

TBR-652, A CHEMOKINE RECEPTOR 5 (CCR5) ANTAGONIST, DEMONSTRATES GOOD ORAL BIOAVAILABILITY AND DESIRABLE PHARMACOKINETIC (PK) AND SAFETY PROFILES IN HEALTHY VOLUNTEERS

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BACKGROUND

TBR-652, formerly known as TAK-652, is a promising CCR5 antagonist in phase 2 clinical development. A phase 1 single oral dose study showed rapid absorption and good bioavailability for TBR-652 tablets.¹ Another study found that, although TBR-652 plasma concentrations were above the in vitro effective concentration level of 90% (EC₉₀) in fasted subjects, a high-fat meal significantly increased the extent of TBR-652 bioavailability and reduced the intersubject variability in plasma TBR-652 concentrations.² This healthy volunteer study (Tobira Therapeutics Study 652-1102; Part II) investigated the safety, tolerability, and PK of multiple doses of TBR-652 administered once daily in one of two tablet formulations at doses ranging from 25 to 200 mg following a high-fat breakfast.

OBJECTIVES

- To determine the safety and tolerability of multiple oral doses of TBR-652 in healthy adult subjects when administered once daily for 10 days.
- To determine the pharmacokinetics of TBR-652 on Day 1 and Day 10 after once daily administration of various doses of TBR-652 for 10 days.

METHODS

Study Design: This was a double-blind, placebo-controlled, randomized, multiple-dose study. Five dose groups of 12 subjects each received TBR-652 in one of 2 tablet formulations daily for 5 days. Dosages ranged from 25 mg/day to 200 mg/day (Table 1). Within each dose group, subjects were randomly assigned in a ratio of 5:3 to TBR-652:placebo administered as either the previously used formulation (F1) or a new formulation (F2). All doses were taken with approximately 240 mL of water within 30 minutes after the start and within 10 minutes after the completion of a standard high-fat breakfast (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). Subjects were sequestered at the clinical research unit (CRU) from the evening before the first dose until after the PK draw 48 hours after the last dose. Subjects returned to the CRU for PK draws at 60 hours, 72 hours, 96 hours, and 120 hours after the last dose. A final follow-up safety examination occurred on Day 20.

Table 1. Treatment Cohorts

Group	Dose and Formulation	TBR-652/Placebo
A	1x25 mg/day F1 tablet	1:1
B	4x25 mg/day F1 tablets	1:1
C	1x100 mg/day F1 tablet	1:1
D	2x100 mg/day F2 tablets	1:1
E	1x200 mg/day F2 tablet	1:1

F1 = prior formulation; F2 = new formulation

Study Population: 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: PK parameters of TBR-652 were calculated using noncompartmental methods and summarized by treatment/dose level using descriptive statistics. Analysis of variance (ANOVA) was used to determine dose proportionality between dose levels within the same tablet formulation. The accumulation ratios in C₂₄ and AUC₀₋₂₄ were determined with ANOVA using a mixed-effect model. Safety and tolerability were assessed by monitoring adverse events, measuring vital signs, obtaining electrocardiograms (ECGs), and collecting clinical laboratory values from blood and urine samples.

RESULTS

Demographics/Disposition: A total of 60 subjects enrolled in the study (Table 2). Three subjects receiving TBR-652 prematurely discontinued the study before the last dose on Day 10 (Table 3).

Table 2. Subject Demographics

Gender, n (%)	Treatment A (N=12) F1 Tablets		Treatment B (N=12) F1 Tablets		Treatment C (N=12) F2 Tablets		Treatment D (N=12) F2 Tablets		Treatment E (N=12) F2 Tablets	
	Placebo (N=6)	TBR-652 1x25 mg (N=6)	Placebo (N=6)	TBR-652 4x25 mg (N=6)	Placebo (N=6)	TBR-652 1x100 mg (N=6)	Placebo (N=6)	TBR-652 2x100 mg (N=6)	Placebo (N=6)	TBR-652 1x200 mg (N=6)
Male	1 (33)	3 (33)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)
Female	2 (87)	6 (67)	0	0	0	5 (50)	2 (22)	3 (100)	3 (33)	3 (33)
Race, n (%)										
Caucasian	3 (100)	8 (89)	3 (100)	8 (89)	2 (67)	8 (89)	3 (100)	9 (100)	3 (100)	6 (67)
Hispanic	0	1 (11)	0	0	0	0	0	0	0	0
Other	0	0	0	1 (11)	1 (33)	1 (11)	0	0	0	1 (33)
Age, years										
Mean (SD)	36.3 (2.76)	42.9 (7.36)	37.7 (12.7)	37.9 (9.39)	42.0 (13.00)	34.4 (8.83)	40.0 (8.89)	36.8 (10.83)	52.3 (2.89)	33.4 (11.53)
Median	38.0	45.0	33.0	37.0	42.0	39.0	43.0	35.0	54.0	32.0
Weight, kg										
Mean (SD)	70.7 (10.07)	62.7 (10.06)	82.3 (4.51)	77.9 (9.40)	81.7 (11.85)	71.3 (9.53)	74.3 (5.77)	76.2 (9.13)	67.7 (4.93)	72.9 (12.65)
Median	72.0	60.0	82.0	79.0	88.0	71.0	71.0	76.0	70.0	75.0
Height, cm										
Mean (SD)	167.7 (7.37)	159.6 (4.75)	176.0 (7.21)	171.4 (5.50)	176.3 (3.06)	166.2 (9.55)	171.0 (5.20)	172.3 (7.42)	158.0 (3.61)	167.7 (11.16)
Median	165.0	158.0	174.0	171.0	177.0	169.0	168.0	171.0	159.0	168.0
BMI, kg/m ²										
Mean (SD)	25.1 (2.77)	24.5 (2.90)	26.7 (2.21)	26.5 (2.51)	26.2 (3.03)	25.8 (2.78)	25.5 (3.01)	25.8 (2.60)	27.2 (2.91)	25.8 (2.06)
Median	25.8	24.0	28.4	26.1	27.8	26.8	25.2	26.0	28.1	24.8

Abbreviations: F1, prior formulation; F2, new formulation; SD, standard deviation.

Table 3. Analysis Populations

Analysis Population	Treatment A (F1 Tablets)		Treatment B (F1 Tablets)		Treatment C (F2 Tablets)		Treatment D (F2 Tablets)		Treatment E (F2 Tablets)	
	Placebo	TBR-652 1x25 mg	Placebo	TBR-652 4x25 mg	Placebo	TBR-652 1x100 mg	Placebo	TBR-652 2x100 mg	Placebo	TBR-652 1x200 mg
PK Population - Day 1	n/A	n/A	n/A	n/A	n/A	n/A	n/A	n/A	n/A	n/A
PK Population - Day 10	n/A	8	n/A	9	n/A	9	n/A	8	n/A	8
Safety Population	3	9	3	9	3	9	3	9	3	9

Abbreviations: F1, prior formulation; F2, new formulation; n/A, not applicable.

Pharmacokinetics

Figure 1. Mean Plasma Concentration vs. Time Curves of TBR-652 in 2 Tablet Formulations, Day 1, Linear and Semilog Plots

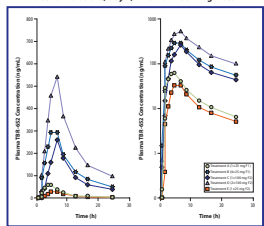


Figure 2. Mean Plasma Concentration vs. Time Curves of TBR-652 in 2 Tablet Formulations, Day 10, Linear and Semilog Plots

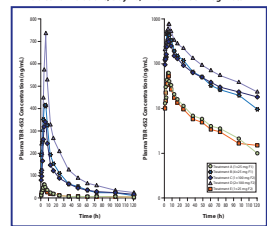


Table 4. Summary of TBR-652 Pharmacokinetic Parameter Estimates by Dose and Day

Treatment	Day	Statistic	C _{max} (ng/mL)	t _{max} (h)	AUC ₀₋₂₄ (h*ng/mL)	C ₂₄ ^b (ng/mL)	t _{1/2} (h)	AUC ₀₋₂₄ Ratio Day 10 vs 1
A	1	Mean	71.3	3.0	406	39	39	
		% CV	15.5	1.9	23	11.7	35.1	1.38
		Range	35.8-115	2.6-6.0	228-927	4.0	29	33
B	10	Mean	65.5	3.0	605	43	21	29
		% CV	19.2	2.4	17	11.7	29	33
		Range	36.2-106	2.6-4.1	329-1096	6.8-26.3	27.4-62.6	0.75-2.09
C	10	Mean	330	4.0	3184	209	31	29
		% CV	25	3.0	21	11.7	29	33
		Range	242-530	2.6-6.0	2386-4577	107.9	34.1	1.65
D	10	Mean	455	6.0	5227	327	22	46
		% CV	29	21	37	22	19	19
		Range	299-569	6.0-6.0	3273-7325	53.4-181.0	23.9-52.8	1.03-2.10
E	10	Mean	281	6.0	2384	209	21	22
		% CV	28	22	22	22	22	22
		Range	113-470	3.6-6.0	1000-3492	64.1-115.0	26.1-58.3	1.33-4.29
1x100 mg/day F2 tablet	10	Mean	332	6.0	4142	412	22	22
		% CV	27	22	22	22	22	22
		Range	255-542	3.6-6.0	3056-5663	64.1-115.0	26.1-58.3	1.33-4.29
2x100 mg/day F2 tablets	10	Mean	366	4.0	3545	309	21	22
		% CV	25	28	21	22	22	22
		Range	388-819	3.6-6.0	1913-7772	188-614	27.1-53.2	0.47-2.16
1x200 mg/day F2 tablet	10	Mean	745	6.0	8592	206.9	38.1	34
		% CV	40	12	40	45	22	35
		Range	207-1080	4.0-6.0	1860-1382	51.8-348.0	27.1-53.2	1.54-2.16
1x25 mg/day F1 tablet	10	Mean	43.3	4.0	309	29	29	29
		% CV	29	31	29	29	29	29
		Range	27.8-80.7	2.6-6.0	224-920	4.3-19.6	24.3-51.0	1.08-2.42

Abbreviations: CV, coefficient of variation; F1, prior formulation; F2, new formulation. ^aValues are median for t_{max} and t_{1/2}. ^bMean C₂₄ was average per dose concentration on Days 9, 10, and 11.

Figure 3. Individual and Mean Day 10 C_{max} for All Treatments

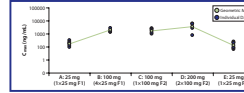
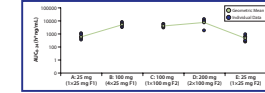


Figure 4. Individual and Mean Day 10 AUC₀₋₂₄ for All Treatments



Safety and Tolerability: TBR-652 was generally well tolerated when administered as 25 to 200 mg once daily over 10 days to healthy volunteers. There were no deaths or serious adverse events (SAEs) during the study (Table 5). One treatment-emergent adverse event was classified by the investigator as grade 3/4, 3 were classified as grade 2, and all others were classified as grade 1 (mild). One subject each in Treatments A and E (the lowest doses studied) experienced adverse events that resulted in treatment discontinuation. The first subject experienced asymptomatic grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations on Day 7, at which time study drug was discontinued. The subject reported no AEs, no physical signs were noted by the investigator, and liver function tests returned to normal by Day 26. The event was attributed to pre-existing, unreported non-alcoholic fatty liver disease. The other subject had a grade 2 AST elevation and an elevated lactate dehydrogenase (LDH) on Day 6, which resolved completely and were thought to be caused by a mild muscle injury. Neither event met Hy's Law, a prognostic indicator of severe liver injury.

No notable effects were noted on vital signs or ECGs in any subject.

Table 5. Treatment-Emergent Adverse Event Reporting Profile (Safety Population)

Subjects with 1 or more adverse events	Number (%) of Subjects					
	Treatment A (N=12) F1 Tablets	Treatment B (N=12) F1 Tablets	Treatment C (N=12) F2 Tablets	Treatment D (N=12) F2 Tablets	Treatment E (N=12) F2 Tablets	Placebo (N=12)
Subjects with 1 or more adverse events	5 (56)	2 (22)	0	3 (33)	5 (56)	3 (28)
Subjects with 1 or more treatment-related adverse events	2 (22)	1 (11)	0	2 (22)	4 (44)	2 (13)
Subjects with 1 or more serious adverse events	0	0	0	0	0	0
Subjects who discontinued study drug due to adverse events	1 (11)	0	0	0	1 (11)	0

Abbreviations: F1, prior formulation; F2, new formulation. *Relationship of possible, probable, or definite.

Treatment-emergent adverse events reported by more than 1 subject in any treatment are noted in Table 6. Treatment-related adverse events reported by more than 1 subject in any treatment included constipation; 2 (22%) subjects each in Treatments D and E, and headache; 2 (13%) subjects in the placebo group.

Table 6. Summary of Treatment - Emergent Adverse Events (Safety Population)

System Organ Class (Preferred Term)	Number (%) of Subjects					
	Treatment A (N=12) F1 Tablets	Treatment B (N=12) F1 Tablets	Treatment C (N=12) F2 Tablets	Treatment D (N=12) F2 Tablets	Treatment E (N=12) F2 Tablets	Placebo (N=12)
Any Treatment-Emergent Adverse Event	5 (56)	2 (22)	0	3 (33)	5 (56)	3 (28)
Cardiac Disorders	0	0	0	0	0	1 (7)
Diagnoses	0	0	0	0	0	1 (7)
Eye Disorders	2 (22)	0	0	0	0	0
Vision Blurred	2 (22)	0	0	0	0	0
Gastrointestinal Disorders	1 (11)	0	0	2 (22)	4 (44)	3 (28)
Constipation	0	0	0	2 (22)	3 (33)	2 (13)
Diarrhea	0	0	0	0	1 (11)	1 (7)
Dyspepsia	0	0	0	0	0	1 (7)
Gastro-esophageal Reflux Disease	0	0	0	0	0	1 (7)
Nausea	0	0	0	0	1 (11)	1 (7)
General Disorders and Administration Site Conditions	0	0	0	0	0	1 (7)
Pain	0	0	0	0	0	1 (7)
Immune System Disorders	0	0	0	0	1 (11)	0
Immune-mediated	0	0	0	0	1 (11)	0
Investigations	1 (11)	1 (11)	0	0	1 (11)	0
Blood Lactate Dehydrogenase Increased	0	0	0	0	1 (11)	0
Blood Pressure Increased	0	0	0	0	0	0
Hepatic Enzyme Increased	1 (11)	0	0	0	1 (11)	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	0	1 (11)	0
Arthralgia	0	0	0	0	1 (11)	0
Back Pain	0	0	0	1 (11)	0	0
Nervous System Disorders	0	2 (22)	0	1 (11)	1 (11)	3 (28)
Headache	0	2 (22)	0	1 (11)	1 (11)	2 (13)
Insomnia	0	0	0	0	0	0
Skin and Subcutaneous Tissue Disorders	1 (11)	0	0	0	0	0
Rash Macular	1 (11)	0	0	0	0	0

Abbreviations: F1, prior formulation; F2, new formulation.

SUMMARY

- TBR-652 was well tolerated at once-daily doses of up to 200 mg for 10 days.
- TBR-652 was readily and well absorbed following single or repeated doses of the tablet formulations with a high-fat meal, achieving mean peak plasma concentrations in 4-6 hours.
- The elimination kinetics of TBR-652 were similar across the dose range of 25 to 200 mg/day with a mean t_{1/2} of approximately 40 hours.
- Plasma concentrations of TBR-652 achieved steady-state after 8 days of once daily dosing.
- The mean accumulation ratios (Day 10 + Day 1) for AUC₀₋₂₄ and C₂₄ of TBR-652 following repeated once-daily doses were 1.3-1.8 and 0.97-1.4, respectively, across the 25 to 200 mg/day dose range, regardless of formulation. These values were less than the predicted value of 2.3 based on a mean t_{1/2} of 40 hours and once-daily dosing frequency, which might be attributable to slightly reduced bioavailability of TBR-652 after repeated doses.
- A 25 mg/day F1 or F2 tablet achieved plasma exposures greater than the target therapeutic level of 2 ng/mL projected from in vitro studies of TBR-652.
- There were no deaths or serious adverse events during the study.
- Treatment-emergent adverse events considered possibly, probably, or definitely related to study drug reported by more than 1 subject in any treatment included constipation and headache.
- Treatment-emergent adverse events were generally mild.
- Two instances of elevated liver enzymes resolved off treatment and were most likely attributable to their underlying conditions not related to study drug (non-alcoholic fatty liver and muscle injury).

CONCLUSION

The safety and PK profiles of TBR-652 support further clinical development of TBR-652 in HIV-infected patients. A Proof of Concept study of TBR-652 in HIV infected patients is underway.

ACKNOWLEDGEMENTS

We thank Robert Grosso and Sally Snyder for their diligence and assistance in preparation of this abstract.

REFERENCES

- Palleja S, et al. Pharmacokinetics (PK), Safety,

BACKGROUND

TBR-652, formerly known as TAK-652, is a promising CCR5 antagonist in phase 2 clinical development. A phase 1 single oral dose study showed rapid absorption and good bioavailability for TBR-652 tablets.¹ Another study found that, although TBR-652 plasma concentrations were above the in vitro effective concentration level of 90% (EC₉₀) in fasted subjects, a high-fat meal significantly increased the extent of TBR-652 bioavailability and reduced the intersubject variability in plasma TBR-652 concentrations.² This healthy volunteer study (Tobira Therapeutics Study 652-1-102, Part II) investigated the safety, tolerability, and PK of multiple doses of TBR-652 administered once daily in one of two tablet formulations at doses ranging from 25 to 200 mg following a high-fat breakfast.

OBJECTIVES

- To determine the safety and tolerability of multiple oral doses of TBR-652 in healthy adult subjects when administered once daily for 10 days.
- To determine the pharmacokinetics of TBR-652 on Day 1 and Day 10 after once daily administration of various doses of TBR-652 for 10 days.

METHODS

Study Design: This was a double-blind, placebo-controlled, randomized, multiple-dose study. Five dose groups of 12 subjects each received TBR-652 in one of 2 tablet formulations daily for 5 days. Dosages ranged from 25 mg/day to 200 mg/day (Table 1). Within each dose group, subjects were randomly assigned in a ratio of 9:3 to TBR-652:placebo administered as either the previously used formulation (F1) or a new formulation (F2). All doses were taken with approximately 240 mL of water within 30 minutes after the start and within 10 minutes after the completion of a standard high-fat breakfast (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). Subjects were sequestered at the clinical research unit (CRU) from the evening before the first dose until after the PK draw 48 hours after the last dose. Subjects returned to the CRU for PK draws at 60 hours, 72 hours, 96 hours, and 120 hours after the last dose. A final follow-up safety examination occurred on Day 20.

Table 1. Treatment Cohorts

Group	Dose and Formulation TBR-652/Placebo
A	1×25 mg/day F1 tablet
B	4×25 mg/day F1 tablets
C	1×100 mg/day F2 tablet
D	2×100 mg/day F2 tablets
E	1×25 mg/day F2 tablet

F1 = prior formulation; F2 = new formulation

Study Population: Subjects were healthy males and females between 19 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: PK parameters of TBR-652 were calculated using noncompartmental methods and summarized by treatment/dose level using descriptive statistics. Analysis of variance (ANOVA) was used to determine dose proportionality between dose levels within the same tablet formulation. The accumulation ratios in C_{max} and AUC₀₋₂₄ were determined with ANOVA using a mixed-effect model. Safety and tolerability were assessed by monitoring adverse events, measuring vital signs, obtaining electrocardiograms (ECGs), and collecting clinical laboratory values from blood and urine samples.

RESULTS

Demographics/Disposition: A total of 60 subjects enrolled in the study (Table 2). Three subjects receiving TBR-652 prematurely discontinued the study before the last dose on Day 10 (Table 3).

Table 2. Subject Demographics

	Treatment A (N=12) F1 Tablets		Treatment B (N=12) F1 Tablets		Treatment C (N=12) F2 Tablets		Treatment D (N=12) F2 Tablets		Treatment E (N=12) F2 Tablets	
	Placebo (N=3)	TBR-652 1×25 mg (N=9)	Placebo (N=3)	TBR-652 4×25 mg (N=9)	Placebo (N=3)	TBR-652 1×100 mg (N=9)	Placebo (N=3)	TBR-652 2×100 mg (N=9)	Placebo (N=3)	TBR-652 1×25 mg (N=9)
Gender, n (%)										
Female	2 (67)	6 (67)	0	0	0	5 (56)	0	2 (22)	3 (100)	3 (33)
Male	1 (33)	3 (33)	3 (100)	9 (100)	3 (100)	4 (44)	3 (100)	7 (78)	0	6 (67)
Race, n (%)										
Caucasian	3 (100)	8 (89)	3 (100)	8 (89)	2 (67)	8 (89)	3 (100)	9 (100)	3 (100)	6 (67)
Hispanic	0	1 (11)	0	0	0	0	0	0	0	0
Other	0	0	0	1 (11)	1 (33)	1 (11)	0	0	0	3 (33)
Age, years										
Mean (SD)	36.3 (3.79)	42.9 (7.36)	37.7 (11.72)	37.9 (9.39)	42.0 (13.00)	34.4 (8.83)	40.0 (8.89)	36.8 (10.03)	52.3 (2.89)	33.4 (11.53)
Median	38.0	45.0	33.0	37.0	42.0	39.0	43.0	35.0	54.0	32.0
Weight, kg										
Mean (SD)	70.7 (10.07)	62.7 (10.06)	82.3 (4.51)	77.9 (9.40)	81.7 (11.85)	71.3 (9.53)	74.3 (5.77)	76.2 (9.13)	67.7 (4.93)	72.9 (12.05)
Median	72.0	60.0	82.0	79.0	88.0	71.0	71.0	76.0	70.0	75.0
Height, cm										
Mean (SD)	167.7 (7.37)	159.6 (4.75)	176.0 (7.21)	171.4 (3.50)	176.3 (3.06)	166.2 (9.55)	171.0 (5.20)	172.3 (7.62)	158.0 (3.61)	167.7 (11.16)
Median	165.0	158.0	174.0	171.0	177.0	166.0	168.0	171.0	159.0	168.0
BMI, kg/m ²										
Mean (SD)	25.1 (2.77)	24.5 (2.90)	26.7 (3.21)	26.5 (2.51)	26.2 (3.03)	25.8 (2.78)	25.5 (3.01)	25.8 (2.06)	27.2 (2.91)	25.8 (2.06)
Median	25.8	24.0	28.4	26.1	27.8	26.8	25.2	26.0	28.1	24.8

Abbreviations: F1, prior formulation; F2, new formulation; SD, standard deviation

Table 3. Analysis Populations

Analysis Population	Treatment A F1 Tablets		Treatment B F1 Tablets		Treatment C F2 Tablets		Treatment D F2 Tablets		Treatment E F2 Tablets	
	Placebo	TBR-652 1×25 mg	Placebo	TBR-652 4×25 mg	Placebo	TBR-652 1×100 mg	Placebo	TBR-652 2×100 mg	Placebo	TBR-652 1×25 mg
PK Population – Day 1	n/a	9	n/a	9	n/a	9	n/a	9	n/a	9
PK Population – Day 10	n/a	8	n/a	9	n/a	9	n/a	8	n/a	8
Safety Population	3	9	3	9	3	9	3	9	3	9

Abbreviations: F1, prior formulation; F2, new formulation; n/a, not applicable

Pharmacokinetics

Figure 1. Mean Plasma Concentration vs. Time Curves of TBR-652 in 2 Tablet Formulations, Day 1, Linear and Semilog Plots

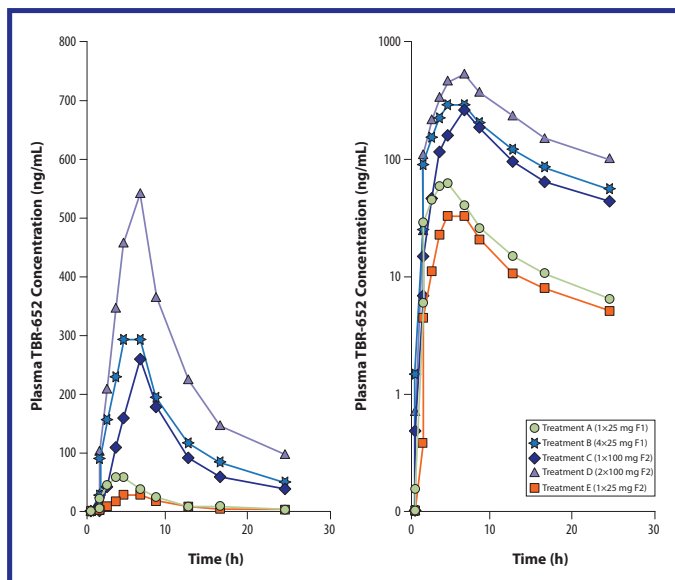


Figure 2. Mean Plasma Concentration vs. Time Curves of TBR-652 in 2 Tablet Formulations, Day 10, Linear and Semilog Plots

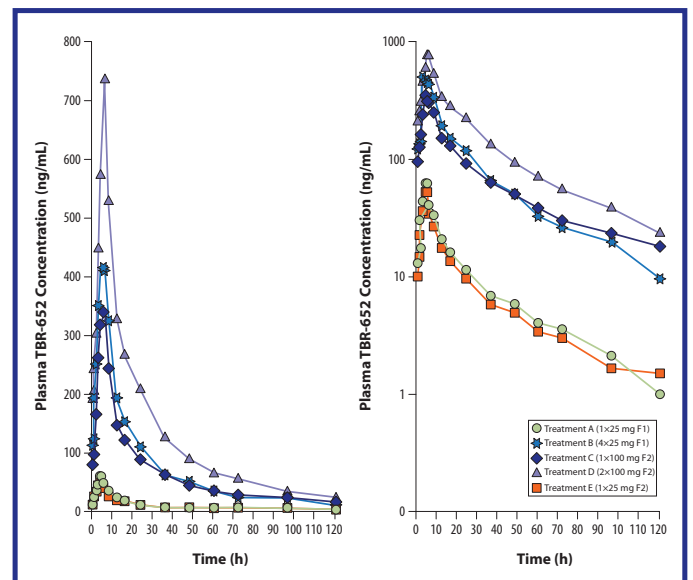


Table 4. Summary of TBR-652 Pharmacokinetic Parameter Estimates by Dose and Day

Treatment	Day	Statistic	C _{max} (ng/mL)	t _{max} (h)	AUC ₀₋₂₄ (h*ng/mL)	C _{min} ^b (ng/mL)	t _{1/2} (h)	AUC ₀₋₂₄ Ratio Day 10 vs 1
A 1x25 mg/day F1 tablet	1 (n=9)	Mean ^a	71.3	3.0	498			
		% CV	39	32	39			
		Range	35.9-135	2.0-6.0	228-927			
10 (n=8)	Mean ^a	65.5	3.0	605	11.7	35.1	1.38	
	% CV	39	22	43	37	28	33	
	Range	36.7-106	2.0-4.1	329-1086	6.8-20.3	29.7-62.6	0.75-2.09	
B 4x25 mg/day F1 tablets	1 (n=9)	Mean ^a	330	4.0	3184			
		% CV	25	30	22			
		Range	242-530	2.0-6.0	2308-4577			
10 (n=9)	Mean ^a	435	6.0	5227	107.9	34.1	1.65	
	% CV	26	21	27	37	22	19	
	Range	293-569	4.0-6.0	3271-7525	53.4-181.0	23.9-52.8	1.07-2.10	
C 1x100 mg/day F2 tablet	1 (n=9)	Mean ^a	281	6.0	2384			
		% CV	38	25	32			
		Range	113-470	3.0-6.0	1000-3492			
10 (n=9)	Mean ^a	382	6.0	4142	91.3	44.7	1.92	
	% CV	25	23	22	21	22	48	
	Range	251-542	3.0-6.0	3056-5663	64.1-115.0	26.1-58.3	1.33-4.29	
D 2x100 mg/day F2 tablets	1 (n=9)	Mean ^a	566	6.0	5545			
		% CV	25	28	21			
		Range	380-819	3.0-8.0	3933-7772			
10 (n=8)	Mean ^a	745	6.0	8592	206.9	38.1	1.54	
	% CV	40	12	40	45	22	35	
	Range	207-1080	4.0-6.0	1860-13262	51.4-348.0	27.1-53.2	0.47-2.16	
E 1x25 mg/day F2 tablet	1 (n=9)	Mean ^a	43.3	4.0	309			
		% CV	29	31	29			
		Range	21.1-59.5	3.0-6.0	188-414			
10 (n=8)	Mean ^a	52.6	4.0	503	9.55	41.4	1.61	
	% CV	38	40	44	57	27	29	
	Range	27.6-80.7	2.0-6.0	254-920	4.3-19.6	24.3-51.0	1.08-2.42	

Abbreviations: CV, coefficient of variation; F1, prior formulation; F2, new formulation. ^aValues are medians for t_{max} and t_{1/2}. ^bMean C_{min} was average pre-dose concentrations on Days 9, 10 and 11.

Figure 3. Individual and Mean Day 10 C_{max} for All Treatments

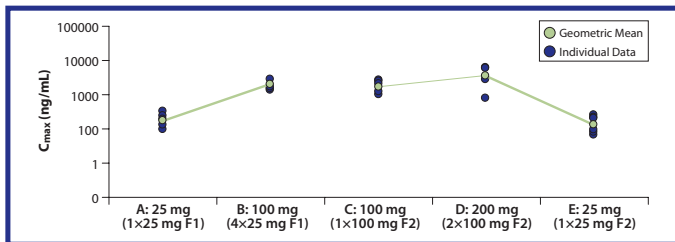
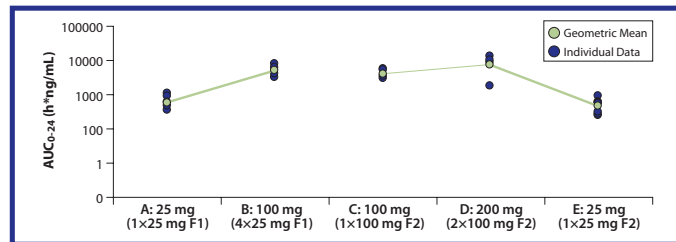


Figure 4. Individual and Mean Day 10 AUC₀₋₂₄ for All Treatments



Safety and Tolerability: TBR-652 was generally well-tolerated when administered as 25 to 200 mg once daily over 10 days to healthy volunteers. There were no deaths or serious adverse events (SAEs) during the study (Table 5). One treatment-emergent adverse event was classified by the investigator as grade 3/4, 3 were classified as grade 2, and all others were classified as grade 1 (mild). One subject each in Treatments A and E (the lowest doses studied) experienced adverse events that resulted in treatment discontinuation. The first subject experienced asymptomatic grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations on Day 7, at which time study drug was discontinued. The subject reported no AEs, no physical signs were noted by the Investigator, and liver function tests returned to normal by Day 26. The event was attributed to pre-existing, unreported non-alcoholic fatty liver disease. The other subject had a grade 2 AST elevation and an elevated lactate dehydrogenase (LDH) on Day 8, which resolved completely and were thought to be caused by a mild muscle injury. Neither event met Hy's law, a prognostic indicator of severe liver injury.

No notable effects were noted on vital signs or ECGs in any subject.

Table 5. Treatment-Emergent Adverse Event Reporting Profile (Safety Population)

	Number (%) of Subjects					
	Treatment A TAK-652 1x25 mg F1 (N=9)	Treatment B TAK-652 4x25 mg F1 (N=9)	Treatment C TAK-652 1x100 mg F2 (N=9)	Treatment D TAK-652 2x100 mg F2 (N=9)	Treatment E TAK-652 1x25 mg F2 (N=9)	Placebo All (N=15)
Subjects with 1 or more adverse events	5 (56)	2 (22)	0	3 (33)	5 (56)	3 (20)
Subjects with 1 or more treatment-related ^a adverse events	2 (22)	1 (11)	0	2 (22)	4 (44)	2 (13)
Subjects with 1 or more grade 3 or 4 adverse events	1 (11)	0	0	0	0	0
Subjects with 1 or more serious adverse events	0	0	0	0	0	0
Subjects who discontinued study drug due to adverse events	1 (11)	0	0	0	1 (11)	0

Abbreviations: F1, prior formulation; F2, new formulation. ^aRelationship of possibly, probable, or definite.

Treatment-emergent adverse events reported by more than 1 subject in any treatment are noted in Table 6. Treatment-related adverse events reported by more than 1 subject in any treatment included constipation: 2 (22%) subjects each in Treatments D and E, and headache: 2 (13%) subjects in the placebo group.

Table 6. Summary of Treatment – Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term	Number (%) of Subjects					
	Treatment A	Treatment B	Treatment C	Treatment D	Treatment E	Placebo
	TAK-652 1×25 mg F1 (N=9)	TAK-652 4×25 mg F1 (N=9)	TAK-652 1×100 mg F2 (N=9)	TAK-652 2×100 mg F2 (N=9)	TAK-652 1×25 mg F2 (N=9)	All (N=15)
Any Treatment-Emergent Adverse Event	5 (56)	2 (22)	0	3 (33)	5 (56)	3 (20)
Cardiac Disorders	0	0	0	0	0	1 (7)
Dizziness	0	0	0	0	0	1 (7)
Eye Disorders	2 (22)	0	0	0	0	0
Vision Blurred	2 (22)	0	0	0	0	0
Gastrointestinal Disorders	1 (11)	0	0	2 (22)	4 (44)	3 (20)
Constipation	1 (11)	0	0	2 (22)	3 (33)	2 (13)
Diarrhea	0	0	0	0	1 (11)	1 (7)
Dyspepsia	0	0	0	0	1 (11)	0
Gastro-esophageal Reflux Disease	0	0	0	0	0	1 (7)
Nausea	0	0	0	0	1 (11)	1 (7)
General Disorders and Administration Site Conditions	0	0	0	0	0	1 (7)
Pyrexia	0	0	0	0	0	1 (7)
Immune System Disorders	0	0	0	1 (11)	0	0
Dermatitis Contact	0	0	0	1 (11)	0	0
Investigations	1 (11)	1 (11)	0	0	1 (11)	0
Blood Lactate Dehydrogenase Increased	0	0	0	0	1 (11)	0
Blood Pressure Increased	0	1 (11)	0	0	0	0
Hepatic Enzyme Increased	1 (11)	0	0	0	1 (11)	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	1 (11)	0	1 (7)
Arthralgia	0	0	0	0	0	1 (7)
Back Pain	0	0	0	1 (11)	0	0
Nervous System Disorders	0	2 (22)	0	1 (11)	1 (11)	3 (20)
Headache	0	2 (22)	0	1 (11)	1 (11)	2 (13)
Insomnia	0	0	0	0	0	1 (7)
Skin and Subcutaneous Tissue Disorders	1 (11)	0	0	0	0	0
Rash Macular	1 (11)	0	0	0	0	0

Abbreviations: F1, prior formulation; F2 new formulation

SUMMARY

- TBR-652 was well tolerated at once-daily doses of up to 200 mg for 10 days.
- TBR-652 was readily and well absorbed following single or repeated doses of the tablet formulations with a high-fat meal, achieving mean peak plasma concentrations in 4-6 hours.
- The elimination kinetics of TBR-652 were similar across the dose range of 25 to 200 mg/day with a mean $t_{1/2}$ of approximately 40 hours.
- Plasma concentrations of TBR-652 achieved steady-state after 8 days of once daily dosing.
- The mean accumulation ratios (Day 10 ÷ Day 1) for AUC_{0-24} and C_{max} of TBR-652 following repeated once-daily doses were 1.3-1.8 and 0.97-1.4, respectively, across the 25 to 200 mg/day dose range, regardless of formulation. These values were less than the predicted value of 2.9 based on a mean $t_{1/2}$ of 40 hours and once-daily dosing frequency, which might be attributable to slightly reduced bioavailability of TBR-652 after repeated doses.
- A 25 mg/day F1 or F2 tablet achieved plasma exposures greater than the target therapeutic level of 2 ng/mL projected from in vitro studies of TBR-652.
- There were no deaths or serious adverse events during the study.
- Treatment-emergent adverse events considered possibly, probably, or definitely related to study drug reported by more than 1 subject in any treatment included constipation and headache.
- Treatment-emergent adverse events were generally mild.
- Two instances of elevated liver enzymes resolved off treatment and were most likely attributable to other underlying conditions not related to study drug (non-alcoholic fatty liver and muscle injury).

CONCLUSION

The safety and PK profiles of TBR-652 support further clinical development of TBR-652 in HIV-infected patients. A Proof of Concept study of TBR-652 in HIV infected patients is underway.

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