

EFFECT OF FOOD ON THE RELATIVE BIOAVAILABILITY AND PHARMACOKINETICS OF TBR-652, A POTENT NEW CHEMOKINE C-C RECEPTOR 5 (CCR5) ANTAGONIST

S. Palleja^{1*}, R. Driz¹, L. Wang-Smith², R. Ogden¹, D. Martin¹, A. Bobbitt¹, J. Sapirstein¹

¹Tobira Pharmaceuticals, Inc., Princeton, NJ; ²INDAPharma, LLC, Chapel Hill, NC

ABSTRACT

Background: TBR-652 is a potent new CCR5 antagonist with about a 0.25nM EC₅₀ against HIV-1 clinical isolates in human PBMC, a mean plasma half-life (t_{1/2}) of about 35 hours supporting once-daily dosing, and good tolerability. Since food can affect the bioavailability of drugs, it was prudent to determine the effect of food on TBR-652 before beginning a proof-of-concept study in HIV-infected patients.

Methods: This was an open-label, two-part, crossover study to investigate the effect of food on the pharmacokinetics (PK) and safety of TBR-652. Three groups of healthy subjects (12 per group) aged 18-55 years received single 100mg F2 formulation tablets or 4x25mg F1 formulation of TBR-652 after an overnight fast, then either after a high-fat (about 56-67g) or a low-fat (about 2-6g) breakfast, with at least 10 days between doses. PK and safety results were summarized by descriptive statistics. Analysis of variance was used to compare fasted and fed PK results.

Results: No subject discontinued the study prematurely. The high-fat meal significantly increased the relative bioavailability and reduced intersubject variability in plasma concentrations of TBR-652. Median (range) time to maximum plasma concentrations were 4 (3-6) hours without food and 6 (3-6) hours with either a high-fat or low-fat meal. Mean maximum plasma concentrations (C_{max}; ng/mL) were 131 and 166 fasted, 182 following a low-fat meal, and 363 following a high-fat meal with the 100 mg F2 tablet. The mean estimated area under the concentration-time curve to infinity (AUC_∞) increased from 2101 to 2813 with a low-fat meal and from 2500 to 5200 following a high-fat meal with the 100 mg F2 tablet. The extent of increase in geometric mean C_{max} and AUC_∞ of TBR-652 following a high-fat meal was more than 3-fold, compared to less than 20% following a low-fat meal with the 100 mg F2 tablet.

Conclusions: TBR-652 tablets are readily bioavailable. To ensure high and consistent plasma exposure, TBR-652 tablets should be taken with food, nevertheless, mean TBR-652 plasma concentrations were well above the predicted target plasma concentration (2ng/mL) with or without food.

BACKGROUND

TBR-652, formerly known as TAK-652, is a potent new CCR5 antagonist with an EC₅₀ of about 0.25 nM against HIV-1 clinical isolates in human peripheral blood mononuclear cells (PBMC), a mean plasma half-life (t_{1/2}) of about 35 hours that supports once-daily dosing, and good tolerability. A phase 1 PK study of TBR-652 in healthy subjects showed that 100 mg of TBR-652 administered as four 25-mg tablets (formulation F1) resulted in much greater plasma exposure than one 100-mg tablet (formulation F2). The 100-mg F2 tablet formulation also resulted in greater intersubject variability (see Poster WEPEB251). Since food can affect the bioavailability of drugs, it was prudent to determine the food effect of TBR-652 before beginning a proof-of-concept study in HIV-infected patients. The effects of a high-fat and a low-fat meal on the relative bioavailability of 2 tablet formulations of TBR-652 were evaluated in Tobira Therapeutics Study 652-1-102.

OBJECTIVES

The objectives of the study were:

- To determine the effect of food (a high-fat meal and a low-fat meal) on the relative bioavailability of TBR-652 following a single 100-mg dose administered in 2 tablet formulations.
- To assess the safety and tolerability of a single 100-mg dose of TBR-652 administered in 2 tablet formulations in healthy adult subjects.

METHODS

Study Design: This was an open-label, 2-period, crossover study to evaluate the effect of a low-fat (20 to 50 calories, 2 to 6 g fat) and a high-fat (500 to 600 calories, 56 to 67 g fat) breakfast on the relative bioavailability of TBR-652 following a single 100-mg dose administered in the F1 tablet formulation (4 x 25 mg) and in the F2 tablet formulation (1 x 100 mg) to healthy subjects (Table 1). Three cohorts of 12 subjects each were enrolled into the study. In Period 1, study drug was administered to fasted subjects (following at least 8 hours with no food or drink except water, and water was restricted for 2 hours before and after administration). In Period 2, following at least a 10-day washout period, drug was administered within 30 minutes after the start and within 10 minutes after the completion of a high-fat or low-fat breakfast. Tablets were taken with approximately 240 mL of water.

Table 1: TBR-652 Administration Sequence

Cohort	Formulation/Dose	Period 1	Period 2
Cohort 1	Tablet F2 (1 x 100 mg)	Fasted	High-fat breakfast
Cohort 2	Tablet F1 (4 x 25 mg)	Fasted	High-fat breakfast
Cohort 3	Tablet F2 (1 x 100 mg)	Fasted	Low-fat breakfast

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 had a body mass index (BMI) of 18 to 30 kg/m² (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: For each subject, plasma concentration vs time data for TBR-652 was analyzed by noncompartmental PK methods. Individual parameter estimates were listed and summarized by treatment/formulation with descriptive statistics. Analysis of variance (ANOVA) was performed on log_e-transformed C_{max}, AUC_∞, and AUC_{0-∞} values to evaluate the effect of food on each tablet formulation. 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.

PHARMACOKINETICS

Figure 1. Mean Plasma Concentration vs Time Curves of TBR-652 in 2 Tablet Formulations, With and Without Food

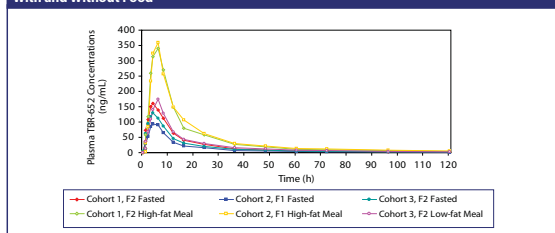


Table 4: Summary of TBR-652 Pharmacokinetic Parameters by Cohort/Treatment and Period

Parameter	Cohort 1 (1 x 100 mg F2)		Cohort 2 (4 x 25 mg F1)		Cohort 3 (1 x 100 mg F2)		
	Period 1 Fasted (n=12)	Period 2 High-fat Meal (n=11)	Period 1 Fasted (n=2)	Period 2 High-fat Meal (n=12)	Period 1 Fasted (n=12)	Period 2 Low-fat Meal (n=11)	
C _{max} (ng/mL)	Mean	166.3	363.0	108.6	407.6	132.0	182.3
	SD	113.0	103.1	72.0	112.1	58.7	118.2
	% CV	68.0	28.0	66.0	27.0	44.0	65.0
t _{max} (h)	Median	4.0	6.0	4.0	6.0	4.0	6.0
	Range	3.0-6.0	3.0-6.0	3.0-6.0	4.0-16.0	3.0-6.0	3.0-6.0
AUC _∞ (h*ng/mL)	Mean	2373	4972	1383	5305	1942	2623
	SD	1747	1925	955	1760	1009	1679
	% CV	74	39	69	33	52	64
AUC _{0-∞} (h*ng/mL)	Mean	2500	5200	1475	5660	2101	2813
	SD	1821	2001	990	1951	1115	1791
	% CV	73	38	67	34	53	64
t _{1/2} (h)	Median	37.7	37.5	36.8	38.9	36.1	38.3
	Range	11.0-48.3	32.3-44.2	10.9-55.4	32.4-50.5	11.9-61.9	15.1-51.7
AUC _{0-∞} (%)	Mean	7.68	4.38	7.70	5.79	7.32	8.76
	SD	6.20	1.20	4.17	2.86	3.34	6.57
	% CV	81.0	27.0	54.0	49.0	46.0	75.0

Table 5: Summary of Food Effect on TBR-652 C_{max} and AUCs

Cohort (Tablet/Meal)	Parameter	LS Mean (Fasted)	LS Mean (Fed)	LS Mean Ratio (Fed:Fasted)	90% CI
1 (F2)	AUC _∞ (h*ng/mL)	1547.0	4897.0	3.17	1.57, 6.38
	AUC _{0-∞} (h*ng/mL)	1425.0	4677.0	3.28	1.57, 6.85
	C _{max} (ng/mL)	112.7	352.2	3.13	1.74, 5.62
2 (F1)	AUC _∞ (h*ng/mL)	1096.0	5259.0	4.80	3.07, 7.49
	AUC _{0-∞} (h*ng/mL)	1010.0	4952.0	4.90	3.10, 7.75
	C _{max} (ng/mL)	83.9	390.2	4.65	3.26, 6.63
3 (F2)	AUC _∞ (h*ng/mL)	1679.0	1962.0	1.17	0.654, 2.09
	AUC _{0-∞} (h*ng/mL)	1555.0	1779.0	1.14	0.618, 2.12
	C _{max} (ng/mL)	113.2	129.8	1.15	0.697, 1.89

Figure 2. Individual and Mean Values of AUC_∞ of TBR-652 by Tablet Formulation and Treatment

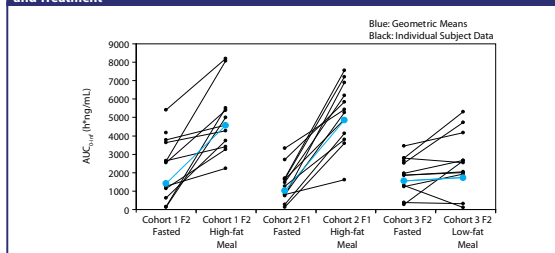
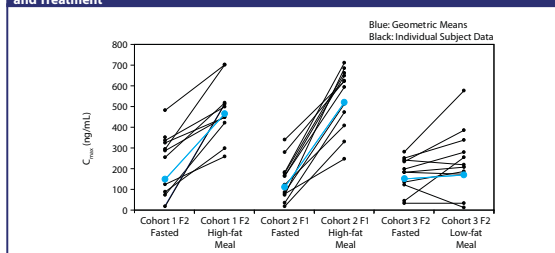


Figure 3. Individual and Mean Values of C_{max} of TBR-652 by Tablet Formulation and Treatment



RESULTS

Demographics/Disposition: 36 subjects were enrolled (Table 2). Two subjects, 1 in Cohort 1, and 1 in Cohort 2, did not complete the study (Table 3).

Table 2: Subject Demographics

	Cohort 1 (1 x 100 mg F2)	Cohort 2 (4 x 25 mg F1)	Cohort 3 (1 x 100 mg F2)
N	12	12	12
Age (years)			
Mean	42.8	40.3	46.9
Median	45.5	41.0	47.0
SD	8.05	9.02	6.07
Range	30.0-51.0	28.0-53.0	36.0-55.0
Gender, n (%)			
Female	7 (58)	10 (83)	7 (58)
Male	5 (42)	2 (17)	5 (42)
Race, n (%)			
African American	0	0	2 (17)
Asian	0	0	0
Caucasian	2 (17)	6 (50)	10 (83)
Hispanic	9 (75)	6 (50)	0
Native American	0	0	0
Other	1 (8)	0	0
Weight, kg			
Mean	71.6	66.2	74.3
Median	70.0	66.5	74.0
SD	10.53	7.98	14.48
Range	56.0-100.0	56.0-82.0	48.0-102.0
Height, cm			
Mean	162.5	160.1	164.9
Median	161.0	159.0	164.0
SD	8.66	6.40	10.93
Range	153.0-184.0	151.0-178.0	150.0-187.0
BMI, kg/m²			
Mean	27.0	25.8	27.0
Median	27.6	26.1	27.7
SD	2.34	1.76	2.50
Range	22.4-29.5	21.6-28.1	21.3-29.8

Table 3: Disposition of Subjects

	Cohort 1 (1 x 100 mg F2)		Cohort 2 (4 x 25 mg F1)		Cohort 3 (1 x 100 mg F2)	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Subjects randomized	12	11	12	12	12	12
Subjects who received study drug	12	11	12	12	12	11
Subjects who completed study	11 (92%)	11 (100%)	11 (92%)	11 (100%)	11 (92%)	11 (92%)
Subjects discontinued from study	1 (8%)	0	0	0	1 (8%)	0
Reason for withdrawal:						
Withdrawal of consent by the subject	1 (8%)	0	0	0	0	0
Positive drug screen, benzodiazepine	0	0	0	0	1 (8%)	0

Note: Period 1 was for fasted conditions; Period 2 was for fed condition

Pharmacokinetic Summary:

- The PK characteristics of TBR-652 following administration of the 2 tablet formulations under fasted conditions were similar to those seen in the previous study (see Poster WEPEB251).
- TBR-652 was readily bioavailable from both tablet formulations administered under fasted or fed conditions.
- Administration of either of the tablet formulations with a high-fat meal greatly increased the extent of TBR-652 bioavailability and greatly reduced the intersubject variability in plasma TBR-652 concentrations.
- The extent of increase in geometric mean C_{max} and AUC_∞ of TBR-652 following a high-fat meal was more than 2-fold, compared with <20% following a low-fat meal administered with a 100-mg F2 tablet.
- Both the 25-mg (F1) and 100-mg (F2) tablet formulations, administered with or without a meal resulted in plasma TBR-652 concentrations that were well above the predicted target plasma concentration (2 ng/mL).

Safety: TBR-652 was well tolerated with few reports of treatment-emergent AEs (Table 6). All AEs were graded as mild except in 1 subject who had moderate severity rectal irritation with mild severity hemorrhoids with bleeding, abdominal cramps, and diarrhea. No grade 3 or 4 laboratory abnormalities were reported, and no clinically significant abnormal ECG results were reported. No subject discontinued prematurely due to an AE (Table 7).

Table 6: Incidence of Treatment-Emergent Adverse Events-Study 652-1-102 Part I Safety Population

Any system by organ class	Cohort 1 (1 x 100 mg F2)		Cohort 2 (4 x 25 mg F1)		Cohort 3 (1 x 100 mg F2)	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Any	0	0	0	1 (8%)	1 (8%)	2 (17%)
Cardiac Disorders						
Any	0	0	0	0	0	1 (9%)
Dizziness	0	0	0	0	0	1 (9%)
GI Disorders						
Any	0	0	0	1 (8%)	1 (8%)	3 (25%)
Abdominal pain	0	0	0	1 (8%)	1 (8%)	0
Anal inflammation	0	0	0	1 (8%)	1 (8%)	0
Constipation	0	0	0	0	0	1 (8%)
Diarrhea	0	0	0	1 (8%)	1 (8%)	0
Nausea	0	0	0	0	0	1 (9%)
Vomiting	0	0	0	0	0	2 (17%)
Nervous System Disorders						
Any	0	0	0	0	0	1 (8%)
Headache	0	0	0	0	0	1 (8%)
Reproductive System and Breast Disorders						
Any	0	0	0	1 (8%)	0	1 (8%)
Metrorrhagia	0	0	0	1 (8%)	0	1 (8%)
Vascular Disorders						
Any	0	0	0	1 (8%)	1 (8%)	0
Rectal hemorrhage	0	0	0	1 (8%)	1 (8%)	0

Table 7: Overall Summary of Adverse and Serious Adverse Events

Category	Cohort 1 (1 x 100 mg F2)		Cohort 2 (4 x 25 mg F1)		Cohort 3 (1 x 100 mg F2)	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Subjects with 1 or more AEs	0	0	0	1 (8%)	2 (17%)	4 (33%)
Subjects with 1 or more related* AEs	0	0	0	1 (8%)	1 (8%)	3 (25%)
Subjects with 1 or more severe or life-threatening (grade 3 or 4) AEs	0	0	0	0	0	0
Subjects with 1 or more serious AEs (SAE)	0	0	0	0	0	0
Subjects with 1 or more related* SAEs	0	0	0	0	0	0
Subjects with 1 or more AEs resulting in discontinuation	0	0	0	0	0	0

*Relationships of possible, probable, or definite

Safety Summary:

- TBR-652 was well tolerated, with GI effects the most commonly encountered treatment-emergent AEs.

CONCLUSIONS

- TBR-652 tablets are readily bioavailable from both tablet formulations under fasted or fed conditions.
- Plasma TBR-652 concentrations achieved above the predicted target concentration of 2 ng/mL when the tablets were administered with or without food.
- A high-fat meal significantly increases the extent of TBR-652 bioavailability and reduces the intersubject variability in plasma TBR-652 concentrations.
- Mean TBR-652 plasma concentrations were well above the predicted target plasma concentration (2 ng/mL) with or without food.
- To ensure high and consistent plasma exposure, TBR-652 tablets should be taken with relatively high-fat food.
- TBR-652 was well tolerated and has progressed to a proof-of-concept study in HIV-infected subjects.

ACKNOWLEDGEMENTS

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