	0	3 (30)	2 (22)
Abdominal pain	1 (10)	1 (11)	0	0	0	1 (11)
Flatulence	0	1 (11)	1 (14)	0	0	1 (11)
Abdominal distension	0	0	0	0	0	1 (11)
Abdominal tenderness	0	1 (11)	0	0	0	0
Dry mouth	0	0	0	0	0	1 (11)
GERD	0	1 (11)	0	0	0	0
Gingival pain	1 (10)	0	0	0	0	0
Glossodynia	1 (10)	0	0	0	0	0
Pancreatitis	0	1 (11)	0	0	0	0
Swollen tongue	1 (10)	0	0	0	0	0
Tongue discoloration	1 (10)	0	0	0	0	0
Vomiting	0	1 (11)	0	0	0	0
General disorders and administration site conditions	0	2 (22)	0	0	1 (10)	5 (56)
Fatigue	0	2 (22)	0	0	1 (10)	3 (33)
Pyrexia	0	0	0	0	0	2 (22)
Nervous system disorders	0	0	1 (14)	0	1 (10)	3 (33)
Headache	0	0	1 (14)	0	0	2 (22)
Altered state of consciousness	0	0	0	0	0	1 (11)
Dizziness	0	0	0	0	0	1 (11)
Somnolence	0	0	0	0	1 (10)	
Psychiatric disorders	0	0	1 (14)	0	0	2 (22)
Abnormal dreams	0	0	1 (14)	0	0	1 (11)
Insomnia	0	0	0	0	0	1 (11)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (10)	2 (22)
Cough	0	0	0	0	0	1 (11)
Pharyngolaryngeal pain	0	0	0	0	1 (11)	0
Sinus congestion	0	0	0	0	0	1 (11)
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (11)
Hyperhidrosis	0	0	0	0	0	1 (11)
Clinically notable laboratory events†	1 (10)	3 (33)	2 (29)	1 (11)	1 (10)	1 (11)
ALT, grade 1	1 (10)	1 (11)	2 (29)	0	0	0
AST, grade 1	1 (10)	1 (11)	1 (14)	1 (11)	1 (10)	1 (11)
Hypophosphatemia, grade 3	0	1 (11)	0	0	0	0
Amylase, grade 3	0	1 (11)	0	0	0	0
Lipase, grade 4	0	1 (11)	0	0	0	0
Triglyceride, grade 4	0	0	1 (14)	0	0	0

If a subject experienced more than 1 AE within a preferred term or more than 1 clinically notable laboratory event, then she/he was counted once per term. If a subject experienced more than 1 AE, then she/he was counted once in "any treatment-emergent drug-related" AE.

*Drug-related AEs were assessed by the investigator as possibly or probably related to study drug. There were no events judged to be definitely related to TBR-652. No AEs were considered serious by investigators.

†Clinically notable events were grades 1–4 alanine aminotransferase or aspartate aminotransferase elevations or any other grade 3 or 4 toxicity based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GERD, gastroesophageal reflux disease; SAE, serious adverse event.

effect. TBR-652 warrants further investigation as a potent, oral, unboosted, once-daily CCR5 receptor antagonist to be used in combination HIV-treatment regimens, especially in treatment-naive patients. Based on the biology of HIV infection, the treatment-naive population is the most appropriate one for treatment with a CCR5 antagonist because CCR5-tropic virus is more prevalent earlier in infection. The prevalence of CCR5-only virus tropism in one study was 88% of treatment-naive patients (n = 263) compared with 67% of treatment-experienced patients (n = 76).[29] In the Multicenter

AIDS Cohort Study (MACS), a large study of HIV natural history, 67 patients who had known HIV-1 seroconversion dates (±5 months) from before 1995 and regular study visits with blood samples that had been tested or were available for tropism testing were assessed for conversion from CCR5-tropic virus to CXCR4-tropic virus. Among these treatment-naive men, 97% had solely CCR5-tropic virus at their first visit.[30] Thirty-three percent converted to dual/mixed virus, which was associated with more rapid disease progression, which included $CD4^+$ cell counts <200 cells per cubic millimeter and AIDS-defining events. Because the prevalence of CXCR4-tropic virus increases in patient populations with more advanced disease and lower $CD4^+$ cell counts, the utility of CCR5 antagonists in those populations becomes limited. Therefore, a larger, randomized, double-blind phase 2b study is being planned that will enroll treatment-naive patients.

Drug–drug interaction studies are underway to enable construction of a combination regimen (or regimens) with an appropriate TBR-652 dose. Given the similar efficacy of the 50 and 150 mg/d doses and the lack of any drug-related AE at the 75-mg dose, the phase 2b study will test 2 doses used in the study reported here and attempt to clarify the best dose for phase 3 study. Given the rapid reductions in HIV-1 RNA in this study, the next study will also include a positive control. In addition, the effect of CCR2 antagonism on hs-CRP, IL-6, and other biomarkers of inflammation will be further investigated, with the hopes of clarifying their usefulness in predicting inflammatory processes and reducing the risk of inflammatory disease with TBR-652 therapy. Changes in $CD4^+$ cell counts, viral tropism, and viral resistance over time will also be assessed in the new study. It is anticipated that TBR-652 will prove a good candidate for coformulation with other once-daily antiretroviral agents, given the once-daily, low-milligram dose profile and good tolerability of TBR-652 thus far.

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