

# PHARMACOKINETICS (PK), SAFETY, AND TOLERABILITY OF SINGLE DOSES OF THE CHEMOKINE C-C RECEPTOR 5 (CCR5) ANTAGONIST TBR-652 IN HEALTHY VOLUNTEERS

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## ABSTRACT

**Background:** Promising treatment for HIV-1 infection is blockade of CCR5, used by HIV-1 to enter target cells. TBR-652 is a potent CCR5 antagonist with a 0.25nM EC<sub>50</sub> against HIV-1 clinical isolates in human PBMC and a mean plasma half-life (t<sub>1/2</sub>) of about 35 hours after oral dosing, which supports once-daily dosing.

**Methods:** This was a double-blind, randomized, placebo-controlled study of two formulations of oral TBR-652 in fasted, healthy subjects 18-55 years old. Two cohorts of 12 subjects received 2x5mg, 1x25mg, and 4x25mg (Cohort 1, F1 tablet formulation) or 1x100mg, 4x100mg, and 8x100mg (Cohort 2, F2 tablet formulation) of TBR-652 sequentially, with a 7- or 10 day washout, respectively, between doses. PK and safety data were summarized descriptively.

**Results:** TBR-652 absorption was similar across most dose groups (median t<sub>max</sub> 3-4 hours). Elimination showed linear kinetics (mean t<sub>1/2</sub> about 35 hours). C<sub>max</sub> and AUC<sub>0-∞</sub> were dose proportional in Cohort 1 (over 10-100mg), but not in Cohort 2 (over 100-800mg). C<sub>max</sub> and AUC were more than 3 times higher after administration of 4x25mg F1 tablets in Cohort 1 compared to 1x100mg F2 tablet in Cohort 2, which was attributed to the differences between formulations. F2 tablets also resulted in greater intersubject variability in TBR-652 concentrations. Of 25 and 12 treatment-emergent adverse events (AEs) in cohorts 1 and 2, respectively, 19 and 6 were thought possibly related to study drug, 92% and 100% were mild in intensity. Headache, diarrhea, abdominal pain, and nausea were the most common AEs and occurred more frequently in cohort 1. Five subjects discontinued dosing early. No subjects were withdrawn due to an AE, and there were no unexpected, severe, or life-threatening AEs.

**Conclusions:** TBR-652 was rapidly and well absorbed and showed a long plasma half-life, supportive of once-daily dosing. TBR-652 was generally well-tolerated and safe across all doses tested. This trial supports further exploration of TBR-652 for potential use in HIV-infected patients.

## BACKGROUND

Promising treatment for human immunodeficiency virus type 1 (HIV-1) infection is blockade of CCR5, the lymphocyte coreceptor commonly used, along with CD4, by HIV-1. Early studies with compounds designed to block CCR5 have shown CCR5 antagonists to be effective in preventing HIV cell entry and subsequent replication when administered in combination with other antiretroviral drugs. TBR-652 (formerly known as TAK-652) is a potent CCR5 antagonist with an EC<sub>50</sub> of 0.25 nM against HIV-1 clinical isolates of human peripheral blood mononuclear cells (PBMC). In addition, TBR-652 has a mean plasma half-life (t<sub>1/2</sub>) of about 35 hours, which supports once-daily dosing. This poster presents the pharmacokinetic and safety data from Tobira Therapeutics Study 652-1-101, a study of TBR-652 administered in single, escalating oral doses in 2 tablet formulations to healthy subjects.

## OBJECTIVES

The objectives of the study were:

- To evaluate the pharmacokinetics of single, escalating doses of TBR-652 in healthy adult subjects.
- To evaluate the safety and tolerability of TBR-652 in healthy adult subjects when administered as a single dose over a wide dose range.

## METHODS

**Study Design:** This was a double-blind, randomized, placebo-controlled study of oral TBR-652 in fasted healthy subjects. Two cohorts of 12 subjects were enrolled sequentially and received up to 3 single, escalating doses of study drug (Table 1), with at least 7 days of washout interval between doses for Cohort 1 and at least 10 days of washout interval between doses for Cohort 2. Subjects were blindly randomized 10:2 to receive TBR-652 or placebo per dose level. Dosing occurred after an overnight fast of at least 8 hours (water was restricted for 2 hours before and after dosing). Each dose was administered with at least 240 mL of water; the 800-mg dose (Treatment F) was administered with up to 480 mL of water.

Table 1: Treatments by Dose and Tablet Formulation

Cohort/Tablet Formulation	Treatment by Number and Strength of TBR-652/Placebo Tablets		
	Period 1	Period 2	Period 3
Cohort 1, F1 tablets	A: 2 x 5 mg	B: 1 x 25 mg	C: 4 x 25 mg
Cohort 2, F2 tablets	D: 1 x 100 mg	E: 4 x 100 mg	F: 8 x 100 mg

**Study Population:** The study subjects were healthy males and females between 18 and 55 years of age who were willing to take appropriate precautions to prevent pregnancy and had no significant metabolic, hepatic, renal, hematologic, pulmonary, cardiovascular, or gastrointestinal (GI) disorders. Subjects were to have a body mass index (BMI) of 18 to 30 kg/m<sup>2</sup> (inclusive), had no recent history (within 30 days) of clinically significant infection, and were negative serologically for hepatitis B and C and HIV. The use of concomitant medications or treatments was restricted except as needed for the subject's well-being.

**Analyses:** Safety and tolerability were assessed by monitoring adverse events (AEs), measuring vital signs, obtaining electrocardiograms (ECGs), and collecting clinical laboratory values from blood and urine samples. PK parameters of TBR-652 were calculated using noncompartmental methods and summarized by descriptive statistics by treatment/dose level.

## PHARMACOKINETICS

Figure 1. Mean Plasma Concentration vs Time Curves of TBR-652 in 2 Tablet Formulations

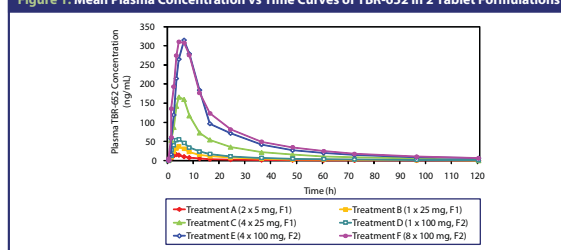


Table 4: Summary of TBR-652 Pharmacokinetic Parameters by Treatment

Treatment (dose)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	AUC <sub>0-∞</sub> (h*ng/mL)	t <sub>1/2</sub> (h)	AUC <sub>0-12h</sub> (h*ng/mL)	CL <sub>F</sub> (mL/min)	Dose Normalized	
							AUC <sub>0-∞</sub> (h*ng/mL/mg)	C <sub>max</sub> (ng/mL/mg)
A (2 x 5 mg) <sup>a</sup>	Mean <sup>b</sup> 15.7	3.0	258	34.1	9.23	679	25.82	1.57
	% CV 22	23	252	33.4	46	24	23	22
	Geometric mean 15.3				662		25.17	1.53
B (1 x 25 mg) <sup>a</sup>	Mean <sup>b</sup> 39.4	4.0	699	30.9	9.59	626	27.94	1.58
	% CV 23	25	681	33.9	52	22	25	23
	Geometric mean 38.6				612		27.25	1.54
C (4 x 25 mg) <sup>a</sup>	Mean <sup>b</sup> 173.4	4.0	3171	33.0	8.63	541	31.71	1.73
	% CV 22	18	3126	32.7	37	18	18	22
	Geometric mean 169.7				31.26		31.26	1.70
D (1 x 100 mg) <sup>a</sup>	Mean <sup>b</sup> 56.9	4.0	1042	36.0	6.23	1971	10.42	0.57
	% CV 54	60	926	36.1	45	41	60	54
	Geometric mean 51.7				1800		9.26	0.52
E (4 x 100 mg) <sup>a</sup>	Mean <sup>b</sup> 320.6	6.0	5639	39.0	7.19	1585	14.10	0.80
	% CV 57	46	4966	38.0	56	69	46	57
	Geometric mean 275.2				1342		12.42	0.69
F (8 x 100 mg) <sup>a</sup>	Mean <sup>b</sup> 325.3	4.0	6864	31.5	4.37	2166	8.58	0.41
	% CV 30	35	6495	31.8	34	34	35	30
	Geometric mean 311.7				2053		8.12	0.39

<sup>a</sup>n=12; <sup>b</sup>n=9 for C<sub>max</sub>, t<sub>max</sub>, AUC<sub>0-∞</sub>, and dose-normalized C<sub>max</sub> and AUC<sub>0-∞</sub> for all other parameters. Values for t<sub>1/2</sub> and t<sub>1/2</sub> are medians.

Figure 2. Individual and Mean Dose-Normalized C<sub>max</sub> for All Treatments

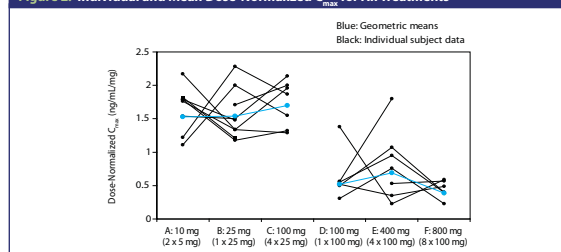


Figure 3. Individual and Mean Dose-Normalized AUC<sub>0-∞</sub> for All Treatments

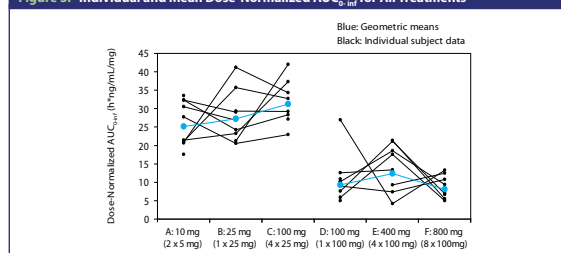
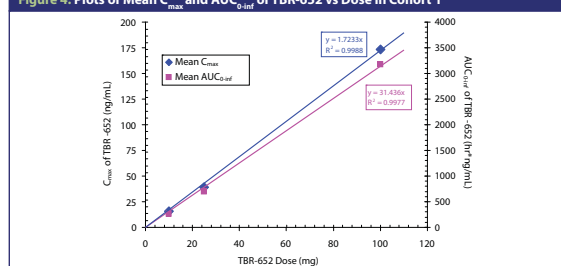


Figure 4. Plots of Mean C<sub>max</sub> and AUC<sub>0-∞</sub> of TBR-652 vs Dose in Cohort 1



## RESULTS

**Demographics/Disposition:** The demographics and disposition of the enrolled population are presented in Tables 2 and 3. A total of 24 subjects were enrolled in the study: 12 subjects in Cohort 1 and 12 subjects in Cohort 2. One subject was terminated from Cohort 1 due to a positive urine drug screen (marijuana), a major protocol violation. Two subjects discontinued from Cohort 2 for personal reasons unrelated to the study. The only other major protocol deviation was a subject from Cohort 2 who exceeded the BMI requirement by 0.1 kg.

Table 2: Subject Demographics

Variable	Cohort 1 (N=12)	Cohort 2 (N=12)
Age, years		
Mean	29.2	27.8
Standard Deviation (SD)	6.78	8.27
Range	19.0-41.0	19.0-47.0
Median	29.0	25.5
Gender, n (%)		
Male	9 (75.0)	9 (75.0)
Female	3 (25.0)	3 (25.0)
Race, n (%)		
Caucasian	5 (41.7)	3 (25.0)
African American	7 (58.3)	8 (66.7)
Asian	0	0
Hispanic	0	0
Other	0	1 (8.3)
BMI (kg/m <sup>2</sup> )		
Mean	25.3	24.9
SD	2.31	3.31
Range	22.5-29.7	20.1-30.1
Median	24.4	25.3
Height (cm)		
Mean	173	174
SD	7.92	6.33
Range	163-188	164-183
Median	175	174
Weight (kg)		
Mean	76.3	75.4
SD	8.87	11.7
Range	62.3-88.0	56.4-93.8
Median	77.55	75.35

Table 3: Disposition of Subjects Who Took at Least 1 Dose of Study Drug

	Cohort 1			Cohort 2		
	Treatment A (10 mg)	Treatment B (25 mg)	Treatment C (100 mg)	Treatment D (100 mg)	Treatment E (400 mg)	Treatment F (800 mg)
Subjects who were randomized	12	12	12	12	11	10
Subjects who received drug	12	12	11	11	10	10
Subjects who discontinued from the study	0	1	0	1	1	0
Reasons for discontinuation						
Positive drug screen, marijuana		1 (8.3%)				
Withdrawal other reasons, personal				1 (8.1%)	1 (10%)	

## Pharmacokinetic Summary:

- TBR-652 was readily absorbed from both tablet formulations, with median t<sub>max</sub> of 3 to 4 hours postdose.
- TBR-652 was eliminated from plasma with linear kinetics with similar half-lives (mean: about 35 hours) across dose levels. This elimination half-life was sufficiently long to support once-daily dosing.
- Administration of the 5-mg and 25-mg F1 tablets of TBR-652 resulted in a dose-proportional increase in C<sub>max</sub> and AUC<sub>0-∞</sub> over the dose range evaluated (10 mg to 100 mg).
- Administration of the 100-mg F2 tablets resulted in lower plasma exposure to TBR-652 and greater intersubject variability compared with the 4 x 25-mg F1 tablets when administered under fasting conditions.
- Plasma TBR-652 concentrations after administration of 4 x 25-mg F1 tablets (Treatment C) were more than 3 times higher than those after administration of 1 x 100-mg F2 tablet (Treatment D), which was attributed to different formulations.
- Administration of the 100-mg F2 tablet formulation over the dose range of 100 mg to 800 mg did not produce dose-proportional increases in C<sub>max</sub> and AUC<sub>0-∞</sub> of TBR-652, and plasma exposure to TBR-652 appeared to plateau between the 400 mg (4 x 100 mg) and the 800 mg (8 x 100 mg) doses.

**Safety:** Of treatment-emergent AEs in Cohorts 1 and 2 (Table 5), 19 and 6 events, respectively, were thought possibly related to study drug. One subject in Cohort 1 Treatment A reported muscle spasms and abdominal pain that was considered moderate in intensity; all other AEs were considered mild in intensity. Treatment-emergent AEs with the highest rate of incidence were: headache (4 subjects in Cohort 1, 1 subject in Cohort 2), diarrhea (3 subjects in Cohort 1, 1 subject in Cohort 2), abdominal pain (3 subjects in Cohort 1), and nausea (2 subjects in Cohort 1, 1 subject in Cohort 2). All treatment-emergent AEs resolved without sequelae by the end of the study. Vital signs, ECGs, and laboratory values were unremarkable, and none were considered to be clinically significant. No subjects were withdrawn from an AE, and there were no unexpected, severe, or life-threatening AEs.

Table 5: Treatment-Emergent Adverse Events

MedDRA System Organ Class Preferred Term	Cohort 1 (N=12) n (%)	Cohort 2 (N=12) n (%)
<b>Subjects with at least 1 event</b>	9 (75.0)	6 (50.0)
<b>Cardiac Disorders</b>		
Dizziness	1 (8.3)	0 (0.0)
Palpitations	1 (8.3)	0 (0.0)
<b>GI Disorders</b>		
Abdominal Distension	7 (58.3)	2 (16.7)
Abdominal Pain	1 (8.3)	0 (0.0)
Abdominal Pain Upper	3 (25.0)	0 (0.0)
Diarrhea	1 (8.3)	1 (8.3)
Dry Mouth	3 (25.0)	1 (8.3)
Nausea	1 (8.3)	1 (8.3)
Oral Herpes	2 (16.7)	1 (8.3)
Vomiting	0 (0.0)	1 (8.3)
<b>Immune System Disorders</b>		
Hypersensitivity	0 (0.0)	2 (16.7)
Seasonal Allergy	0 (0.0)	1 (8.3)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back Pain	1 (8.3)	1 (8.3)
Muscle Spasms	0 (0.0)	1 (8.3)
<b>Nervous System Disorders</b>		
Headache	4 (33.3)	1 (8.3)
Memory Impairment	1 (8.3)	0 (0.0)
<b>Psychiatric Disorders</b>		
Somnolence	0 (0.0)	1 (8.3)
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Nasal Congestion	0 (0.0)	1 (8.3)
Rhinorrhea	0 (0.0)	1 (8.3)
<b>Reproductive System and Breast Disorders</b>		
Metrorrhagia	3 (25.0)	0 (0.0)
Polymenorrhea	1 (8.3)	0 (0.0)
Vaginal Discharge	1 (8.3)	0 (0.0)
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash Papular	0 (0.0)	1 (8.3)

## Safety Summary:

- TBR-652 was well tolerated at all dose levels, with headache, diarrhea, abdominal pain, and nausea the most commonly encountered treatment-emergent AEs.
- There was no clear trend for increasing occurrence or incidence of treatment-emergent AEs with increasing dose of TBR-652.
- All AEs were mild or moderate in severity and resolved without sequelae at the end of the study.
- Fewer AEs were seen with the 100-mg tablets.

## CONCLUSIONS

- TBR-652 was rapidly absorbed from both tablet formulations, and both tablet formulations demonstrate relatively good oral bioavailability, as shown by the plasma TBR-652 concentration data.
- The relatively long plasma half-life of TBR-652 (mean: about 35 hours) supports once-daily dosing.
- TBR-652 was safe and well tolerated in this healthy subject population when administered over a dose range of 10 mg to 800 mg in 2 tablet formulations.
- The results of this trial supported further investigation of this new CCR5 antagonist, including the effects of food on bioavailability (see Poster WEPEB252).

## ACKNOWLEDGEMENTS

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