period culminating in the final study visit. Digoxin was given at approximately 8AM and tetrabenazine was given at approximately 8AM and 8PM. All doses of study drug were given with 200 ml of mineral water at room temperature.

The rationale for the doses of study drug was as follows: A dose of 25 mg TBZ twice daily was chosen as the target dose. According to the Sponsor, the usual single dose in Huntington's chorea is 12.5-37.5 mg, but healthy volunteers become sedated at greater than 25 mg. The loading dose format of digoxin dosing was intended to achieve "steady state" concentrations prior to initiating TBZ.

On the morning of Day 1, subjects had an assessment of vital signs and 12-lead ECG done within 90 minutes prior to study drug administration. Subjects had blood and urine samples taken for digoxin concentration determination and a blood sample for TBZ and α- and β- HTBZ plasma concentration measurements prior to dosing with digoxin. On the mornings of Days 2-5, pre-dose assessments were made prior to digoxin dosing. On the morning of Day 6, while still in the fasted state, subjects had a pre-dose assessment including vital signs, 12-lead ECG, clinical laboratory tests, and physical exam prior to receiving digoxin at approximately 8AM. Blood samples for digoxin plasma concentration measurements were taking within 15 minutes prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose. A 24-hour urine collection for digoxin concentration measurement was begun on each subject immediately following digoxin dosing. A standardized lunch and dinner were served 4 and 9 hours, respectively after the dose of study drug. Fluid intake on Day 6 was standardized to 2 liters of water or herbal tea over the 24-hour period.

On the mornings of Days 7—9, all subjects had a pre-dose assessment including vital signs and 12-lead ECG. At approximately 8AM each subject received 0.25 mg digoxin and 25 mg TBZ. A second 25 mg oral dose of TBZ was given at approximately 8PM on the evenings of Days 7, 8, and 9. Blood samples for digoxin were taken pre-dose on Days 7, 8, and 9. At approximately 9PM on Day 9, subjects were given a light snack prior to overnight fast.

On the morning of Day 10, in the fasted state, subjects had a pre-doses assessment that included vital signs and a 12-lead ECG. At approximately 8AM, each subject received a dose of 0.25 mg digoxin and 25 mg TBZ. A second dose of 25 mg TBZ was given at 8PM. On Day 10, blood samples were collected for digoxin plasma concentration determinations within 15 minutes before dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours post-dose. In addition on Day 10, blood samples were taken for TBZ, α- and β-HTBZ plasma concentration measurements within 30 minutes before the 8AM dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the morning dose. On Day 10 a 24-hour urine collection for digoxin concentration measurement was begun following the 8AM digoxin dose. Fluid intake on Day 10 was standardized to 2 liters of water or herbal tea over the 24 hour period.

During the confinement period, the consumption of alcohol, caffeinated tea, coffee, cola, grapefruit, and grapefruit-containing beverages was not permitted. Smoking was also not permitted. Bran and food containing bran fiber were also excluded from the diet for the duration of the study. With the exception of oral contraceptives prescription or OTC medications were not allowed.

Inclusion criteria included healthy males or females, between the ages of 18 and 45 years of age (inclusive). Females had to be surgically sterile or practice an acceptable method of birth control. Exclusion criteria included intake of any type of drug during the 2 weeks preceding the screening visit (except acetaminophen, up to 1 g/day), current nicotine consumption of more than 10 cigarettes per day, excessive consumption of coffee, tea, or chocolate or caffeine-containing drinks,

Safety monitoring included adverse event assessments, vital signs (including supine and standing systolic and diastolic blood pressure, pulse, and oral temperature), laboratory tests including hematology, serum chemistry, and urinalysis, 12-lead ECG, and physical exam.

ASSAY:

Plasma concentrations were measured using a validated LC/MS/MS method ~< 1266/1).

Table 2. Performance of Analytical Method for TBZ 203-009

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
TBZ	LC/MS/MS	0.2-200 ng/ml	r > 0.991	0.2	0.5	9.0	-1.6
					25.0	3.5	4.3
					100.0	4.3	-0.1
α- HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.992	0.5	1.0	8.2	0.2
					25.0	2.3	4.3
					100.0	3.0	1.0
β-HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.990	0.5	1.0	6.9	-1.7
					25.0	2.9	2.6
					100.0	4.5	0.9

For TBZ, and α- and β-HTBZ, samples were stored at -20° C or lower before shipping to ~ for analysis. Two calibration curves and duplicate QC samples were analyzed with each batch of study samples. Study samples were to be stored nominally at –80° C. Samples were analyzed within the period for which the samples are stable at –70° C. The performance of the assays for all analytes is considered acceptable.

Table 3. Performance of Analytical Method for Digoxin in Plasma and Urine in Study TBZ 203-009

	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Plasma	RIA	0.1-8.0 ng/ml	r > 0.999	0.15	0.45	12.2	-4.99
					2.0	4.94	-2.12
					4.0	5.89	-6.48
Urine	RIA	1.0-40.0 ng/ml	r > 0.999	1.0	3.0	6.56	-2.04
					10.0	4.53	8.34
					20.0	5.46	6.10

Neither TBZ nor its metabolites interfere with quantitation of digoxin in human plasma or urine. For digoxin, plasma and urine samples were stored at -70° C to -80 °C. One calibration curve and duplicate QC samples were analyzed with each batch of study samples for digoxin plasma and urine analysis. Samples were analyzed within the period for which the samples are stable. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Sixteen subjects entered the study (6 males and 10 females). Twelve subjects (6 males, 6 females) completed the study. Four females were withdrawn from the study; one for personal reasons (after a single dose of digoxin) and three because of AEs. One withdrew prior to dosing either with digoxin or TBZ. One subject withdrew after dosing of digoxin due to increased ALT and AST (<2x ULN). An additional subject withdrew due to increased ALT during the dosing period of digoxin with TBZ, but the ALT was noted to be increased when the subject was receiving digoxin only (>2X ULN); slight increases in AST and also in bilirubin (< 2x ULN) were observed as well. Demographics of subjects completing the PK portion of the study are shown in the table below.

Table 4. Demographics of Subjects Completing Study 203-009

Mean Age (Range)	Gender	Weight (mean ± SD)	Race*
29 (21-42)	6 males 6 females	64 ± 10 kg (n=12) 70 ± 8 kg (male) 57 ± 7 kg (female)	

Four of the 6 females used hormonal contraceptives. One subject was a smoker (10 cigarettes/day).

*The Sponsor states that this study was conducted in France, and French law prohibits recording of race in clinical studies.

Pharmacokinetics

Digoxin

The pharmacokinetic parameters were calculated using noncompartmental analysis. The digoxin plasma trough levels on Days 5-11 and the digoxin plasma concentration time course on Days 6 and 10 are shown in the Figures 1 and 2 below, as provided by the Sponsor. The pharmacokinetic parameters for digoxin on Days 6 and 10 and the bioequivalence comparison of Days 6 and 10 are shown in Tables 5 and 6, below. The results were calculated by the reviewer and are in agreement with those reported by the Sponsor. Urinary parameters are as provided by the Sponsor.

Figure 1 (Mean (± SD) pre-dose (trough) plasma concentrations of digoxin in Study 203,009.

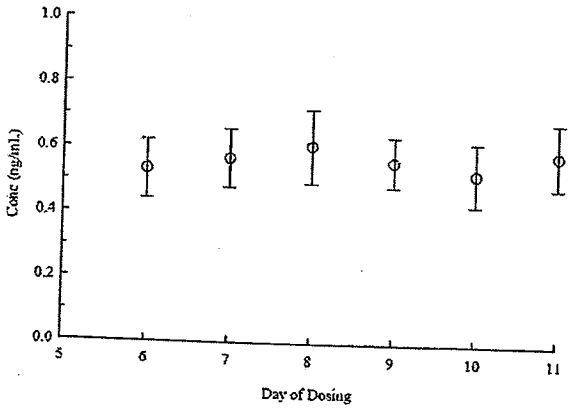


Figure 2. Mean steady state plasma concentrations of digoxin after oral administration of 0.25 mg/day to healthy volunteers alone (Day 6) and concurrent with TBZ 25 mg BID (Day 10).

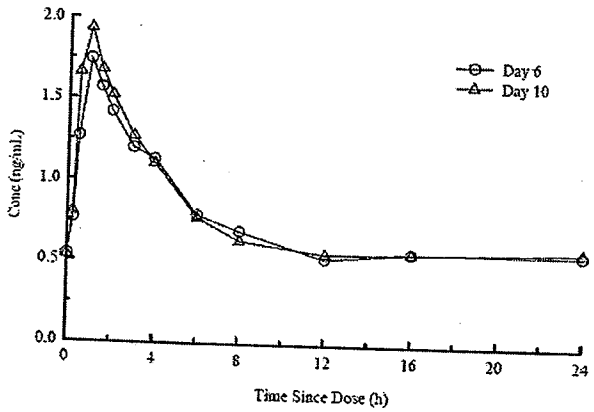


Table 5. Pharmacokinetic parameters (arithmetic mean, %CV) for Digoxin (Study TBZ 203,009)

	Day 6	Day 10
t_{max} (h)[a]	1.0 (0.5-1.5)	1.0 (0.5-2.0)
C_{max} (ng/mL)	1.81 (13)	2.03 (10)
AUC $_{0-t}$ (ng*h/mL)	17.73 (10)	18.11 (13)
Clr (ml/min)	133 (18)	137 (24)
Ue (mg)	0.141 (16)	0.147 (17)

[a] median (range)

Table 6. Bioequivalence Assessment for Study TBZ 203,009

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Day 6	Day 10		
C_{max} (ng/ml)	1.79	2.02	112.9	(1.06, 1.21)
AUC_{0-t} (ng*h/ml)	17.7	18.0	101.8	(0.97, 1.07)

Plasma concentrations were not collected for a sufficient period to determine elimination half-life. The PK results suggest that the addition of TBZ at doses of 25 mg twice daily did not have an effect on exposure to digoxin. Similarly, statistical comparison of the urinary parameters, as provided by the Sponsor and that are in agreement with parameters reported in the literature, did not show a difference between Days 6 and 10, with 90% CI for the ratio of geometric means within the BE interval of 80-125%.

Tetrabenazine

TBZ plasma concentrations were less than the LOQ for the majority of sampling times in all subjects. Six subjects had detectable TBZ plasma concentrations. The highest TBZ concentration was 1.49 ng/ml. The mean pre-dose plasma concentrations of α-HTBZ and β-HTBZ and the mean plasma concentration time curves for α-HTBZ and β-HTBZ are shown in Figures 3 and 4, below, as provided by the Sponsor. The pharmacokinetic parameters for α-HTBZ and β-HTBZ were calculated using noncompartmental analysis. The results below, as calculated by the reviewer, are in agreement with those provided by the Sponsor.

Figure 3 . Mean pre-dose (trough) plasma concentrations of α-HTBZ and β-HTBZ on Day 10.

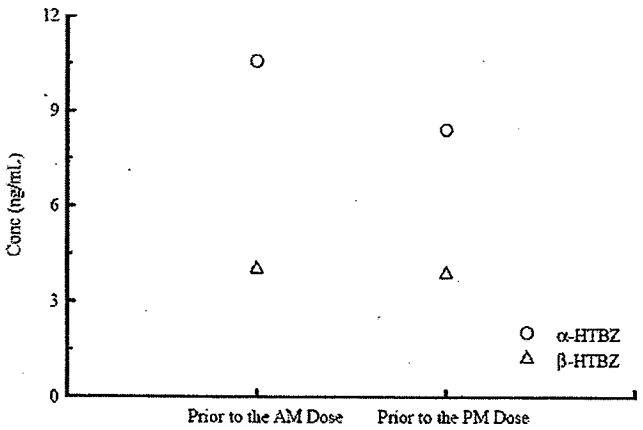


Figure 4. Mean steady-state plasma concentrations of α-HTBZ and β-HTBZ on Day 10.

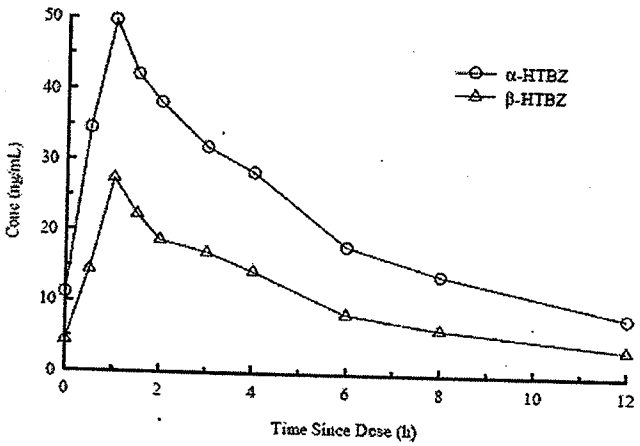


Table 7. Pharmacokinetic parameters (arithmetic mean) for α-HTBZ and β-HTBZ (Study TBZ 203,009)

	(% CV) n=12
α-HTBZ	
t_{max} (h)[a]	1.0 (.05-2.0)
C_{max} (ng/mL)	52.6 (36)
AUC_{0-t} (ng*h/mL)	261.6 (40)
λz (hr^{-1})	0.151 (33)
$t_{1/2}$ (h)	5.3 (43)
β-HTBZ	
t_{max} (h)[a]	1.0 (0.5-3.0)
C_{max} (ng/mL)	28.8 (59)
AUC_{0-t} (ng*h/mL)	129.1 (111)
λz (hr^{-1})	0.243 (36)
$t_{1/2}$ (h)	3.6 (76)

[a] median (range)

The trough concentrations of α-HTBZ and β-HTBZ were similar prior to both doses, suggesting that steady state had been reached. Exposure to α-HTBZ was approximately 2-fold higher than exposure to β-HTBZ. Values for λz and $t_{1/2}$ are in agreement with results from other PK studies in healthy subjects.

Safety

There were no deaths or serious adverse events reported. Adverse events included nausea that occurred with digoxin alone in 1 subject and in 2 subjects on digoxin and TBZ, dizziness that occurred twice in one patient taking TBZ and digoxin, and asthenia in 1 subject taking digoxin alone and in 1 subject taking TBZ and digoxin.

CONCLUSIONS:

Tetrabenazine given as 25 mg twice daily did not affect the PK parameters of digoxin when both drugs were co-administered to healthy volunteers, suggesting no effect of TBZ on P-glycoprotein at this dose. The effect of greater exposure to TBZ is unknown.

4.2.17 BIOANALYTICAL METHOD FOR DIGOXIN IN PLASMA

The method to quantitate digoxin in heparinized human plasma is a radioimmunoassay detection method using the [redacted] kit, using a modified method. The minimum quantifiable level is 0.15 ng/ml (the commercial product has a calibration range of 0.5ng/ml to 8 ng/ml).

Selectivity, Accuracy, Precision, and Recovery

Specificity was shown in blank human plasma from 6 individuals.

The range of the calibration curves, LOQ, and nominal values for the QC samples are shown in the Table below.

Table 3. Performance of Analytical Method for Digoxin in Plasma

	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Plasma	RIA	0.1 0.15 0.2 0.5 1.0 2.0 4.0 8.0	r > 0.999	0.15	0.45 2.0 4.0	12.2 4.94 5.89	-4.99 -2.12 -6.48

Each run included a calibration curve (in singlicate) that consisted of 8 standards and for each run all of the standards were within 15% of the nominal concentration. Accuracy and precision for each standard was acceptable. Linearity was established (4 parameter logistic regression). Intra-assay accuracy and precision for 6 replicates of each QC ranged from -3.49-0.675% and from 1.11-13.8%, respectively. Inter-assay accuracy and precision are shown in the table above. These values are acceptable.

Stability

Stability of digoxin in human plasma was demonstrated as follows. Freeze-thaw stability was demonstrated for 3 cycles. In-process stability was demonstrated for 4 hours at room temperature. During the sample analysis, long-term stability at -80° C was demonstrated for 376 days. Extraction stability and sample recovery were not evaluated since this is a direct radioimmunoassay.

Conclusion

The bioanalytical method **ICD 11.1** used for analysis of human plasma samples with respect to digoxin is adequately documented and validated.

4.2.18 BIOANALYTICAL METHOD FOR DIGOXIN IN URINE

The method to quantitate digoxin in human urine is a radioimmunoassay detection method using the [redacted] kit. The minimum quantifiable level is 0.1.0 ng/ml. [redacted] has performed a validation of the method and performed the analysis of the urine samples for digoxin in Study TBZ 203,009.

Selectivity, Accuracy, Precision, and Recovery

Selectivity was determined by analysis of blank samples from 6 independent sources of blank human urine for the presence of interfering peaks.

The range of the calibration curves, LOQ, and nominal values for the QC samples are shown in the Table below.

Table 1. Performance of Analytical Method for Digoxin in Urine

	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Urine	RIA	1.0 2.0 3.0 8.0 16.0 20.0 40.0	r > 0.999	1.0	1.5 10 20	9.24 6.27 3.17	-6.89 2.85 -2.39

Each run included a calibration curve (in singlicate) that consisted of 7 standards and for each run all of the standards were within 15% of the nominal concentration. Accuracy and precision for each standard was acceptable. Linearity was established (4 parameter logistic regression). Intra-assay accuracy and precision for 6 replicates of each QC ranged from 1.21-10.4% and from 1.82-10.5%, respectively. Inter-assay accuracy and precision are shown in the table above. These values are acceptable.

Stability

Stability of digoxin in human urine was demonstrated as follows.
Freeze-thaw stability was demonstrated for 3 cycles. In-process stability was demonstrated for 4 hours at room temperature. Extraction stability and sample recovery were not evaluated since this is a direct radioimmunoassay. During the sample analysis, long-term stability at -80° C was demonstrated for 575 days. Also during sample analysis, dilution integrity was demonstrated for dilution by a factor of 100-fold.

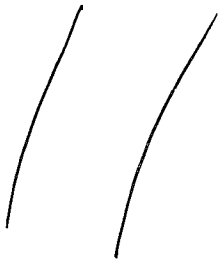
Conclusion

The bioanalytical method **ICD 11.2** used for analysis of human urine specimens with respect to digoxin is adequately documented and validated.

4.2.19 HEPATIC IMPAIRMENT

A COMPARISON OF THE PHARMACOKINETIC CHARACTERISTICS OF A SINGLE DOSE OF TETRABENAZINE IN LIVER IMPAIRED AND IN HEALTHY SUBJECTS

Study Investigators and Site:



Protocol Number: TBZ 203,010

Note: an interim report (dated February 28, 2005) was provided, stating in the submission of October 18, 2005 that the study is ongoing.

OBJECTIVES:

The primary objective is to compare the PK characteristics of TBZ and α- and β-dihydrotetrabenazine (HTBZ) in subjects with mild or moderate liver impairment to those of age-matched (+/- 5 years) healthy subjects.

The secondary objective is to evaluate safety and tolerability of a single 25 mg oral dose (2x 12.5 mg tablets) of TBZ administered to subjects with mild or moderate liver impairment as well as age-matched (+/- 5 years) healthy subjects.

FORMULATIONS:

Table 1. Product used in TBZ 203,010

	Batch No.	Exp. Date (Dates of Study)
Tetrabenazine 12.5 mg tablet	6573804	6/8/05 (9/7/04 – ongoing as of 2/28/05)

STUDY DESIGN:

This is a multi-center, single-dose, open-label study of the PK characteristics of TBZ, α-HTBZ, and β-HTBZ in liver-impaired and healthy subjects.

Inclusion criteria included male subjects 18-65 years of age, inclusive, with a body mass index ranging from 19-30 kg/m^2. Liver impaired subjects must have mild or moderate liver impairment (Child-Pugh classification 5 to 9) and stable chronic impairment of hepatic parenchymal function due to causes other than heart failure. Exclusion criteria included past history of depression or current depressive episode, subjects who consume more then 40 g of alcohol per day, subjects who currently smoke more than 10 cigarettes per day, subjects who drink more than 6 cups per day of caffeinated coffee, tea, or chocolate, or more than 6 glasses per day of cola/caffeine containing drinks. Also excluded were subjects with intake of any medication within less than 5 times its elimination half-life prior to study drug intake (with the exception of acetaminophen), and for healthy subjects, existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism, or excretion of study drug. Subjects with liver impairment must not suffer from CHF, severe hepatic encephalopathy, or abnormal renal function.

Eligible subjects were admitted to the clinic on the day before treatment (Day -1). On Day 1, subjects who continue to be eligible received a 25 mg oral dose of TBZ with 200 ml of water at 8AM after a 10 hour fast. Subjects continued to fast for 4 hours after drug administration. Blood samples were drawn at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 224, 36, and 48 hours after the dose of TBZ. Plasma was to be stored at -20 C or lower.

Safety monitoring included vital signs (supine and standing) 12-lead ECG, laboratory panel, and physical examination. Tolerability was evaluated on adverse events within each group (liver impaired and age-matched healthy subject).

ASSAY:

Plasma concentrations were measured using a validated LC/MS/MS method — 1266/1).

Table 3. Performance of Analytical Method for TBZ 203,010

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
TBZ	LC/MS/MS	0.2-200 ng/ml	r > 0.990	0.2	0.5	6.3	-0.1
					25.0	2.1	5.7
					100.0	4.4	0.7
α- HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.990	0.5	1.0	4.0	4.6
					25.0	3.1	9.8
					100.0	4.9	-6.2
β-HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.984	0.5	1.0	8.2	1.0
					25.0	7.5	1.3
					100.0	3.6	1.2

One calibration curves and duplicate QC samples were analyzed with each batch of study samples. Study samples were to be stored at –70° C according to the — analysis plan. Samples were analyzed within the period for which the samples are stable at –70° C. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Twelve male subjects have completed the study to date (6 healthy, 6 liver impaired). One subject (healthy) was a smoker. The control group is similar to the hepatic impaired group with respect to age, weight, and gender. Although the control group is not from the intended target population of Huntington's disease, the age range in the present study is within the age range enrolled in the pivotal efficacy study 103,004.

Table 4. Demographics of Subjects Completing the Study

Mean Age (Range)	Weight (mean ± SD)	Race *
57 (41-66) (n=12)	76 ± 11 kg (n=12)	Not available
55 (41-63) (healthy)	74 ± 6 kg (healthy)	
58 (46-66) (hepatic)	77 ± 16 kg (hepatic)	

*This study was conducted in France. French law prohibits recording of race in clinical studies.

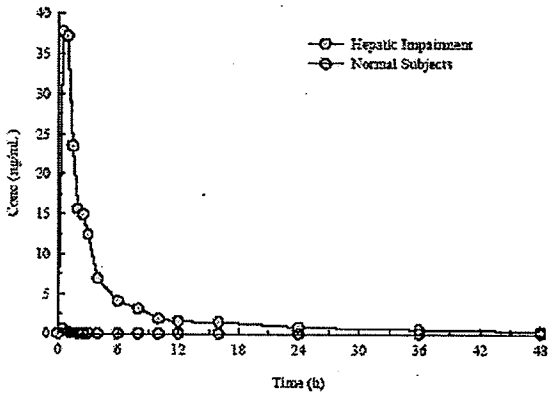
The Child-Pugh classification for the hepatic impaired subjects is as follows:

Subject	Classification
13	5
14	5
15	6
16	9
17	6
18	5

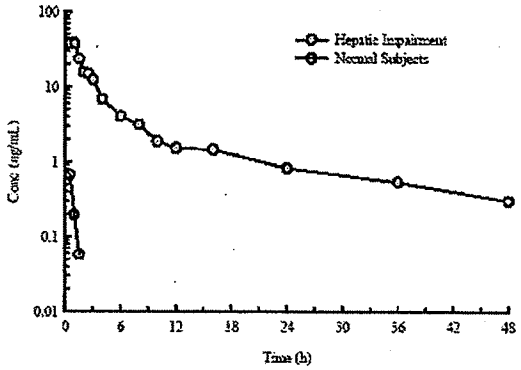
Pharmacokinetics

Pharmacokinetic parameters were determined using noncompartmental analysis. The plasma concentration time course (provided by the sponsor) and the pertinent pharmacokinetic parameters (as calculated by the reviewer) for TBZ and for α-HTBZ and β-HTBZ are shown in Figure 1 and Table 6, below. TBZ concentrations were less than the LOQ for the majority of sampling times in normal subjects. The results shown below are generally in agreement with those provided by the Sponsor, except that the Sponsor reports lower AUCinf and shorter elimination half-lives for hepatically impaired subjects.

Figures 1 and 2. Mean Plasma concentrations of TBZ after administration of TBZ to normal and hepatic impaired subjects.



re 1. **Mean plasma concentrations of tetrabenazine after administration of 25 mg of tetrabenazine (2×12.5 mg tablets) fasting conditions to subjects with liver impairment and h subjects — linear axes - Protocol TBZ 203,010**



2. **Mean plasma concentrations of tetrabenazine after oral administration of 25 mg of tetrabenazine (2×12.5 mg tablets) under fasting conditions to subjects with liver impairment and healthy subjects — semi-logarithmic axes.**

Figures 3 and 4. Mean Plasma Concentration Time Course for α-HTBZ after administration of TBZ to normal and hepatic impaired subjects.

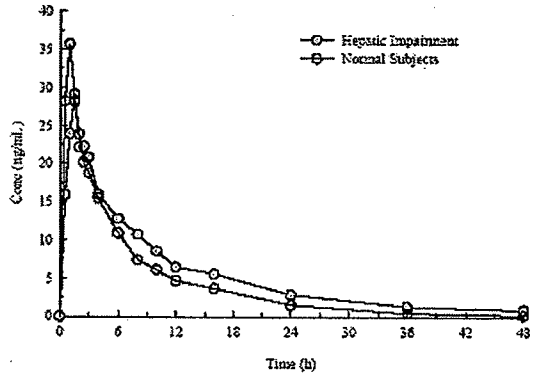
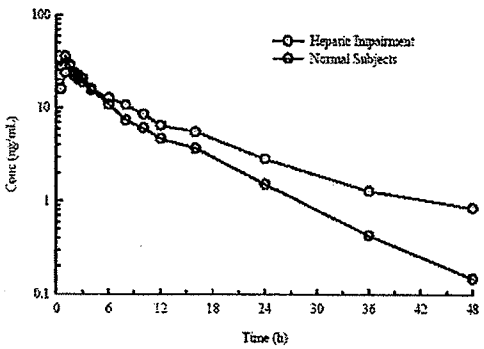
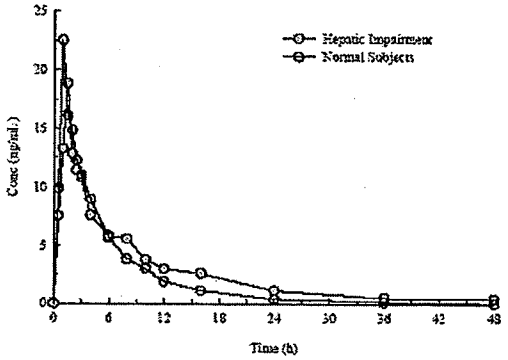


Figure 3. Mean plasma concentrations of α-HTBZ after oral administration o 25 mg of tetrabenazine (2×12.5 mg tablets) under fasting condition to subjects with liver impairment and healthy subjects— linear axe – Protocol TBZ 203,010.

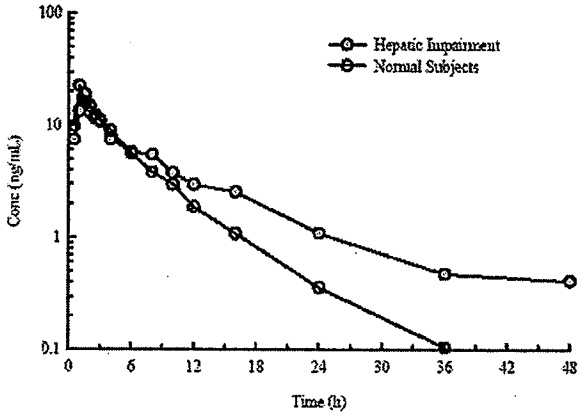


4. **Mean plasma concentrations of α-HTBZ after oral administration of 25 mg of tetrabenazine (2×12.5 mg tablets) under fasting conditions to subjects with liver impairment and healthy subjects — semi-logarithmic axes – Protocol TBZ 203,010.**

Figures 5 and 6. Mean Plasma Concentration Time Course for β-HTBZ after administration of TBZ to normal and hepatic impaired subjects.



gure 5. Mean plasma concentrations of β-HTBZ after oral administra
25 mg of tetrabenazine (2×12.5 mg tablets) under fasting con
to subjects with liver impairment and healthy subjects — lines
– Protocol TBZ 203,010.



re 6. Mean plasma concentrations of β-HTBZ after oral administration of 25 mg of tetrabenazine (2×12.5 mg tablets) under fasting conditions to subjects with liver impairment and healthy subjects — semi-logarithmic axes – Protocol TBZ 203,010.

Table 5. Pharmacokinetic parameters (arithmetic mean) for α-HTBZ and β-HTBZ (Study TBZ 203,010)

	Normal (% CV) n=6	Hepatic Impairment (% CV) n=6
TBZ		
t_{max} (h)[a]	0.5 (0.5-0.5)	1.0 (0.5-1.5)
C_{max} (ng/mL)	0.67 (106)	47.0 (98)
AUC $_{0-t}$ (ng*h/mL)	0.5 (112)	131.6 (112)
AUC $_{0-\infty}$ (ng*h/mL)	1.5	170.0 (97)
λz (hr^{-1})	1.67	0.201 (174)
$t_{1/2}$ (h)	.41	12.8 (54)
α-HTBZ		
t_{max} (h)[a]	1.0 (0.5-1.05)	1.75 (0.5-3.03)
C_{max} (ng/mL)	38.4 (21)	34.8 (44)
AUC $_{0-t}$ (ng*h/mL)	211.0 (50)	262.2 (34)
AUC $_{0-\infty}$ (ng*h/mL)	215.1 (50)	282.7 (40)
λz (hr^{-1})	0.136 (44)	0.073 (44)
$t_{1/2}$ (h)	6.1 (45)	10.9 (39)
β-HTBZ		
t_{max} (h)[a]	1.0 (0.5-1.05)	1.75 (0.5-7.98)
C_{max} (ng/mL)	23.4 (44)	22.7 (66)
AUC $_{0-t}$ (ng*h/mL)	101.3 (82)	125.2 (30)
AUC $_{0-\infty}$ (ng*h/mL)	103.1 (81)[d]	146.4 (52)
λz (hr^{-1})	0.201 (36)[d]	0.101 (58)
$t_{1/2}$ (h)	4.0 (51)[d]	10.7 (92)

[a] median (range)

In the hepatic impairment patients, there were detectable concentrations of TBZ that were similar to or higher than exposures seen with α- or β-HTBZ. The mean TBZ Cmax concentration in hepatic subjects was 70-fold higher than the mean in healthy subjects. The mean AUC_t and AUC_{inf} were approximately 200-fold and 113-fold, respectively, greater in hepatic subjects than in healthy subjects.

In addition, there were increases in exposure to α- and β-HTBZ, in general, although to a lesser extent than the increase in exposure to TBZ. The AUC_{0-t} was approximately 24% higher in hepatic impairment for either α- or β-HTBZ than in normal subjects. The $AUC_{0-\infty}$ for α- HTBZ was approximately 32% greater and the $AUC_{0-\infty}$ for β-HTBZ was approximately 42% greater in hepatic impaired patients than in normal subjects. The half-life was also prolonged.

The table below, as provided by the Sponsor shows the individual PK parameters for TBZ for each liver impaired subject, and shows that the subject with moderate impairment (subject 16) had greater exposure to TBZ than the subjects with mild impairment. In addition, his Cmax for α-HTBZ and β-HTBZ were lower than that of the patients with mild impairment, although his AUC_{0-t} for α-HTBZ and β-HTBZ were higher than those of the patients with mild impairment. These data are shown in the tables below.

TBZ PK parameters by hepatic impairment subject

Subject Number	Child-Pugh Classification	Cmax (ng/ml)	AUC0-t (ng*hr/ml)	$t_{1/2}$ (h)
13	5	No conc ≥ LOQ	No conc ≥ LOQ	No conc ≥ LOQ
14	5	42.5	158.9	13.5
15	6	5.6	8.72	0.8
16	9	126.3	400.4	18.8
17	6	66.6	145.0	16.3
18	5	41.0	76.3	14.6

α-HTBZ PK parameters by hepatic impairment subject

Subject Number	Child-Pugh Classification	Cmax (ng/ml)	AUC0-t (ng*hr/ml)	$t_{1/2}$ (h)
13	5	39.8	170.4	7.0
14	5	31.3	251.8	9.4
15	6	62.1	320.6	8.5
16	9	17	361.8	Could not be estimated
17	6	33.1	320.9	9.0
18	5	25.7	137	9.8

α-HTBZ PK parameters by hepatic impairment subject

Subject Number	Child-Pugh Classification	Cmax (ng/ml)	AUC0-t (ng*hr/ml)	$t_{1/2}$ (h)
13	5	29.0	84.5	Could not be estimated
14	5	14.8	111.8	Could not be estimated
15	6	50.6	142.9	5.3
16	9	9.0	183.5	Could not be estimated
17	6	16.6	127.6	7.3
18	5	16.4	76.6	6.7

Safety

The Sponsor reports that no safety or tolerability analysis was performed for the purposes of the interim pharmacokinetic analysis, but that no deaths or serious adverse events were reported for the first 12 participants who had completed the study as of the data cut-off date of February 28, 2005. One subject (hepatic impaired) had a single episode of asthenia considered to be mild in severity.

CONCLUSIONS:

1. Hepatic impairment reduces the metabolism of TBZ resulting in substantial exposures relative to normal subjects (approximately 7-fold for Cmax and 100-200-fold for AUC) in whom minimal exposure to TBZ occurs. This was true for both mild and moderate hepatic impairment, and the subject with moderate hepatic impairment had the highest TBZ exposure.

2. Exposure to α- and β-HTBZ was 24-42% greater in the hepatically impaired subjects than in healthy controls. The subject with moderate hepatic impairment had reduced Cmax compared to the subjects with mild hepatic impairment, but AUC higher than the mean for hepatic impairment.

3. The increase in TBZ exposure is not entirely accounted for by changes in exposure to α- and β-HTBZ. Since the relationship between substantially increased exposure to TBZ in hepatic impairment to the exposure circulating metabolites other than α- and β-HTBZ is not known, and the contribution of those other metabolites to efficacy and safety is not known, it is not possible to adjust the dosage of TBZ for hepatic impairment. The label should contraindicate TBZ in hepatic impairment.

4.2.20 EFFICACY STUDY TBZ 103,004

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF TETRABENAZINE FOR THE TREATMENT OF HUNTIGNTON'S CHOREA (TETRA HD)

Study Investigators and Site:

Frederick Marshall, MD
University of Rochester, Department of Neurology

Francis Walker, MD
Wake Forest University, Department of Neurology

16 Huntington's Study Group (HSG) sites in the US

Protocol Number: TBZ 103,004
Note: This review only evaluates data from a PK perspective

OBJECTIVES:

The primary objective was to establish the absolute reduction of chorea in participants with Huntington's disease (HD) treated with optimized doses of TBZ and placebo.

The secondary objective was to determine the mean and standard deviation (SD) of the optimal dose and the percentage of participants responding at each dose level.

FORMULATION:

Table 1. Product used in TBZ 103,004

	Batch No.	Exp. Date (Dates of Study)
Tetrabenazine 12.5 mg tablet	6573804	12/31/04 (7/9/03-3/15/04)
Placebo tablet	6573872	12/8/04 (7/9/03-3/15/04)

STUDY DESIGN:

This was a multi-center, randomized, double-blind, placebo-controlled, study in 2 parallel unbalanced (2:1) groups (TBZ titrated to best dose; placebo) of HD participants. During the first 7 weeks (titration phase) , ascending doses of TBZ were given, starting at 12.5 mg/day and titrated up weekly by 12.5 mg increments to each participants "best dose" based on efficacy and depending on tolerability. If at any time during the titration phase intolerance developed, the dose of study drug could be decreased to the participant's previous well-tolerated dose. The minimum dose was 12.5 mg/day. The maximum dose was 100 mg/day (3 tablets in the morning, 2 tablets at noon, and three tablets in the evening) so that the maximum dose at any given administration time was 37.5 mg. During the last 5 weeks of the study (maintenance phase) the

daily dose and dose regimen were to be kept constant unless an intolerable adverse event occurred. Dose regimen was qd or bid at lower doses of 12.5 and 25 mg/day, respectively, and tid at all other higher doses. Treatment could be suspended for up to 7 days, although only 1 treatment suspension was allowed during the 12-week treatment period. Efficacy was evaluated primarily on Total Chorea Score of the UHDRS motor portion. The primary outcome measure was the change in Total Chorea Score from Baseline to the average of the values at Week 9 and Week 12. Safety and tolerability were evaluated on adverse events as well as the 17-item HAM-D to screen for development of depression, the UHDRS parkinsonism score, Barnes Akathisia Scale, UHDRS part VIII, UHDRS part VI, UPDRS dysphagia score, UPDRS dysarthria score, Functional Impact Scale, and Epworth Sleepiness Scale. Safety was also evaluated on vital signs, 12-lead ECG, laboratory panel, neurological examination, and physical examination.

Blood was drawn for $CAG_{(n)}$ repeat determination at screening. (This test is used for confirmatory testing in an individual with clear symptoms of Huntington's disease and a documented family history, according to "Guidelines for Genetic Testing for Huntington's Disease" from the Huntington's Disease Society of America). Samples were sent to the [redacted] under the direction of [redacted] The method is a polymerase chain reaction (PCR) based assay (modified from the method of Warner et al. Mol Cell Probes 1993; 7:235-239). [redacted] The assay is performed in a research laboratory and Dr. [redacted] states that the laboratory's procedures are in keeping with current clinical standards, and the reliability of the CAG analyses has been independently verified.

Blood samples were drawn at the end of Week 9 and Week 12 visits (during the maintenance phase) to measure the plasma concentrations of TBZ, α-, and β-HTBZ.

Inclusion criteria included males or females, ≥ 18 years of age, suffering from manifest HD as confirmed by a characteristic movement disorder (chorea) with a total Chorea Score ≥ 10, a positive family history, and an expanded cytosine-adenine-guanine (CAG) repeat (n ≥ 37). The main exclusion criteria were previous treatment with TBZ, unstable or serious medical or psychiatric illness, concomitant use of DA-depleting drugs, DA D2 receptor blockers, MAO Inhibitors, levodopa, DA agonists, untreated depression, or lack of a care giver. Participants on other drugs (including psychotropic drugs) could be enrolled in the study, with the exception of participants on the drugs listed above. Participants on antidepressant drugs could be enrolled in the study provided they were no longer depressed and the dosage of antidepressants had been stable for at least 8 weeks prior to randomization.

ASSAY:

Plasma concentrations for Study 103,004 were measured using a validated LC/MS/MS method — 1266/1).

Table 3. Performance of Analytical Method for TBZ 103-004

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
TBZ	LC/MS/MS	0.2-200 ng/ml	r > 0.990	0.2	0.5	9.4	1.0
					25.0	6.0	0.2
					100.0	7.1	-4.6
α- HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.990	0.5	1.0	6.6	-2.6
					25.0	6.5	0.8
					100.0	7.6	-2.3
β-HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.990	0.5	1.0	5.9	2.0
					25.0	4.6	3.7
					100.0	7.3	2.5

For TBZ, and α- and β-HTBZ, samples were stored at -20° C or lower before shipping to — for analysis. Two calibration curves and duplicate QC samples were analyzed with each batch of study samples. Study samples were to be stored nominally at –80° C and assays were run in batches as they were received. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Subject Disposition

Fifty four subjects were randomized to TBZ and 30 were randomized to placebo. Fifty-one TBZ subjects completed 9 weeks of treatment and 49 completed 12 weeks of treatment. For placebo, 29 subjects completed 12 weeks of treatment and 1 subject withdrew prior to week 7.

Demographic characteristics of the subjects enrolled in the study and randomized to TBZ or placebo are shown in the table below, as provided by the Sponsor.

Table 8. Demographic Characteristics of 84 Participants Enrolled in Tetra HD and Randomized to Tetrabenazine (N=54) or Placebo (N=30)

Demographic Characteristic	Tetrabenazine (N= 54)	Placebo (N=30)	P-Value
Gender			
Male	21 (39%)	11 (37%)	Fisher's Exact Test
Female	33 (61%)	19 (63%)	1.0
Age (years)			
Mean	49.4	48.8	
Median	49.5	49	t-test
Standard Deviation	12.3	10.5	0.83
Range	25 – 77	28 – 67	
Race			
White	50 (93%)	29 (97%)	Fisher's Exact
Other	4 (7%)	1 (3%)	Test
			0.65
Years of Education			
Mean	13.7	13.7	
Median	13.5	13.5	t-test
Standard Deviation	2.34	2.25	0.99
Range	6 – 18	9 – 18	

Source: Table 14.1.1 in Section 14.1

The CAG repeat length ranged fror —— and was comparable in both groups. The mean CAG repeat length was 44.9 in the TBZ group and 44.3 in the Placebo group. Two subjects had CAG repeat lengths of —and the rest were > 40.

Pharmacodynamic Results

The primary efficacy outcome variable was the difference between the baseline chorea score and the average of the Weeks 9 and 12 chorea scores. The number and percentage of participants with a 3-point or greater decrease in total chorea score at the end of the study is shown by dose at the end of the study in the table below, as provided by the Sponsor. The most common dose was 100 mg/day.

Table 23. Number and Percentage of Participants with a 3-Point of Greater Decrease in Total Chorea Scores at the End of Study According to Dose of Tetrabenazine (N=54) at the End of the Study

TBZ Dosage (mg/day)	End of Treatment		Percent Responders	
	N	%	N	%†
12.5	0	0%	0	0%
25.0	1	2%	1	100%
37.5	7	13%	3	43%
50.0	11	20%	10	91%
62.5	2	4%	1	50%
75.0	2	4%	2	100%
87.5	4	7%	3	75%
100.0	22	41%	13	59%

Source: Appendix 16.2.6.2
TBZ = tetrabenazine
* Percentage calculated based on 54 participants receiving tetrabenazine.
† Percentage calculated based on number of participants in each tetrabenazine dose groups.

The Sponsor states that during the treatment period, chorea scores for participants in the drug group declined by an estimated 5.0 unites, while those in the placebo group declined by an estimated 1.5 units, and this treatment effect of 3.5 units was significant ($p < 0.0001$). A total of 69% of participants on TBZ vs 23% of participants on placebo had at least a 3-point decrease in Total Chorea Score ($p < 0.0001$) that was considered by the Sponsor to be a meaningful effect.

Twenty-two of the 54 TBZ subjects reached and maintained a dose of 100 mg/day. Three subjects discontinued dose escalation because the desired effect had been achieved. Twenty-eight subjects in the TBZ group discontinued upward titration because of an adverse event that included sedation, akathisia, depression, Parkinsonism, or other including anorexia, restlessness, fatigue, diarrhea, bradykinesia, bradyphrenia, or insomnia. Participants who reported akathisia, Parkinsonism, or depression had all responded to treatment prior to the occurrence of the dose limiting AE. Four of the 15 subjects who reported sedation were not responding to treatment at the time sedation occurred, and 3 did not respond to treatment following the occurrence of the AE.

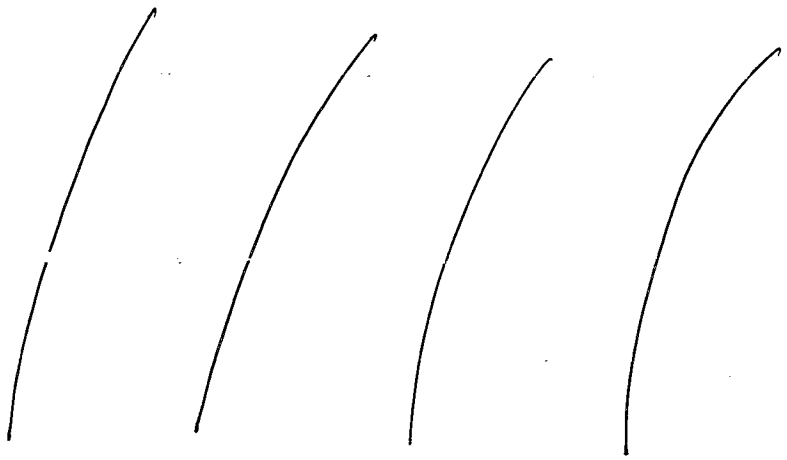
Pharmacokinetics

The Sponsor provided the PK data in the Population PK report and did not include a PK discussion in the Study report for 103,004. However, plasma concentrations were provided. Blood samples were reportedly collected approximately < 30 minutes to 7 hours after the dose, except in 3 blood draws that were performed approximately 15-20 hours after the dose.

The highest recorded concentration for TBZ was —— ng/ml. The highest concentration of α-HTBZ was —— ng/ml, and the highest concentration of β-HTBZ recorded was —— ng/ml. (These were observed in a subject taking clomipramine). For the highest dosing regimen (100 mg/day), with the 37.5 mg dose being the last dose given before the blood sample was drawn, the following figure shows the range of concentrations for α-HTBZ and β-HTBZ within approximately 2 hours after the last dose. Similarly, the range of concentrations is shown for the 50 mg/day regimen, with the 12.5 mg dose being the last dose given before the blood samples was drawn.

Analyte Concentration Within 2 Hours of Last Dose

(Last dose was 12.5 mg for 50 mg/day regimen or 37.5 mg for 100 mg/day regimen)



The ratio of alpha to beta ranged from 0.43 to 6.4. In 26 of 47 samples in which the ratio was < 1.6 (and in 21 of 25 samples in which the ratio was < 1), subjects were taking CYP2D6 inhibitors. These included diphenhydramine, paroxetine, fluoxetine, clomipramine, methadone, and bupropion. There was 1 additional case in which a subject taking the weak CYP2D6 inhibitor sertraline as the sole CYP2D6 inhibitor had a ratio of 1.4. (There were several cases in which sertraline was given with another CYP2D6 inhibitor with ratios of < 1.6). There were 6 samples with ratios > 1.6 in subjects taking sertraline as the sole CYP2D6 inhibitor. For all other

α: β ratios > 1.6, there was no concomitant medication identified by the Reviewer as being a CYP2D6 inhibitor.

Relationship of PK or Dose to Safety Information

Five TBZ subjects withdrew from the study prematurely. Of these, 4 withdrew prior to the week 9 PK assessment and are not considered here. The 5th subject who withdrew after 71 days due to suicidal ideation, psychosis, and paranoia was taking a dose of 12.5 mg daily and was also taking bupropion. Blood samples were collected approximately 2 hours pre-dose and were less than 4 ng/ml for either α- or β-HTBZ.

Relationship of PK or Dose to Efficacy

As shown above, the most common dose was 100 mg/day at which 59% of subjects responded (this number may reflect subjects who tolerated the drug but who had not responded). The second most common dose was 50 mg/day at which 91% of subjects were responders.

Concentration response relationships are not possible to evaluate due to the dosing regimens, variability in PK, and timing of samples in relation to dose. For the 50 mg/day doses, the highest concentration for α-HTBZ was — ng/ml and for β-HTBZ was — ng/ml, both at approximately 1 hour after a dose. For the 100 mg/day doses, the highest concentration reported was — ng/ml for α-HTBZ and — for β-HTBZ, both at approximately 1 hour after a dose.

The Sponsor has provided the following analysis of participants who responded to tetrabenazine, comparing patients on antidepressants and patients who did not take antidepressants at baseline. Antidepressants included CYP2D6 inhibitors paroxetine, fluoxetine, clomipramine, and bupropion, as well as non-CYP2D6 inhibitors such as amitriptyline, citalopram, imipramine, mirtazapine, sertraline, and trazodone. The distribution of TBZ dose by antidepressant use did not differ by this factor.

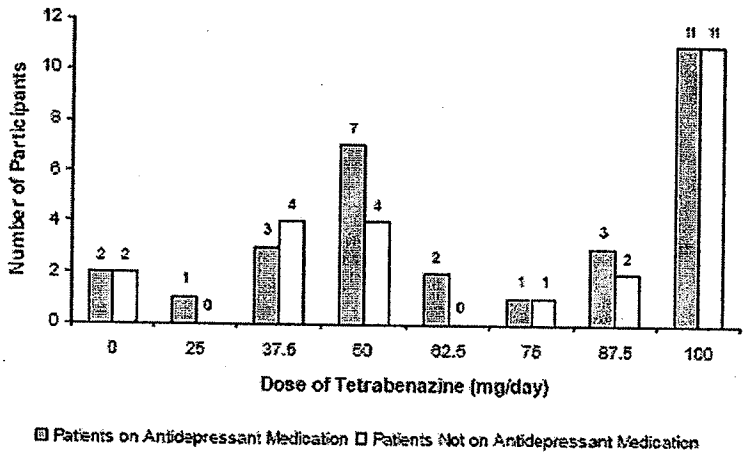


Figure 9. **Dose of Tetrabenazine used by participants on and off antidepressant medication at baseline.**

Safety

Adverse events were more common in the TBZ group than in the placebo group. Forty-nine of the 54 (91%) of participants randomized to TBZ experienced one or more AEs, and the majority occurred during the titration phase. However, 19 of 54 (35%) participants had one or more new onset adverse events during the maintenance phase. The most commonly reported AEs were fatigue (22% vs 13% in placebo group), insomnia (22%), depression (15%), fall (15% vs 13% in placebo group), and sedation (15%). Adverse events leading to discontinuation of dose titration or reduction in dose in subjects on TBZ included sedation (15 participants), akathisia (5 participants), parkinsonism (3 participants), depression (3 participants).

One participant committed suicide during the study. At the time, the dose of TBZ was 87.5 mg.

Five participants (4 TBZ and 1 placebo) were withdrawn prematurely. In the TBZ this was due to serious adverse events: fall complicated by subarachnoid hemorrhage in 1 subject; suicidal ideation, psychosis, and paranoia in 1 subject; akathisia in 1 subject; and breast cancer in 1 subject. The doses represented the range of doses used and it is therefore not possible to use this information to assess a dose-response.

CONCLUSIONS:

A dose-response relationship cannot be determined since TBZ is titrated to "best dose". The most common doses were 100 mg/day and 50 mg/day.

There is not enough data to determine a concentration-response relationship.

A lower ratio of α: β HTBZ was observed in patients taking concomitant CYP2D6 inhibitors. The role of CYP2D6 in the PK of TBZ and its metabolites should be further evaluated.

4.2.21 EFFICACY STUDY TBZ 103,005

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STAGGERED WITHDRAWAL STUDY IN PATIENTS WITH HUNGTINGTON'S DISEASE TREATED WITH TETRABENAZINE

Study Investigators and Site:

Joseph Jankovic, MD
Stanley Fahn, MD
Parkinson's Disease Center and Movement Disorders Clinic
Baylor College of Medicine
Houston, TX

Protocol Number: TBZ 103,005

OBJECTIVES:

The primary objective was to evaluate efficacy of TBZ in Huntington's chorea by determining whether the withdrawal of TBZ from patients led to a return of chorea.

The secondary objectives were 1) to evaluate whether chorea observed in patients 5 days following TBZ discontinuation was more severe than chorea observed in patients 3 days after TBZ discontinuation.

FORMULATION:

Table 1. Product used in TBZ 103,005

	Batch No.	Exp. Date (Dates of Study)
Tetrabenazine 12.5 mg tablet	6573804	12/31/04 (11/11/03-12/10/04)
Placebo tablet	6573872	12/31/04 (11/11/03-12/10/04)

STUDY DESIGN:

This study was a single-center, randomized, double-blind, placebo-controlled, staggered withdrawal of TBZ in three parallel unbalanced groups of participants suffering from manifest HD and treated with TBZ (administered at "best dose"). "Best dose" was defined as the dose that provided moderate to marked improvement in the patient's condition while causing either no side effects or side effects that do not significantly interfere with the patient's function, as determined by the Clinical Global Impression rating. The duration of the double-blind staggered withdrawal study was 5 days for each participant, although if participants experienced intolerable

chorea they could be discontinued from the study. Screening evaluation could occur not more than 2 weeks prior to initiation of randomized withdrawal.

The Sponsor states that the duration of the study (5 days) was based on the half-life of TBZ (5.5 hours) and on published reports indicating the rapid return of chorea (within less than 24 hours) when TBZ treatment is stopped.

On enrollment, participants were taking 25 mg tablets, since these are the only TBZ tablets available to patients treated in the US under physician INDs. Participants were switched to either TBZ 12.5 mg tablets or identical placebo. Study drug was administered at the same dose regimen the participants were on when they were randomized. Subjects were evaluated at Screening, Baseline/Randomization, Day 3, and Day 5 (end of study).

Eligible subjects were randomized to one of the following treatment groups:

Screening (All Patients)	Double-Blind Staggered Withdrawal (5 Day Duration)			
	Treatment Assignment Group	Baseline Visit	Day 3	Day 5
Within 2 weeks prior to randomization	Group 1	Switches to placebo	Continues on placebo	Continues on placebo
	Group 2	Remains on tetrabenazine	Switches to placebo	Continues on placebo
	Group 3	Remains on tetrabenazine	Remains on tetrabenazine	Remains on tetrabenazine

Figure 1. Overall Design of Protocol TBZ 103,005

After randomization and prior to intake of first dose of study drug, participants were evaluated to establish baseline values on the UHDRS and Total Functional Capacity (Baseline visit). Adverse events were to be recorded and sitting vital signs were measured. Prior to the morning dose of TBZ, a sample of blood was drawn for determination of plasma concentration of TBZ and alpha and beta-HTBZ. Thereafter, study drug was to be given according to the subject's dose prior to the study and as per the randomization groups, with clinical evaluations in all subjects and PK evaluations in 10 subjects at specific time points.

At the Time of Day 3 evaluations, Group 1 had withdrawn from TBZ since the Baseline Visit (as planned). Group 2 had withdrawn from TBZ since the evening of Day 2 (earlier than planned), and therefore, clinical evaluations were performed 12-18 hours after the last dose of TBZ. Group 3 remained on TBZ. At the time of the Day 5 evaluation, Group 3 had withdrawn from TBZ since the evening of Day 4. (Therefore, all PK subjects should have good samples on Baseline (Day 1) and Group 3 should have good samples on Day 3 as well. In the present review only Day 1 (baseline) concentrations will be considered).

A subset of 10 participants underwent a full PK study at Baseline and on Day 3 with blood drawn at the following time points.

For patients on TID regimen:

Pre-dose tetrabenazine (the Baseline Visit) or pre-dose study drug (Day 3), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24 and 48 hours following their initial dose of tetrabenazine (the Baseline Visit) or study drug (Day 3);

For patients on BID regimen:

Pre-dose tetrabenazine (the Baseline Visit) or pre-dose study drug (Day 3), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 and 48 hours following their initial dose of tetrabenazine (the Baseline Visit) or study drug (Day 3).

Plasma was stored at -20° C or lower and sent to —— for analysis.

Inclusion criteria included males or females, ≥18 years of age, suffering from manifest HD with a confirmatory CAG repeat (n ≥ 37), being treated with TBZ and responding to TBZ, and on a stable dose considered to be the "best dose" for at least 2 months prior to randomization. Women of childbearing potential had to be on an adequate form of contraception. Exclusion criteria included significant unstable medical condition, life-threatening disease or neurological processes or use of therapies that my have obscured with results of treatment, concomitant use of certain drugs including DA-depleting medication other than TBZ, DA2 receptor blockers such as neuroleptics or certain anti-nausea drugs, selective and non-selective MAO inhibitors, levodopa, and dopamine agonists, a change in the dosage of any concomitant antidepressant within 8 weeks of the Baseline (Randomization) visit, and pregnant/lactating females.

Safety monitoring included adverse event assessments, UHDRS Parkinsonism, TFC, sitting vital signs (systolic and diastolic blood pressure, pulse), 12-lead ECG, laboratory values, and physical examination including body weight. If at any point in time the Investigator judged that a participant was developing depression the participant was evaluated on the 17-item HAM-D.

Pharmacogenomic Determination: Blood was drawn for $CAG_{(n)}$ repeat determination at screening. Samples were sent to the ——

ASSAY:

Plasma concentrations for Study 103,005 were measured using a validated LC/MS/MS method [redacted]1266/1).

Table 3. Performance of Analytical Method for TBZ 103-005

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
TBZ	LC/MS/MS	0.2-200 ng/ml	r > 0.990	0.2	0.5	7.1	1.8
					25.0	4.2	2.0
					100.0	6.1	-1.9
α- HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.990	0.5	1.0	8.9	1.0
					25.0	4.5	6.4
					100.0	8.3	3.0
β-HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.982	0.5	1.0	7.0	2.0
					25.0	7.6	2.4
					100.0	7.8	3.0

For TBZ, and α- and β-HTBZ, samples were stored at -20° C or lower before shipping tc [redacted] for analysis. Two calibration curves and duplicate QC samples were analyzed with each batch of study samples. Study samples were to be stored nominally at –80° C, and were analyzed within the period for which the samples are stable. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Thirty subjects entered the study (12 males and 18 females). The age range was 39-75. Two subjects were Black/African American and 28 subjects were White. Demographics of the 10 subjects completing the full PK portion of the study are shown in the table below.

Table 4. Demographics of Subjects Completing Study 103,005

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
61 (39-75)	7 males	75 ± 15 kg (n=10)	White 8
	3 females	79 ± 7 kg (male)	Black/African American 2
		64 ± 25 kg (female)	

Concomitant medications in the PK subjects included oral contraceptives in subject 2. Other concomitant medications known to interact with P450s are listed in the table below (subject # in parentheses).

	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Substrate	Glyburide (#4) Celocoxib (#18)	Diazepam (#1) Lansoprazole (#18)	Amitriptyline (#3) Paroxetine (#4)	Alprazolam (#2) Felodipine (#4) Simvastatin (#4) Triazolam (#10, Diazepam (#11) Nifedipine (#18)
Inhibitor		Provigil (#6)	Sertraline (#2, 10, 11) Paroxetine (#4) Celocoxib (#18)	
Inducer				Provigil (#6)

Distribution of the daily TBZ doses at study entry for all 30 subjects is shown in the figure below, as provided by the Sponsor. *However, based on the data they provided in Appendix 16.2.5.5 there were 4 subjects taking 25 mg daily, 9 subjects taking 37.5 mg daily, 9 subjects taking 75 mg daily, and 1 subject taking 112.5 mg daily, as well as 1 subject taking 12.5 mg daily, 5 subjects taking 50 mg daily, and 1 subject taking 150 mg daily.*

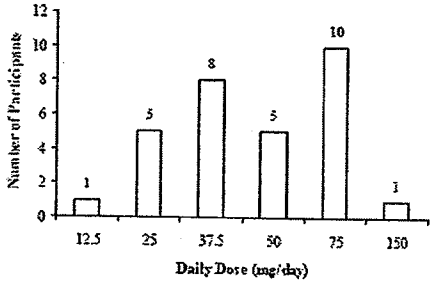


Figure 3. **Daily Tetrabenazine Dose Distribution for 30 HD Participants in Protocol TBZ 103,005**

The doses of the full PK subjects were identified in the study report as follows:

Subject	Treatment Group	Dose	Total Daily Dose
1	3	25 mg tid	75
2	2	25 mg bid	50
3	1	25 mg tid	75
4	2	25 mg tid	75
5	1	25 mg bid	50
6	1	25 mg tid	75
7	3	12.5 mg bid	25
10	1	37.5mg tid	112.5
11	2	25 mg bid	50
18	1	25 mg tid	75

However, in data listings, subject 10 is included in the group dosed at 25 mg tid.

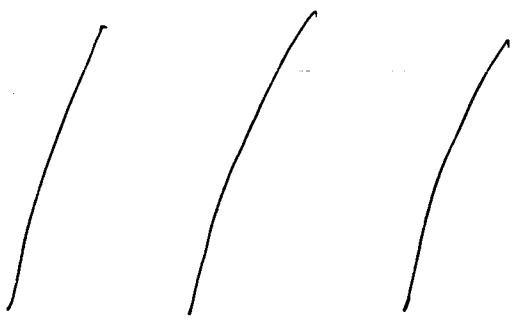
Pharmacokinetics

The Sponsor provided the PK study report in the submission of December 13, 2005. Study drug was given while the patient was awake. Thus for TID regimens the dosing interval was approximately 4 hours. The dosing regimen and actual dosing interval for each subject is shown in the table below. In the study report, subject 10 was identified as receiving 25 mg tid and is listed as such below.

Subject #	Treatment Group Assignment	TBZ Dosing Regimen	Actual Dosing Interval
3	1	25 mg tid	4
5	1	25 mg bid	8
6	1	25 mg tid	5
10	1	25 mg tid	2
18	1	25 mg tid	4
2	2	25 mg bid	10
4	2	25 mg tid	5
11	2	25 mg bid	12
1	3	25 mg tid	4
7	3	12.5 mg bid	12

The highest recorded concentration for TBZ was — ıg/ml. The figures below shows the plasma concentration time course for α-HTBZ on Day 1 for each subject treated with 25 mg bid and 25 mg tid, respectively. The highest concentration in the tid dosing group was — ng/ml and this was the highest seen with either the 25 mg bid or tid regimen. Subject 10, although listed above as having 37.5 mg tid was included by the Sponsor in the 25 mg tid dosing group. His Cmax for α-HTBZ and β-HTBZ were 54.3 and 51.2 ng/ml respectively. Subject 2 was in Group 2 and therefore received an additional dose on Day 2 at approximately 34 hours, accounting for the observed concentrations at the 36 hour and 48 hour time points. There was no 24 hour sample for that subject.

Plasma Concentration Time Course After 25 mg BID Dosing on Day 1



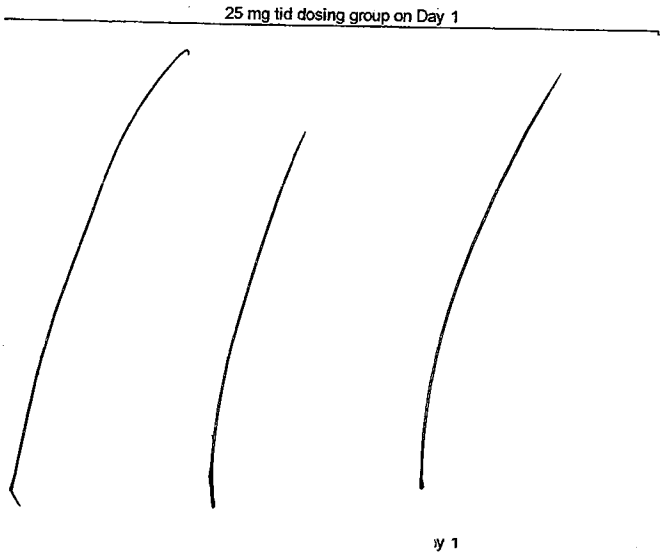


Table 5. Pharmacokinetic parameters (arithmetic mean) for α-HTBZ and β-HTBZ (Study TBZ 103,005) on Day 1

	25 mg BID (% CV) n=3	**25 mg TID** (% CV) n=6
α-HTBZ		
C_{max} (ng/mL)	40.5 (66)	47.8 (65)
AUC_{0-t} (ng*h/mL)[a]	237.3 (63)	121.6 (39)
β-HTBZ		
C_{max} (ng/mL)	25.7 (47)	40.9 (69)
AUC_{0-t} (ng*h/mL)[a]	152.2 (85)	93.1 (55)

[a] AUC, as calculated by Sponsor, based on a 12 hour dosing interval for bid regiments and a 4 hour dosing interval for tid regimens.

The AUC for the 25 mg BID dose was generally what would be expected based on the results from Study 203,008 (prolactin repeat dose study), although the Cmax was not. There was no apparent relationship between Cmax and dose or AUC and dose. This may have been due to the lack of standard dosing intervals and the variability in the time from the last dose, as well as variability in drug metabolism. In fact, some individuals may not have received doses according to their regimens – for example subject 5 (bid regimen) has only 1 peak, although 2 would be expected.

The ratio of α- to β-HTBZ ranged from 0.3 to 6.8 and this is consistent with the ratio reported in other studies. The ratio in the subject taking the strong 2D6 inhibitor paroxetine was a mean of 1.74 over all time points. The subjects taking sertraline (weak CYP2D6 inhibitor) had mean

ratios of 1.1, 2.0, and 3.1. A subject taking amitriptyline (CYP2D6 substrate) had a ratio of 0.6. Subjects taking no identifiable CYP2D6 inhibitors had mean ratios of 1.5 to 4.1.

Efficacy

The primary efficacy endpoint was the Total Maximal Chorea Score of the UHDRS. The primary outcome measure was the change in Total maximal Chorea Score from the Baseline Visit to Day 3. The mean (± SD) total maximal chorea scores throughout the study by withdrawal group and study day are shown in the table below (as provided by the Sponsor). At the Time of Day 3 evaluations, Group 1 had withdrawn from TBZ since the Baseline Visit (as planned). As described above, due to confusion with the protocol, Group 2 had withdrawn from TBZ since the evening of Day 2 (earlier than planned), and therefore, clinical evaluations were performed 12-18 hours after the last dose of TBZ. Group 3 remained on TBZ. At the time of the Day 5 evaluation, Group 3 had withdrawn from TBZ since the evening of Day 4.

Withdrawal Group	Baseline	Day 3		Day 5
	On TBZ	On TBZ	Off TBZ	Off TBZ
Group 1 (N=12)	9.4 ± 4.9	-	14.8 ± 5.4	14.8 ± 7.1
Group 2 (N=12)	9.1 ± 6.2	-	12.7 ± 5.3	14.6 ± 5.4
Group 3 (N=6)	11.2 ± 4.4	12.8 ± 6.0	-	15.2 ± 6.0

TBZ = Tetrabenazine

The table below shows the mean (± SD) change scores with p-value of Total maximal Chorea Scores by treatment group from Day 5 to Day 3 and Day 3 to Baseline, as provided by the Sponsor. .

Treatment Assignment Group	Study Day	
	Day 3 to Baseline Visit	Day 5 to Baseline Visit
Group 1 (N=12)	5.3 ± 3.5; p-value = 0.000245*	5.3 ± 3.8; p-value = 0.000499†
Group 2 (N=12)	3.6 ± 2.8; p-value = 0.000951*	5.5 ± 3.4; p-value = 0.000159†
Group 3 (N=6)	1.7 ± 4.7; p-value = 0.426*	4.0 ± 3.0; p-value = 0.02†

Source: Table 14.2.6 in Section 14.2

* Within-group difference, Day 3 versus the Baseline Visit

† Within-group difference, Day 5 versus the Baseline Visit

Safety

There were no serious adverse events or deaths reported during this study. Six subjects experienced a total of 14 adverse events. Four of the participants were in Group 1 and were on placebo at the time that the AE occurred. All adverse events were mild or moderate, and all were considered by the investigator to be unrelated to study drug.

CONCLUSIONS:

The limitations of this study with respect to the clinical pharmacology evaluation include variable baseline exposure to TBZ, a small PK population with small numbers of subjects at a given dose, inconsistent dosing regimens, and errors in dosing and withdrawal in the clinical study.

Exposure (AUC) for the 25 mg BID dose (n=3) was generally what would have been expected based on Study 203,008 in healthy volunteers following similar dosing.

Co-administration of a CYP2D6 inhibitor did not appear to influence dose in the PK group. Ratios of α:β-HTBZ were less than 1.8 in subjects taking CYP2D6 inhibitors.

4.2.22 EFFECT OF TBZ ON QTc

EFFECT OF TETRABENAZINE ON QT AND QTC INTERVALS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, ACTIVE COMPARATOR, CROSSOVER STUDY IN HEALTHY ADULT VOLUNTEERS

Study Investigators and Site:

Protocol Number: TBZ 104,015

Note: A draft report of the PK data was submitted 12/9/05. An executive summary of the full study was submitted on December 23, 2005.

OBJECTIVES:

The primary objective was to assess whether administration of a single dose of TBZ (25 or 50 mg) has the potential to cause QTc prolongation in healthy male and female adults.

The secondary objective was to characterize the PK of TBZ and/or its metabolites α-HTBZ and β-HTBZ after administration of a single 25 mg or 50 mg dose of TBZ.

The exploratory objective was to investigate the PK/PD relationship between plasma concentrations of TBZ and/or α-HTBZ and β-HTBZ and its effect, if any, on cardiac repolarization.

FORMULATIONS:

Table 1. Products used in TBZ 104,015

	Batch No.	Exp. Date (Dates of Study)
Tetrabenazine 25 mg tablet	1MM	05/07 (2/8/05-7/13/05)
Moxifloxacin 400 mg tablet	5400GJT	(2/8/05-7/13/05)
Placebo	14481576	(2/8/05-7/13/05)

STUDY DESIGN:

This study was restricted randomized, double-blind, placebo, and active-controlled crossover design. There were 4 treatment periods: placebo, tetrabenazine 25 mg, tetrabenazine 50 mg and moxifloxacin 400 mg. During the study, the 25 mg dose of TBZ was always administered prior

to the 50 mg dose and moxifloxacin was always administered during the last treatment period. At study entry subjects were randomized to one of 3 possible sequences:

Placebo – TBZ 25 – TBZ 50 – Moxifloxacin
TBZ 25 – Placebo – TBZ 50 – Moxifloxacin
TBZ 25 – TBZ 50 – Placebo – Moxifloxacin

Each treatment period consisted of a 24-hour baseline period (Day 0), immediately followed by a 24-hour treatment period (Day 1). Each treatment period was separated from the next by 2 drug-free washout days (Days 2 and 3). The protocol specified that blood samples for PK analysis were to be collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 23 hours following dosing for determination of TBZ and α-HTBZ, and β-HTBZ in plasma.

Twelve-lead ECG data were digitally obtained using a continuous recording. With 24 hours of continuous recorded at Baseline (Day 0) and Treatment (Day 1). The ECG data were read by an experienced cardiologist in a central laboratory who was blinded to treatment, sequence, and time of recording. For both Baseline (Day 0) and Treatment (Day 1), triplicate ECGs were extracted from the flash card at 2-minute intervals at times immediately prior to each of the following pre-specified time points: predose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 23 hours post-dose. The PD population consisted of all subjects who received at a minimum, one of the 4 treatments and had sufficient Baseline (Day 0) ECGs to calculate QTcI, and had Treatment (Day 1) data to facilitate calculating a change from Baseline.

Healthy male and female subjects between the ages of 18 and 50 years (inclusive) were included in the study. Subjects were nonsmokers, with normal or clinically non-significant abnormalities in 12-lead ECG at screening; no medical history of cardiac disease; resting heart rate between 45 and 100 bpm, and calculated creatinine clearance greater than 50 ml/min; and on adequate contraception (that could include hormonal contraception) if female. Exclusion criteria included current depressive episode, history of or current significant severe allergy (anaphylaxis, angioneurotic edema), PR > 210 msec, QRS > 120 msec, and QTc > 450 msec, serum potassium,, sodium, calcium, or magnesium le el not within normal limits, consumption of any known hepatic or renal clearance altering agents for a period of 3 months prior to the first dose of study medication, use of any prescription medication within 30 days prior to Check-in, use of any non-prescription medications (including St. John's Wort) for 7 days prior to first dose administration, and excessive consumption of caffeinated coffee, tea, or chocolate.

ASSAY:

Plasma concentrations were measured using a validated LC/MS/MS method (— 1266/1).

Table 3. Performance of Analytical Method for TBZ 104,015

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
TBZ	LC/MS/MS	0.2-200 ng/ml	r > 0.989	0.2	0.5	9.5	3.9
					25.0	6.5	1.2
					100.0	6.6	-4.1
α- HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.985	0.5	1.0	9.5	2.8
					25.0	10.0	2.4
					100.0	7.0	-1.9
β-HTBZ	LC/MS/MS	0.5-200 ng/ml	r > 0.986	0.5	1.0	10.6	1.5
					25.0	9.3	2.6
					100.0	6.741	-1.4

Two calibration curves and duplicate QC samples were analyzed with each batch of study samples. (Batches 3, 6 19, 37, 40, 46 did not have did not have acceptable calibration standards at the highest concentration of 200 ng/ml and those standards were not included in the calibration line for TBZ. One batch (Batch 8) for α-HTBZ did not have acceptable calibration standards at 2 ng/ml and those standards were not included in the Batch 8 calibration curve). Study samples were to be stored –70° C or lower. Samples were analyzed within the period for which they are stable at –70° C. The performance of the assays for all analytes is acceptable.

RESULTS:

Demographics

A total of 51 subjects received at least 1 treatment and are included in the safety and PD analysis. Forty-two healthy volunteers completed the PK part of the study (21 males and 21 females). Demographics of all 51 subjects are shown in the table below.

Table 4. Demographics of Subjects Completing the Study

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
29 (18-49)	22 males 29 females	73 ± 13 kg (n=51) 83 ± 9 kg (male) 66 ± 10 kg (female)	Caucasian/Asian 1 Black 16 Caucasian 29 Hispanic 5

Two subjects (#181 and 198) were identified by genotype as poor metabolizers of CYP2D6. CYP2D6 genotype analysis was performed by ——— using PCR-based approaches. CYP2D6 alleles analyzed were *3, *4, *5, *6, *7, and *8. In addition, Asian subjects were tested for *2 and *10, and African American subjects were tested for *17.

Six subjects (#157, 174, 175, 181, 183, and 192) did not receive the 50 mg treatment and subjects #173 and #199 discontinued 3h and 2.5 h, respectively after administration of 50 mg.

Pharmacokinetics

TBZ concentrations were less than the LOQ for the majority of sampling times in most subjects. However, in some subjects TBZ was detectable for both doses, with concentrations up to approximately 2.39 ng/ml.

The mean plasma concentration time courses for α-HTBZ and β-HTBZ are shown in the figures below, as provided by the Sponsor. Pharmacokinetic parameters were determined using noncompartmental analysis and are summarized in the tables below, as provided by the Sponsor. The PK parameters are shown for all of the subjects, as well as for the 2 subjects identified as being CYP2D6 poor metabolizers.

Figure 1. Mean plasma concentration of α-HTBZ after oral administration of 25 mg and 50 mg TBZ in healthy volunteers

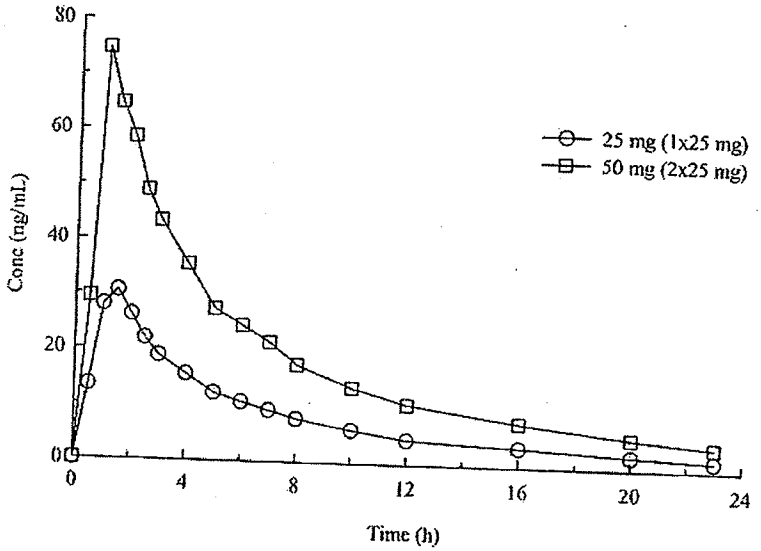


Figure 2. Mean plasma concentrations of β-HTBZ after oral administration of 25 mg and 50 mg TBZ in healthy volunteers.

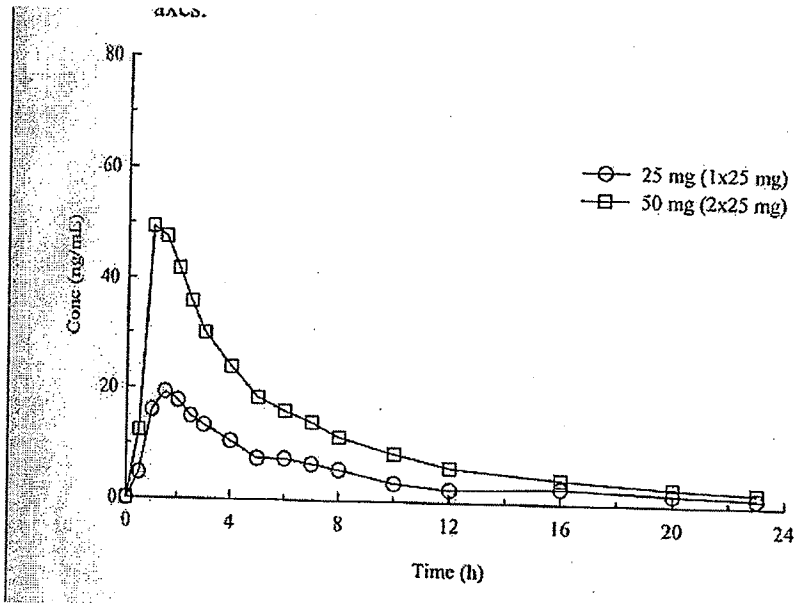


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Table 5. Summary of PK parameters for α-HTBZ and β-HTBZ in healthy volunteers after administration of 25 mg and 50 mg TBZ.

Panel 1
Summary of pharmacokinetic parameters for α-HTBZ for the population and for CYP2D6 poor metabolizers (Subjects 0181 and 0198)

Dose	Parameter	Mean ± SD (Range)	Subject 0181	Subject 0198
25 mg	C_{max} (ng/mL)	38.2 ± 17.9 (14.5 – 97.5)	40.1	60.9
	T_{max} (h)	1.50[1] (0.50 – 2.50)	1	1.5
	$AUC_{(0-t)}$ (h*ng/mL)	186 ± 104 (50.2 – 512)	398	414
	$AUC_{(inf)}$ (h*ng/mL)	214 ± 131 (53.7 – 593)	521	515
	$t_{½}$ (h)	6.26 ± 2.28 (2.58 – 11.6)	11.1	9.45
50 mg	C_{max} (ng/mL)	88.4 ± 42.7 (36.9 – 263)	—[2]	143
	T_{max} (h)	1.00[1] (0.50 – 4.00)	—[2]	1.5
	$AUC_{(0-t)}$ (h*ng/mL)	426 ± 224 (141 – 1,144)	—[2]	1,036
	$AUC_{(inf)}$ (h*ng/mL)	459 ± 264 (153 – 1,433)	—[2]	—[3]
	$t_{½(h)}$	6.49 ± 2.11 (3.67 – 11.2)	—[2]	—[3]

[1]Median (Range) for T_{max}.
[2]Subject 0181 did not receive the 50 mg Treatment.
[3]Parameter could not be estimated.

Panel 2
Summary of pharmacokinetic parameters for β-HTBZ for the population and for CYP2D6 poor metabolizers (Subjects 0181 and 0198)

Dose	Parameter	Mean ± SD (Range)	Subject 0181	Subject 0198
25 mg	C_{max} (ng/mL)	24.2 ± 17.3 (4.47 – 85.5)	85.5	60.9
	T_{max} (h)	1.50[1] (0.50 – 3.02)	3.02	2.00
	$AUC_{(0-t)}$ (h*ng/mL)	127 ± 210 (61.3 – 1,364)	1,364	629
	$AUC_{(inf)}$ (h*ng/mL)	161 ± 314 (9.82 – 1,882)	1,882	1,091
	t½ (h)	4.23 ± 2.88 (1.21 – 19.8)	9.95	19.8
50 mg	C_{max} (ng/mL)	61.4 ± 36.2 (5.65 – 175)	—[2]	151
	T_{max} (h)	1.00[1] (0.50 – 3.00)	—[2]	1.5
	$AUC_{(0-t)}$ (h*ng/mL)	274 ± 274 (38.1 – 1,429)	—[2]	1,429
	$AUC_{(inf)}$ (h*ng/mL)	326 ± 404 (43.9 – 2,334)	—[2]	2,334
	t½ (h)	4.90 ± 2.60 (2.35 – 16.3)	—[2]	16.5

[1]Median (Range) for T_{max}.

[2]Subject 0181 did not receive the 50 mg Treatment.

The PK results for the 25 mg dose are generally in agreement with those reported in other studies including the BE study TBZ 104,012, food effect study and Study 104,012 the repeat dose prolactin study, although the Cmax for β-HTBZ in the present study is higher than previously reported. (Notably, from Efficacy study103,004 in which sparse sampling was performed, the highest recorded concentration for α-HTBZ was — ng/ml and the highest recorded concentration of β-HTBZ was — ng/ml. These concentrations were in a subject taking 100 mg/day, and were observed approximately 1 hour after the dose.

Neither of the CYP2D6 poor metabolizers had significant concentrations of TBZ in the plasma. Subject 181 had no detectable TBZ in the plasma, and concentrations for Subject 198 were less than or equal to approximately 0.5 ng/ml.

For the CYP2D6 poor metabolizers (both female), for α-HTBZ the AUC and half-life were near the top of the range, although Cmax was in the middle of the range. For β -HTBZ in Subject 181 the PK parameters Cmax and AUC were at the top of the range, with half-life in the middle of the range. For β -HTBZ for subject 198, Cmax and AUC were mid-range, with half-life the highest of the group for the 25 mg dose. For β -HTBZ for the 50 mg dose, AUC and half-life were highest, and Cmax was in the upper part of the range. It should be noted, that the time

course for evaluation of plasma concentrations (23 hours post-dose) was not sufficient for accurate evaluation of elimination half-life for these subjects. However, with half-lives of approximately 10-20 hours, as reported for the PMs, accumulation of approximately 2- to 3-fold would be expected for q 12 hour dosing and accumulation of up to 4-fold for q8h dosing. The ratio of α-HTBZ: β –HTBZ was ≤ 1 (range 0.29-1.0) in the two PMs for Cmax and AUC.

Dose Proportionality

For α-HTBZ, a doubling in the dose led to an approximate 2.3-fold increase in Cmax and AUCt and a 2.1-fold increase in AUCinf. For β-HTBZ a doubling of the dose led to an approximate 2.5-fold increase in Cmax and an approximate 2.2 fold increase in AUCt and a 2 fold increase in AUCinf. Thus there is a slightly greater than dose-proportional increase in exposure with an increase in dose when arithmetic means are compared.

The following table shows the results of the statistical analysis of the comparison of the 25 mg dose and the 50 mg dose (dose normalized), as provided by the Sponsor. In contrast to the comparison of arithmetic means, an assessment of the geometric means shows a less than dose proportional increase in exposure with an increase in dose. The differences in these 2 findings may be due to the large variability in the PK that has been observed.

Assay	Parameter	Geometric mean		Geometric Mean Ratio	90% CI
		50 mg*	25 mg		
α-HTBZ	Cmax (ng/ml)	33.15	42.41	78.15	0.56-1.09
	AUC_{0-t} (ng*h/ml)	162.07	187.95	86.23	0.74-1.00
	AUC_{inf}(ng*h/ml)	174.97	208.51	83.91	0.73-0.96
β-HTBZ	Cmax (ng/ml)	19.96	25.05	79.66	0.54-1.17
	AUC_{0-t} (ng*h/ml)	80.79	84.49	95.62	0.74-1.23
	AUC_{inf}(ng*h/ml)	84.52	93.16	90.73	0.71-1.14

* Values for the 50 mg dose were divided by 2 prior to the analysis.

Stereoselectivity in the pharmacokinetics of the HTBZ enantiomers was observed, with exposure to α-HTBZ greater than exposure to β-HTBZ. The mean Cmax and AUC_{0-t} for α-HTBZ were approximately 1.5x greater than for β-HTBZ. AUCinf was approximately 1.3 fold greater for α-HTBZ than for β-HTBZ. The elimination rate constant was approximately 2-fold greater for β-HTBZ than for α-HTBZ. The mean elimination half-life for α -HTBZ was approximately 1.3-1.5x longer than for β -HTBZ. Variability in the stereoselectivity is described, with AUCinf ratios ranging form 0.3 to 5.5, an approximate 18 fold range. (As discussed above, for PMs the ratios of α-HTBZ: β-HTBZ were ≤ 1 for CYP2D6 PMs, suggesting that there may be a role for CYP2D6 in stereoselective formation of HTBZ.

Pharmacodynamics: QT Evaluation

The Sponsor's primary analysis was based on QTcI where QTcI = QT/RR*. This was an individually defined QT correction using least squares regression of log-transformed QT on log-

transformed RR using the baseline data (Baseline Day 0) and Treatment (Day 1) predose from all Treatment periods for each subject. Up to 216 points were used in the estimation of the correction factor. This analysis assumed no relationship between QTc and RR. The slope of the estimated regression equation was the exponent x for RR required to calculate a corrected QT all of that subjects ECGs.

Other corrections evaluated as secondary variables were QTcF = $\frac{QT}{\sqrt[3]{RR}}$ and QTcB = $\frac{QT}{\sqrt{RR}}$.

Analysis of Central Tendency

To calculate time-matched change from baseline, baseline was defined as the average of triplicate ECGs at each time point on Day 0 (predose up to 23 hours). The time-matched change from baseline is the difference between the average of the triplicate on-treatment ECG intervals at a given time point on Day 1 and the corresponding baseline (Day 0) for that time point. The primary analysis of central tendency used the maximum time matched change from baseline of QTc interval between drug and placebo over the collection period. For all inference on the measures of central tendency, treatment comparisons were performed for maximum time-matched mean change on Day 1. For moxifloxacin minus placebo and for each dose of TBZ minus placebo, the mean for each time is calculated. The results for maximum mean time-matched, placebo adjusted change from baseline for QTcI and for QTcF are shown below.

Summary of the Maximum Mean ΔΔ QTcI by Regimen

Regimen	Time (h)	N	Mean (msec)	Upper 95% CI
Moxifloxacin 400 mg	2.5		12.5	15.3
TBZ 25 mg	2.5		3.6	6.2
TBZ 50 mg	2.5		7.7	10.4

Summary of the Maximum Mean ΔΔ QTcF by Regimen

Regimen	Time (h)	N	Mean (msec)	Upper 95% CI
Moxifloxacin 400 mg	2.5		11.9	14.7
TBZ 25 mg	2.5		3.4	6.0
TBZ 50 mg	2.5		7.3	10.0

A positive signal was seen with moxifloxacin, indicating the sensitivity of the assay.
TBZ 50 mg results in a mean change in QTc of approximately 7 msec and a change of 10 msec cannot be excluded based on the 95% CI.

Categorical Analyses

Treatment Group	Correction	Maximum post-dose QTc (msec), number of subjects		
		>450 - ≤ 480	>480 - ≤ 500	> 500
Placebo	QTcB	4 (8.9)	0 (0)	0 (0)
	QTcF	2 (4.4)	0 (0)	0 (0)
	QTcI	2 (4.4)	0 (0)	0 (0)
TBZ 25 mg	QTcB	8 (16.0)	0 (0)	0 (0)
	QTcF	4 (8.0)	0 (0)	0 (0)
	QTcI	4 (8.0)	0 (0)	0 (0)
TBZ 50 mg	QTcB	7 (15.9)	1 (2.3)	0 (0)
	QTcF	4 (9.1)	0 (0)	0 (0)
	QTcI	4 (9.1)	0 (0)	0 (0)
Moxifloxacin 400 mg	QTcB	9 (22.0)	0 (0)	0 (0)
	QTcF	2 (4.9)	0 (0)	0 (0)
	QTcI	4 (9.8)	0 (0)	0 (0)

Treatment Group	Correction	Maximum change in QTc (msec), number of subjects (%)	
		>30 - < 60	≥ 60
Placebo	QTcB	13 (28.9)	1 (2.2)
	QTcF	3 (6.7)	0 (0)
	QTcI	1 (2.2)	0 (0)
TBZ 25 mg	QTcB	12 (24.0)	0 (0)
	QTcF	3 (6.0)	0 (0)
	QTcI	3 (6.0)	0 (0)
TBZ 50 mg	QTcB	14 (31.8)	1 (2.3)
	QTcF	5 (11.4)	1 (2.3)
	QTcI	5 (11.4)	0 (0)
Moxifloxacin 400 mg	QTcB	19 (46.3)	0 (0.0)
	QTcF	5 (12.2)	0 (0)
	QTcI	4 (9.8)	0 (0)

There were no post-dose QTc values of > 500 msec. A change in QTcB > 480 msec for QTcB was seen in 1 subject for TBZ 50 mg, but this was not seen for the other corrections. As measured by either QTcF or QTcI, TBZ at either the 25 mg or 50 mg dose had approximately twice as many subjects with QTc >450 - ≤ 480 than did placebo.

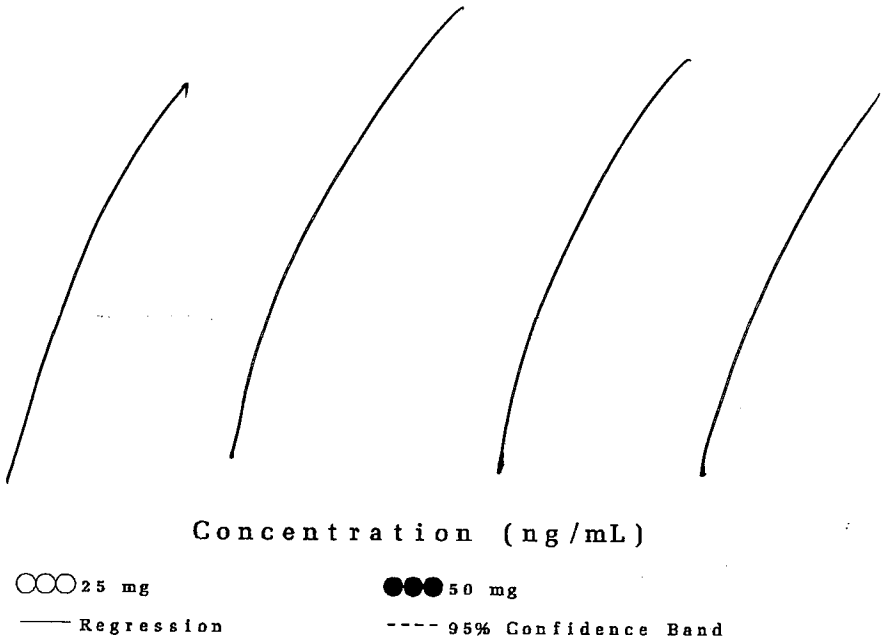
The only change in QTc of ≥ 60 msec was in 1 subject after administration of TBZ 50 mg. The percent of patients with change in QTc of >30 - < 60 msec was slightly greater for TBZ 50 mg than for either TBZ 25 mg or placebo.

The CYP2D6 poor metabolizers were not outliers in this analysis.

Exposure-Response

The PK-PD relationship was modeled by the Sponsor using regression of individual change from baseline QTc interval vs plasma concentration of α-, β-, and total (α- plus β)-HTBZ at each time point. The 95% CI of the estimate of the slope of the relationship for β-HTBZ did not include zero (0.246, 1.07 for QTcI) indicating a relationship between plasma concentration and change from baseline QTcI. (A similar relationship was seen for QTcF. This relationship is shown in the Figure below, as provided by the Sponsor. The Sponsor is further investigating this relationship as of 12/23/05. There was no significant relationship between total metabolite concentration or α-HTBZ and change in QTcI from baseline.

Figure 6.7 Scatterplot of Change from Baseline QTcI versus Beta-H Tetrabenazine Plasma Concentration on Day 1



Note: Regression line is based on repeated measures model for change in QTc predicted by Log analyte concentration and baseline QTc (see Table 20). BLQ samples are excluded.
Equation: Mean Change in QTc = 257.31 + 0.8560*Log(Concentration) + -0.8420*Baseline Interval

Safety

Safety data will be reviewed in detail by the medical officer. The incidence of treatment emergent adverse events was as follows: Placebo (26.7%), TBZ 25 mg (42%), TBZ 50 mg (56.8%), and moxifloxacin (63.4%). Adverse events in either TBZ 25 mg or 50 mg dosing groups occurring at least twice as frequently as placebo included dizziness, contact dermatitis, somnolence, headache, nausea (in the 50 mg group), as well as anxiety, irritability, restlessness, and palpitations in the 50 mg TBZ group.

There were no deaths or serious adverse events reported. Three subjects were withdrawn from the study because of adverse events that resolved without sequelae. They were as follows. Subject 175 experienced accelerated junctional rhythm beginning 3 hours and 50 minutes following administration of TBZ 25 mg. Subject 183 had a chest contusion prior to receiving TBZ 50 mg and study drug was not administered. This was not thought to be related to study medication. Subject 199 experienced continuous restlessness starting 1 hour and 40 minutes following administration of TBZ 50 mg that persisted for 20 hours and 10 minutes and resolved without therapy. She also experienced irritability and jitteriness. These resolved and her adverse events were thought to be related to study treatment.

Adverse events in the CYP2D6 PMs were as follows. Subject 181 experienced intermittent postural dizziness of moderate intensity following administration of TBZ 25 mg. The dizziness lasted for 10 hours and 45 minutes. The subject was put in the Trendelberg position. The same subject also experienced drowsiness of moderate intensity following administration of TBZ 25 mg. The drowsiness lasted for 11 hours and 30 minutes. Subject 198 experienced continuous headache of moderate intensity 4 days following administration of TBZ 50 mg that lasted for 4 hours and 30 minutes.

CONCLUSIONS:

PK

5. Increasing the dose of TBZ from 25 to 50 mg led to a slightly more than dose proportional increase in exposure to α-HTBZ and β-HTBZ.
6. TBZ was detectable in the plasma of several individuals in concentrations up to approximately 2.39 ng/ml.
7. The role of CYP2D6 in the PK was difficult to ascertain since only 2 subjects were included, although the exposure for α-HTBZ and β-HTBZ in those 2 subjects was at the upper end of the ranges (or the highest), and the half-life was at least twice as long (approximately 10-20 hours). CYP2D6 did not appear to affect exposure to parent TBZ.
8. The ratios of α-HTBZ: β-HTBZ were ≤ 1 for CYP2D6 PMs compared to a range of 0.3 to 5.5 in all subjects, suggesting that there may be a role for CYP2D6 in stereoselective formation of HTBZ.

QT

1. The 50 dose of TBZ in the present study was higher than any planned single dose to be given clinically. The range of exposures exceeded the highest concentrations observed with sparse sampling in the efficacy studies (with some of the samples within approximately 1 hour of dosing). However, the means from the QT study were lower than the highest observed concentrations in the clinical studies.
2. Analysis of central tendency resulted in a maximum mean time-matched, placebo adjusted changed from baseline for QTcI and for QTcF of approximately 7 msec with 90% CI that could not exclude a change of 10 msec. A slight relationship between change in QTcI or QTcF and concentration of β-HTBZ is suggested. Categorical

analysis showed that the absolute QTc did not surpass the 500 ms threshold of concern. The relationship between the observed increase in QTc interval and proarrhythmic risk is not clear.

3. The exposure to TBZ was significantly increased in hepatic impairment (Study TBZ 203,010), and the effect of TBZ on QT interval has not been evaluated.

(Note: The Clinical Safety Reviewer identified several patients with QTc changes from baseline of **>30 - < 60**msec in the ISS, and one subject with a change in QTcF of 62.4 msec. No patient had on-treatment QTc exceeding 450 msec).

4.2.23 DISSOLUTION METHOD DEVELOPMENT

The proposed dissolution method and specifications in the present NDA (21-894) were developed using the following lot numbers:

Strength	**Lot Number**	
12.5 mg	6573804	Stability and Clinical Trial
	3986988	Stability and Clinical Trial?
	11378272	Stability and Clinical Trial?
25 mg	1 MM	Stability and Phase I BE study and QT study
	2 MM	Stability
	1 VV	Stability
	2 VV	Stability

Rationale for Selection of Dissolution Method and Media TBZ tablets

Solubility Profile

The Solubility profile was provided in the submission of January 18, 2006. Solubility decreased as the pH increased, as shown in the table below.

pH of Solution	Concentration of Tetrabenazine (tetrabenazine/pH adjusted water)	*USP* Solubility Classification
2		
3		
4		
6		
8		
10		
12		

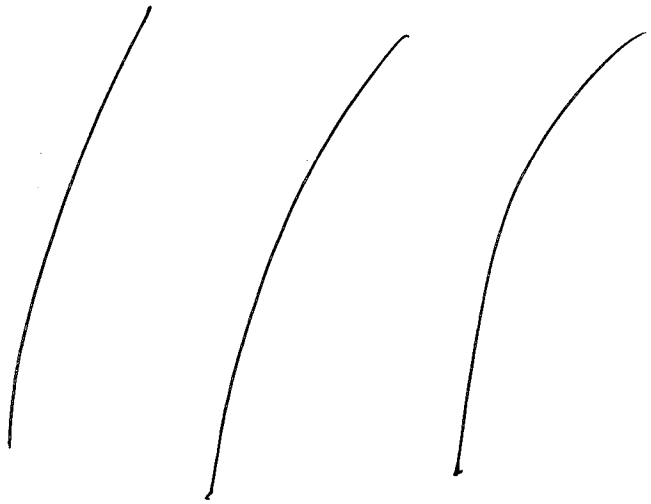
Dissolution in Multiple Media

Three dissolution media (0.1 M HCl, were evaluated in developing the dissolution methodology. These media were evaluated using the 12.5 mg tablets batch number 6573804 and 25 mg tablets Lot 1MM, with the test performed in duplicate on 6 tablets from each strength. The method was performed in 900 ml using USP Apparatus II at 50 rpm at a temperature of 37° C, with sampling at 5, 10, 15, 20, 30, 45, and 60 minutes using filters and discarding the first 5 ml. For the 0.1 M HCl, the method was modified to use 100 rpm. The results are summarized in the table below, as provided by the Sponsor.

0.1M HCl – modified to 100rpm.

Label claim	5 min / %	10 min / %	15 min / %	20 min / %	30 min / %	45 min / %	60 min / %
12.5 mg (Mean n=12)	114.6	111.7	110.5	109.4	109.4	109.2	110.7
CV%	2.9	2.3	2.9	2.4	2.9	3.5	4.7

Label claim	5 min / %	10 min / %	15 min / %	20 min / %	30 min / %	45 min / %	60 min / %
25.0 mg	102.8	104.9	103.6	102.6	101.7	101.5	101.3
CV%	3.8	2.3	2.1	2.1	2.3	2.9	2.9



Graphs showing the dissolution results performed in different media are below, as provided by the Sponsor.

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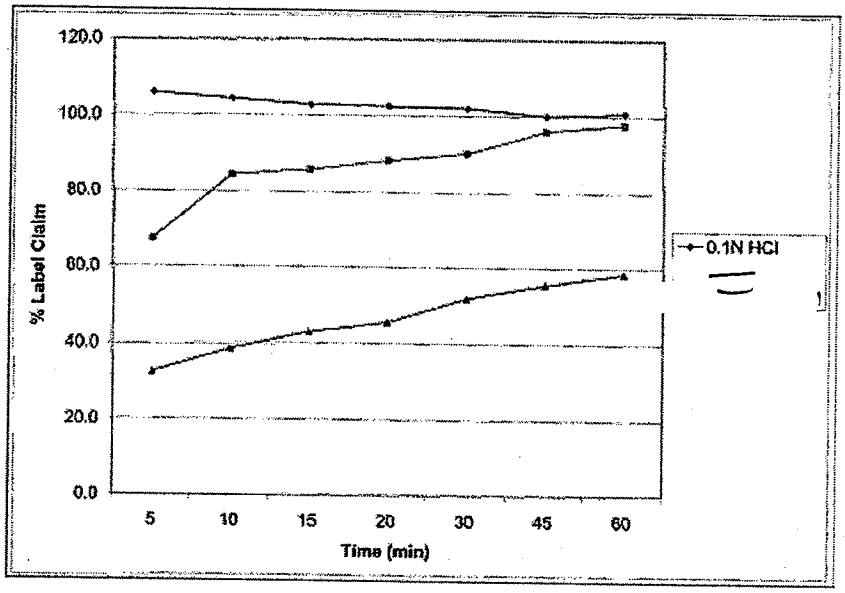

Figure 3.2.P.5-4. Graph of 12.5-mg Tetrabenazine Tablets in Different Dissolution Media

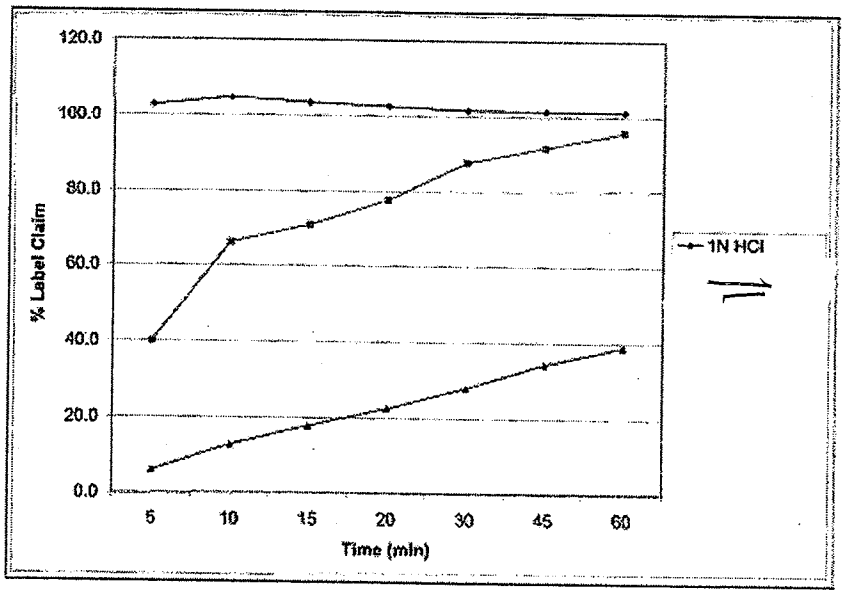

Figure 3.2.P.5-5. Graph of 25-mg Tetrabenazine Tablets in Different Dissolution Media

Ability of the Proposed Dissolution Method to Discriminate

This has not been demonstrated.

Dissolution Using Proposed Methodology

The method was developed, according to the data submitted by the Sponsor, with USP apparatus II at 100 rpm and proposes a method using 50 rpm. The rotation speed used to generate the following data was 50 rpm according to Section 3.2.(.5-2 of the submission that provides the method for determining dissolution profiles in the proposed media. A clarification was requested from the Sponsor on 1/24/06 to confirm that this was performed at 50 rpm, whereas the method was apparently developed at 100 rpm, but as of 2/14/06 there has been no response.

The following Tables (as provided by the Sponsor) show dissolution results of the 12.5 mg strength and 25 mg strength tablets using USP apparatus 2 (paddles), 0.1 N HCl, 9000 ml. The rotation speed was 50 rpm based on the Analytical Procedures listed in Section 3.2.P.5-2 in the original submission. The data are from the Stability Data.

Table 1. Dissolution Data for 12.5-mg Tetrabenazine Tablets

Product: 12.5-mg Tetrabenazine Tablets		Time Point: Initial		
		Result (Batch)		
Test	Specification	3986988	6573804	11378272
Dissolution: 5 minutes	For information only	99%	101%	85%
10 minutes	For information only	100%	103%	97%
15 minutes	For information only	101%	103%	97%
20 minutes	—	100%	103%	97%
30 minutes	For information only	101%	103%	97%

Table 2. Dissolution Data for 25-mg Tetrabenazine Tablets

Product: 25-mg Tetrabenazine Tablets		Time Point: Initial			
		Result (Batch)			
Test	Specification	1 MM	2 MM	1 VV	2 VV
Dissolution: 5 minutes	For information only	62%	36%	50%	79%
10 minutes	For information only	98%	78%	95%	97%
15 minutes	For information only	99%	97%	98%	98%
20 minutes	—	98%	99%	97%	98%
30 minutes	For information only	99%	98%	97%	97%

Proposed Dissolution Method and Specifications

The Sponsor has proposed the following dissolution method and specifications for tetrabenazine:

Apparatus: USP Apparatus 2 (Paddles)
Medium: 0.1 M HCl
Volume: 900 ml
Rotation Speed: 50 rpm
Specification: ≥ — at 20 minutes.

The Office of New Drug Chemistry has recommended changing the specification to ≥ — (Q) in 30 minutes (with the specification o — based on ICH Q6 and the 30 minute time point to account for possible accumulation of the drug at time points beyond 20 minutes).

RECOMMENDATION:

It is not clear whether the submitted data for dissolution using the proposed media in apparatus II were generated at 50 rpm or 100rpm. The Sponsor has been requested to clarify this, but as of 3/2/06 it has not been clarified.

The sponsor has not provided data to show that the method can discriminate poorly performing tablets.

The Office of Clinical Pharmacology and Biopharmaceutics finds that the proposed dissolution method of USP Apparatus 2 (paddles) at 50 rpm and 900 ml of 0.1 N HCl dissolution media, and the dissolution specification of NLT —(Q) at 30 minutes could be acceptable pending resolution of the 2 issues identified above (clarification of rotation speed in the data submitted and demonstration of discriminatory ability).

4.2.24 POPULATION PK STUDY

POPULATION PHARMACOKINETIC ANALYSIS OF TETRABENAZINE

Study Investigators and Site:

Protocol Number:

OBJECTIVES:

To evaluate PK of TBZ and its two primary metabolites.

To determine which covariates influence the distribution and elimination of TBZ and the formation, distribution, and elimination of the two primary metabolites.

STUDY DESIGN:

Data from the following 6 studies were analyzed:

TBZ 103,003 (Food Effect)
TBZ 104,012 (BE of 12.5 mg and 25 mg)
TBZ 203,008 (Single and Repeat Dose in Healthy Male Volunteers)
TBZ 203,009 (P-glycoprotein Study)
TBZ 103,005 (Randomized Withdrawal in Patients)
TBZ 103,004 (Randomized, Double-Blind, Placebo Controlled Study in HD)

There were 73 healthy subjects in 4 studies and 59 patients in 2 studies.

Demographics are shown in the table below, as provided by the Sponsor.

Table 7. Demographic data (mean ± SD, range in parentheses, except for gender).

Study	N	Age (yrs)	Weight (kg)	Gender (male/female)
TBZ 103,003	25	27.5±7.5 (19-43)	70.8±9.0 (55.4-86.4)	14/11
TBZ 104,012	23	27.3±6.8 (18-44)	70.1±11.6 (50-102)	11/12
TBZ 203,008	13	27.7±5.3 (18-35)	73.4±7.4 (58-88)	13/0
TBZ 203,009	12	28.7±6.3 (21-42)	63.7±10.1 (47-79)	6/6
TBZ 103,005	10	60.7±11.7 (39-75)	74.9±14.7 (37.7-88.6.6)	7/3
TBZ 103,004	49	50.2±12.6 (25-77)	69.7±16.1 (43.4-114.2)	20/29
All	132	38.6±15.7 (18-77)	70.2±12.9 (37.7-114.2)	71/61

Creatinine clearance (estimated based on the Cockcroft-Gault formula) in efficacy study 103,005 ranged from 56-176.95 ml/min , with all but one value > 71 ml/min, 5 subjects with 50-80 ml/min (mild renal impairment), and 5 subjects with creatinine clearance > 80 ml/min (normal). In Study 103,004 there were 16 subjects with creatinine clearance from > 57 ml/min -80 ml/min, and 33 subjects had creatinine clearance values > 80 ml/min. Creatinine clearance in the Phase I studies was > 74.27.

For the two studies in patients, information about the nominal dosing regimen consisted only of the number and magnitude of doses per day (i.e. specific times were known only for a limited number of doses). It was assumed that a BID dosing regimen represented a dose at 8AM and another at 6PM, and for a TID dosing regimen, doses were presumed to have been administered at 8AM, noon, and 6PM. It is stated that these values were confirmed by the Sponsor. (However, a review of the study reports suggests that these dosing intervals were not necessarily adhered to during periods in which the PK data were collected, and several subjects were deleted from this analysis due to such inconsistencies).

Data analysis was performed using NONMEM. PK parameters were calculated from plasma concentrations of TBZ and of α- and β-HTBZ that were assumed to be its two primary metabolites. The role of covariates was evaluated through their relationship to the post hoc parameters that were estimated using NONMEM. Covariates included age, weight, height, healthy subjects vs patients, race, hematocrit, SGPT, SGOT, alkaline phosphatase, and creatinine clearance.

RESULTS:

A 2-compartment model was used to describe and quantify the PK characteristics of TBZ and α- and β-HTBZ.

Two covariates showed significant statistical relationships with PK parameters: 1) age and 2) patient vs subject. More rapid absorption and decreased clearance is predicted with increasing age. However, the other covariate that showed a statistical relationship with the PK parameters was patients vs subjects. The four studies in healthy subjects used only younger subjects (maximum age 44 years), whereas the studies in patients included elderly subjects. Thus some of the effects attributed to age may results from status (patient vs healthy subject).

The Sponsor reports that there was no evidence that hepatic or renal function affected the PK of TBZ or α- or β-HTBZ, but states that this finding must be considered with caution because none of the subjects had significant hepatic or renal disease. In fact, evaluation of the hepatic impairment study (not included in the POP PK analysis) suggests a significant effect of hepatic disease on the PK of TBZ, and the mechanism for this finding has not been explained.

There was no evidence that PK differs between women and men.

The number of non-Caucasian subjects was insufficient to permit statistical comparisons of the effects of race on PK.

CONCLUSIONS:

The data available to contribute to the population PK analysis was deficient in several ways (including little PK data in patients, age of healthy subjects vs age of patients, assumptions about the PK of TBZ and its metabolism, and lack of substantial numbers of subjects in subpopulations including age, race, renal or hepatic disease). In addition, concomitant medications were not considered as covariates, although there may be a role for CYP2D6 (and CYP2D6 inhibitors) in stereoselective formation or elimination of TBZ metabolites. Because of this, the population PK

analysis does not contribute substantially to an understanding of the clinical pharmacology of TBZ.

4.3 Consult Reviews (Including Pharmacometric Reviews)

There were no consults in the present OCPB review.

4.4 Cover Sheet and OCPB Filing/Review Form

4.4.1 Office of Clinical Pharmacology and Biopharmaceutics

5 New Drug Application Filing and Review Form

5.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	**21-894**	**Brand Name**	**Xenazine**
OCPB Division (I, II, III)	**DPE-I**	**Generic Name**	**Tetrabenazine**
Medical Division	**HFD-120**	**Drug Class**	**Huntington's Disease; Monoamine depletor**
OCPB Reviewer	**Sally Usdin Yasuda, MS, PharmD**	**Indication(s)**	**Chorea associated with Huntington's disease**
OCPB Team Leader	**Ramana Uppoor, PhD**	**Dosage Form**	**Tablets 12.5 mg 25 mg**
		Dosing Regimen	**12.5 mg – 100 mg/day (given as divided doses, generally tid)**
Date of Submission	**9/23/05**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	***2/5/06***	**Sponsor**	**Prestwick Pharmaceuticals, Inc.**
PDUFA Due Date	**3/26/06**	**Priority Classification**	**Priority NDA**
Division Due Date	**2/19/06**		

Clin. Pharm. and Biopharm. Information

Summary: This priority NDA is for an NME in the United States, although it has been available for treatment of chorea in the UK since 1971 and is registered in several other countries. A bioequivalence study (TBZ 104,012) compared the two strengths of tablets, and the effect of food on the highest strength tablet has been evaluated (TBZ 103,003). Dose proportionality of single doses up to 50 mg has been studied and multiple dosing (5 days) with 25 mg has been evaluated in healthy volunteers (1700114). These studies evaluated only the concentrations of the metabolites α- and β-HTBZ (or total HTBZ) as the concentrations of TBZ were below the limit of detection. The α-enantiomer of the metabolite as well as the parent compound (but not β-HTBZ) appear to be active at the presumed site of action (VMAT2). A hepatic impairment study has also been performed. Two pivotal clinical efficacy studies have been submitted. According to the summary, the tablets used in the Prestwick-sponsored development plan are the to-be-marketed tablets.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			It would be helpful to have labeling as a word document

Reference Bioanalytical and Analytical Methods	X	3	6	
I. Clinical Pharmacology				
Mass balance:	X	1	2	
Isozyme characterization:	X	2	2	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
5.2 Healthy Volunteers-				
single dose:	X	5	6	
multiple dose:	X	3	3	3 days and 5 days
5.2.1 *Patients-*				
single dose:	-	-	-	
multiple dose:	X	2	2	Trough samples in Phase III efficacy studies as well as more extensive PK in 10 subjects in Phase III.
Dose proportionality -				
fasting / non-fasting single dose:	X	1	2	Combined from 2 different groups of subjects; only evaluated 12.5-50mg; also evaluated across studies
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	X	1	1	Digoxin (P-glycoprotein)
In-vitro:	X	1	1	
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	See Pop PK and study reviews
pediatrics:	-	-	-	
geriatrics:	-	-	-	See Pop PK
renal impairment:	-	-	-	
hepatic impairment:	X	1	1	
PD:				
Phase 2:	-	-	-	
Phase 3:	X	5	2	2 pivotal clinical efficacy studies titrated to optimal dose; endpoint was total chorea score (Item 12 of UHDRS); 2 open label long term extension studies; 1 open label dose-titration study (Investigator IND)
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2	2	Prolactin study; prolactin and other hormones
Phase 3 clinical trial:	X	2	2	2 Prospective, placebo-controlled efficacy studies
Population Analyses -				
Data rich:	-	-		Looked at PK in terms of gender and age

Data sparse:	X	1	1	Combined Phase I (data rich) studies with 1 study in 49 patients that had 1-2 time points per patient for blood draws and 1 study with about 18 samples from each of 10 patients receiving various doses; Sponsor reports age effect but subject vs patient was significant covariate (healthy volunteers ≤45 y.o.).
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	Not done
Relative bioavailability -				Not done
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	1	1	Food effect on highest strength
Dissolution:	X	1	1	
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-		
BCS class	-			Reviewed based on available data
III. Other CPB Studies				PET studies in literature reviewed by Sponsor
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			
Total Number of Studies		22	23	
Filability and QBR comments				

5.2.1.1	"X" if yes	*Comments*
5.2.1.2 **Application filable ?**	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
5.2.1.3 **Comments sent to firm ?** 5.2.1.4		Comments have been sent to firm (or attachment included). FDA letter date if applicable. Please forward to sponsor : We have attached a set of comments to the Sponsor regarding data presentation from specific studies. Please send and ask the Sponsor to provide this information by December 5. In addition, the sponsor has performed a mass balance study that has not been included in this submission, but would most likely be helpful in the review of the NDA. Please ask the Sponsor to submit this ASAP.
QBR questions (key issues to be considered)	What information is available that contributes to assessment of clinical pharmacology/dose response? Are the bioanalytical methods adequate to assess concentrations? Have the pharmacokinetics been adequately characterized to support safety and efficacy? Have appropriate in vivo drug interaction studies been done based on results of in vitro drug metabolism studies? Do the dissolution conditions and specifications assure in vivo performance and quality of the product?	
Other comments or information not included above	Comments to the Project Manager:	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-894, HFD-850(Electronic Entry or Lee), HFD-120(Wheelous), HFD-860 (R. Uppoor, M. Mehta)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sally Yasuda
3/6/2006 02:50:06 PM
BIOPHARMACEUTICS

Mehul Mehta
3/7/2006 11:17:25 AM
BIOPHARMACEUTICS