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APPLICATION NUMBER:

NDA 21-894

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA #	021894 (protocol submitted by e-mail on 4/24/2008)
Sponsor:	Prestwick Pharmaceuticals, Inc.
Drugs:	Tetrabenazine, α -Dihydrotetrabenazine and β -Dihydrotetrabenazine
Proposed Indication:	Chorea associated with Huntington's disease
Material Submitted:	New Protocol
Correspondence Date:	4/24/2008
Reviewer:	Sripal R. Mada, Ph.D.
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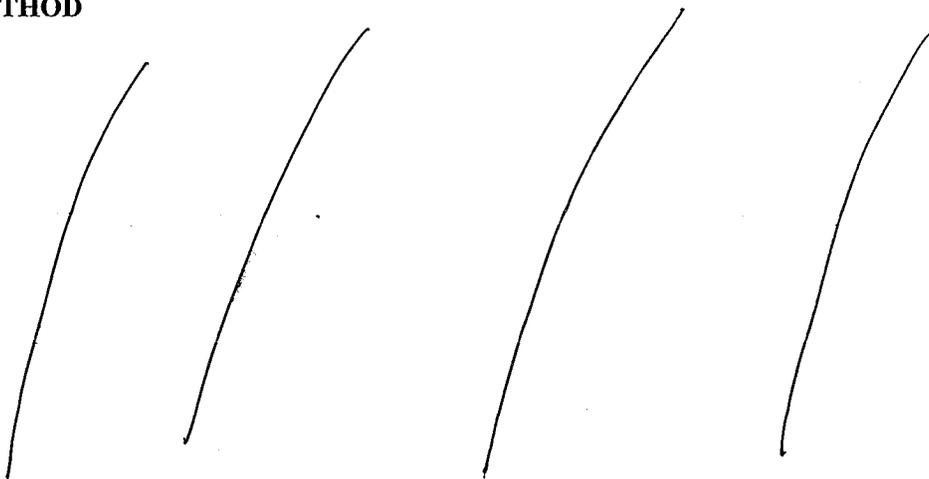
Pharmacological Class: Selective, centrally-acting monoamine depletor

Proposed Indication: **Chorea associated with Huntington's disease**

This protocol was submitted based on the agency recommendation dated 12/26/2007 from Clinical Pharmacology review that an *in vitro* metabolism study should be performed to characterize the inhibitory effect of tetrabenazine, α -dihydrotetrabenazine and β -dihydrotetrabenazine on CYP2B6. The results of this study will guide the need for further *in vivo* drug-drug interaction studies.

Objective: To study the inhibition effect of tetrabenazine, α -dihydrotetrabenazine, and β -dihydrotetrabenazine on CYP2B6.

METHOD



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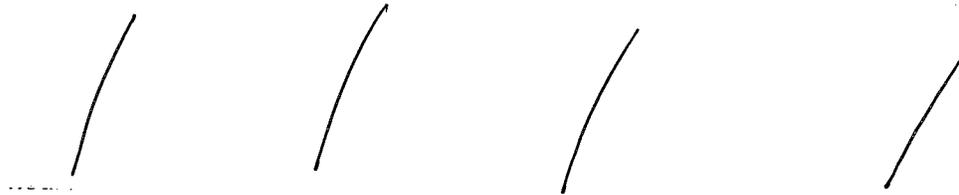
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Executive Summary

Tetrabenazine is being proposed for the treatment of chorea associated with Huntington's disease. Sponsor conducted 2 double-blind, controlled clinical trials – TBZ 103,004 and TBZ 103,005. The sponsor also conducted 2 additional open-label, uncontrolled studies, Studies TBZ 103,007 and TBZ103,006. These are extensions of studies TBZ 103,004 and TBZ103,005. The following are the key inferences from the Pharmacometrics analyses of these data:

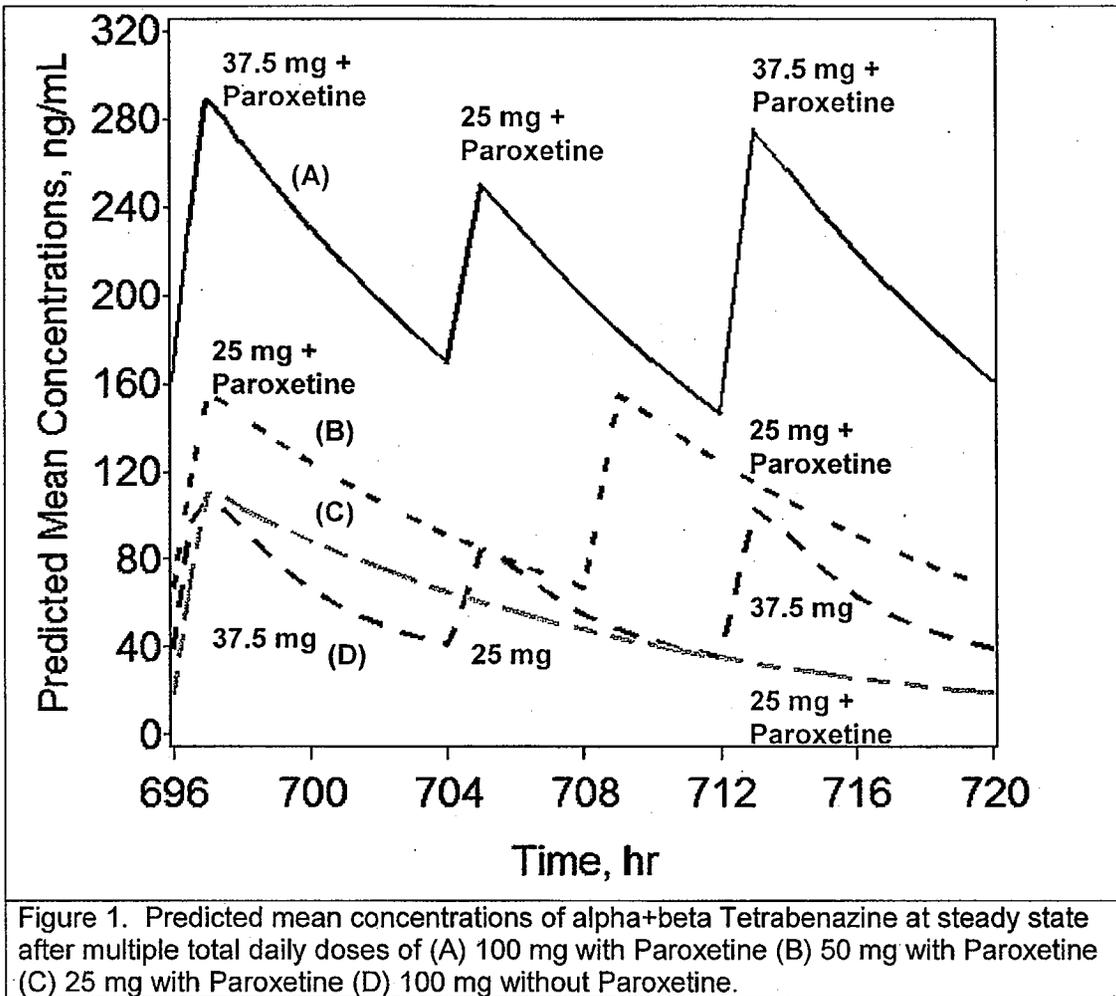
- In TBZ 103, 004 the primary endpoint is met and the trial is positive. In addition, there is a clear dose-response relationship for the Chorea scores confirming that Tetrabenazine significantly affects Chorea scores.
- About 40% of patients required 100 mg dose by week 12 for optimal benefit, in Study TBZ 103,004.
- Patients with higher baseline symptoms had greater lowering of Chorea score. The drug effect was found to be proportional to baseline Chorea scores.
- The trend in Changes in the Functional Assessment, Cognitive Scores, Sedative Scores with dose, if any, is not obvious.

Labeling Comments



Reviewer's Comments: This proposal is based on the simulations conducted by the reviewer. Shown are the predicted mean concentrations (sum of alpha and beta tetrabenazine) at steady state after:

- (A) 100 mg total daily dose + Paroxetine
 - (B) 50 mg total daily dose + Paroxetine
 - (C) 25 mg total daily dose+ Paroxetine and
 - (D) 100 mg total daily dose without Paroxetine.
1. Paroxetine is a strong CYP2D6 inhibitor. The mean C_{max} of alpha+beta TBZ after 50 mg total daily dose given as two doses (i.e., 25 mg morning + 25 mg evening) in the presence of paroxetine are about 160 ng/mL. The mean C_{max} at 100 mg in the absence of paroxetine is about 120 ng/mL.



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Table 1 shows the highest dose during titration and the final maintenance dose in patients from Study 004. It shows that the the dose in patients was adjusted to manage the safety events and the maintenance dose is around 50 mg.

Patient ID	2D6 inhibitor at baseline	Highest Dose (mg)	Maintenance Dose (mg)
447-201	Fluoxetine 20 mg QD	50	37.5
447-207	Paroxetine 20 mg QD	62.5	25
447-210 ^{1,2}	Fluoxetine 40 mg QD	100	100
447-228	Paroxetine 40 mg QD	62.5	50
447-231	Fluoxetine 20 mg QD	75	50
447-236	Paroxetine 40 mg QD	62.5	37.5
447-251	Paroxetine 20 mg QD	75	50
447-267	Paroxetine 40 mg QD	62.5	50
447-279	Paroxetine 30 mg QD	75	37.5

¹Patient 447-210 had an AE for somnolence that started on study day 15 when taking TBZ 37.5 mg/day. No action was taken. The AE resolved on study day 20 when the patient was taking 50 mg/day. The patient also experienced an AE for diarrhea that started on study day 12 and stopped on study day 10.

²Patient 447-210 BL chorea score = 15; chorea score at end of treatment = 4.

We recommend that the dose of tetrabenazine should be reduced by 50% in patients taking concomitant strong CYP2D6 inhibitors. The maximum dose in patients taking CYP2D6 inhibitors should be 50 mg. These recommendations are based on the following reasons:

1. The 50% reduction works well given the available dose strengths.
2. Patients in Study 004 taking CYP2D6 inhibitors were taking maintenance dose of about 50 mg.
3. Also, this dose adjustment is fairly easy for prescribers/patients to remember. The prescriber can further reduce the dose if safety events are not resolved.
4. Serum concentrations greater than 160 ng/mL were observed in Study TBZ 107,018 (Interaction with Paroxetine) and were not associated with QT prolongation greater than 10 msec.

Introduction

The purpose of the pharmacometrics review is to address the following questions:

1. Does the dose-response for the Chorea scores provide confirmatory evidence for the effectiveness of Tetrabenazine?
2. Is the worsening of Functional Scores, Cognitive Scores, Sedative Scores dose related?
3. Will lowering of tetrabenazine dose for management of safety events result in total loss of reduction in chorea scores?

Dr Joga Gobburu previously analyzed the dose-response analysis for tetrabenazine. Please refer to his review in DFS dated: 03/20/2006. Also please refer to the review by IRT-QT team for dose/exposure-response analysis of QTc prolongation.

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Key Questions

1. Does the dose-response for the Chorea scores provide confirmatory evidence for the effectiveness of Tetrabenazine?

There is substantial evidence for the sustained effectiveness of Tetrabenazine, as measured by chorea scores, and this is internally consistent across clinical trials. Specifically, the evidence arises from the following:

1. TBZ 103,004 demonstrates that Tetrabenazine treatment over 5 weeks of maintenance offers superior lowering of chorea scores, relative to placebo.
2. TBZ, 103, 004 also clearly shows a dose-response. Further, the drug effect at week 12 is completely washed-out by week 13 upon withdrawal.
3. TBZ 103,007 demonstrates that Tetrabenazine effects are consistent with those observed in TBZ 103,004 and are sustained between week 11 and week 24. The fact that the same patients from TBZ 103,004 upon washout and re-titration gained similar effects on chorea scores supports that the drug effect is reproducible.
4. TBZ 103,006, which is an extension of TBZ 103,005, demonstrated that Tetrabenazine treatment led to significant lowering of chorea scores.

Analyses of Clinical Trial Data

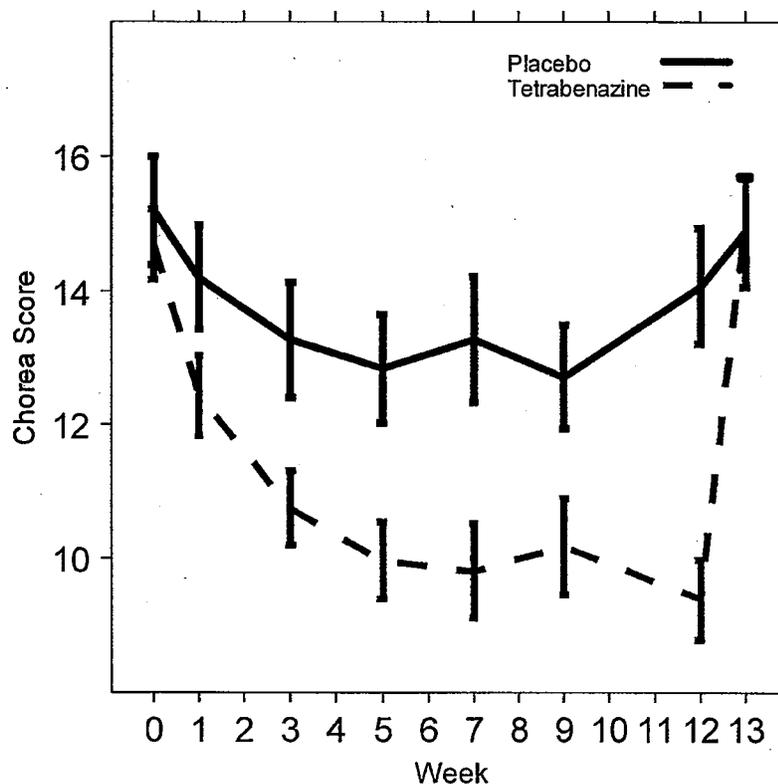
Study TBZ 103,004

Patients (total N=84) were randomized to placebo (N=30) or Tetrabenazine (N=54). Weekly dose titration was allowed until week 7 and doses maintained beyond that time for 5 weeks. The lowest Tetrabenazine dose available was 12.5 mg and the highest allowed was 100 mg. Chorea scores were collected at weeks 1, 3, 5, 7, 9 and 12 on treatment.

The primary analysis considered scores at week 12. During the treatment period, chorea scores for participants in the drug group declined by an estimated 5.0 units, as shown in Figure 2, while those in the placebo group declined by an estimated 1.5 units. The treatment effect of 3.5 units is highly significant ($p < 0.0001$).

In study 103,004, the Tetrabenazine group beat placebo according to the pre-specified analysis.

Figure 2. Mean (± 1 standard error) chorea scores in placebo and Tetrabenazine treatment groups in Study TBZ 103,004. The patients were withdrawn from treatment at 12 weeks and hence the scores are back at baseline levels at Week 13.



In addition to the primary analysis, FDA conducted a dose-response analysis by considering the doses (closest to each visit) and chorea scores. There were a total of 574 observations in 84 subjects. The first challenge in investigating a dose-response relationship when the doses are titrated is to ensure that dose and time are not confounded. That is to say, we should not mis-attribute a time effect as a dose-effect. First, the half-life of Tetrabenazine is about 5 hrs. The pharmacokinetics (PK) are at steady-state by the end of each day. **Hence, the PK will not confound the dose-response.**

The placebo data across 12 weeks were employed to further ensure that the chorea scores do not change over time. Figure 1 above suggests that chorea scores decline slightly till week 3 and by week 9 they start increasing back to baseline. However, a closer look at the individual time profiles of placebo patients as shown in Figure 3,

Figure 4, Figure 5, Figure 6 and Figure 7 suggests that chorea scores remain reasonably unchanged over time in most patients.

Figure 3. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by adding 447,000 to all ID numbers - Protocol TBZ 103,004.

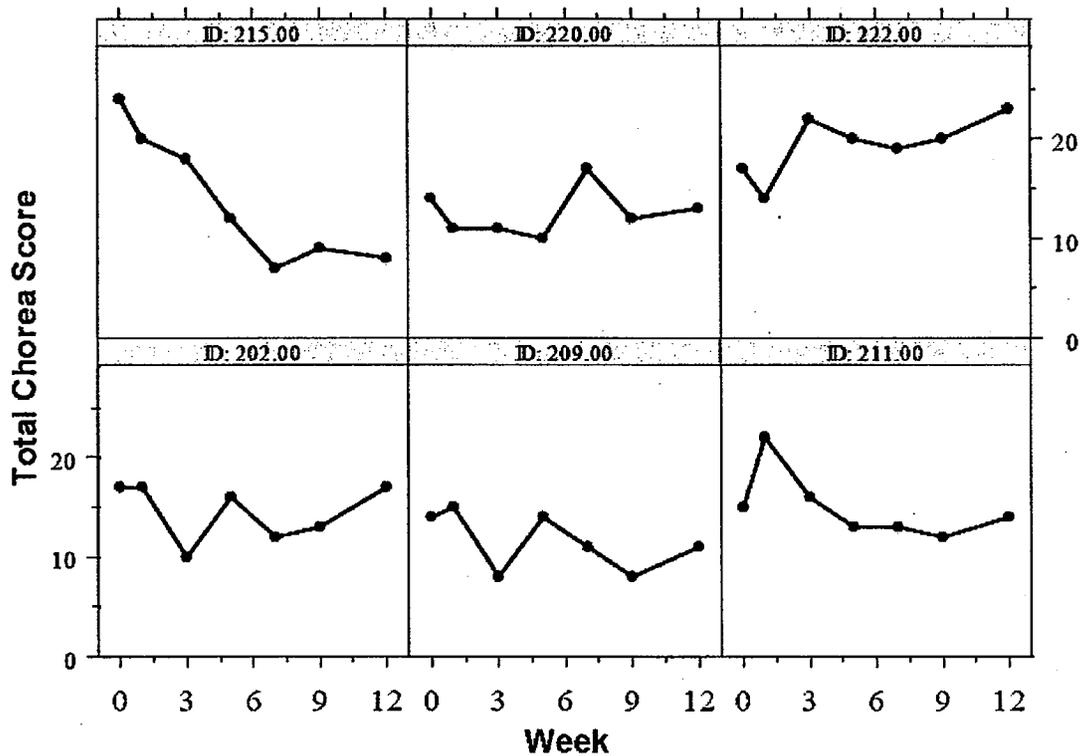


Figure 4. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by adding 447,000 to all ID numbers - Protocol TBZ 103,004.

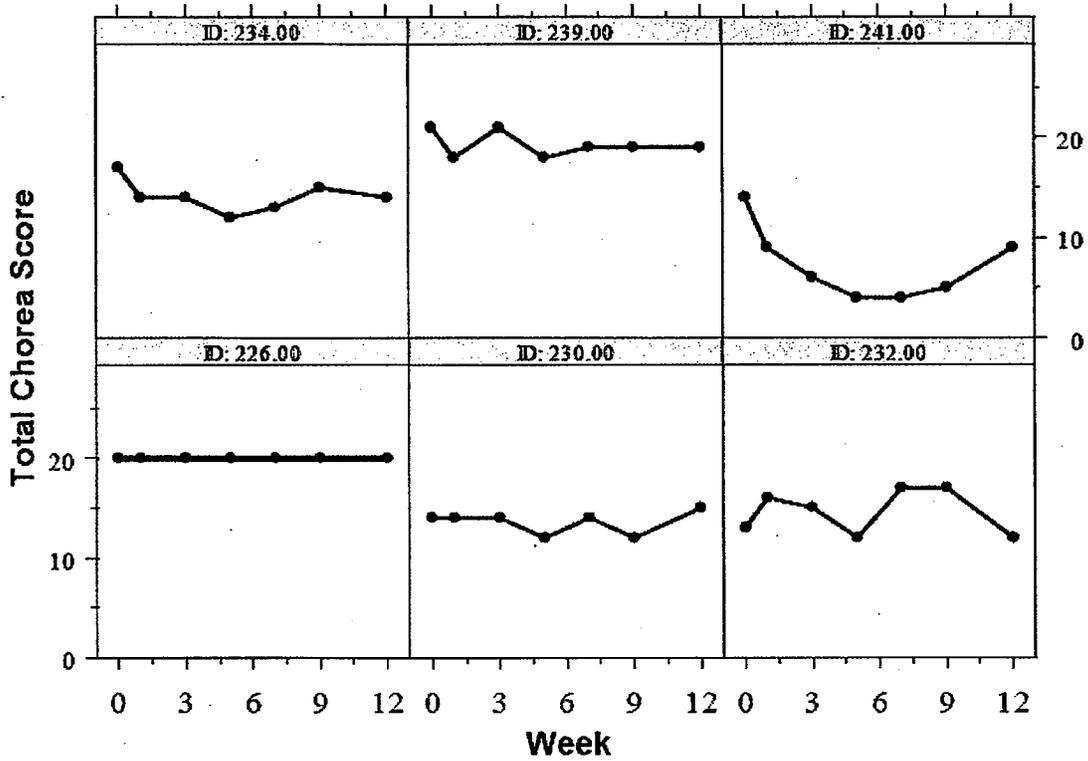


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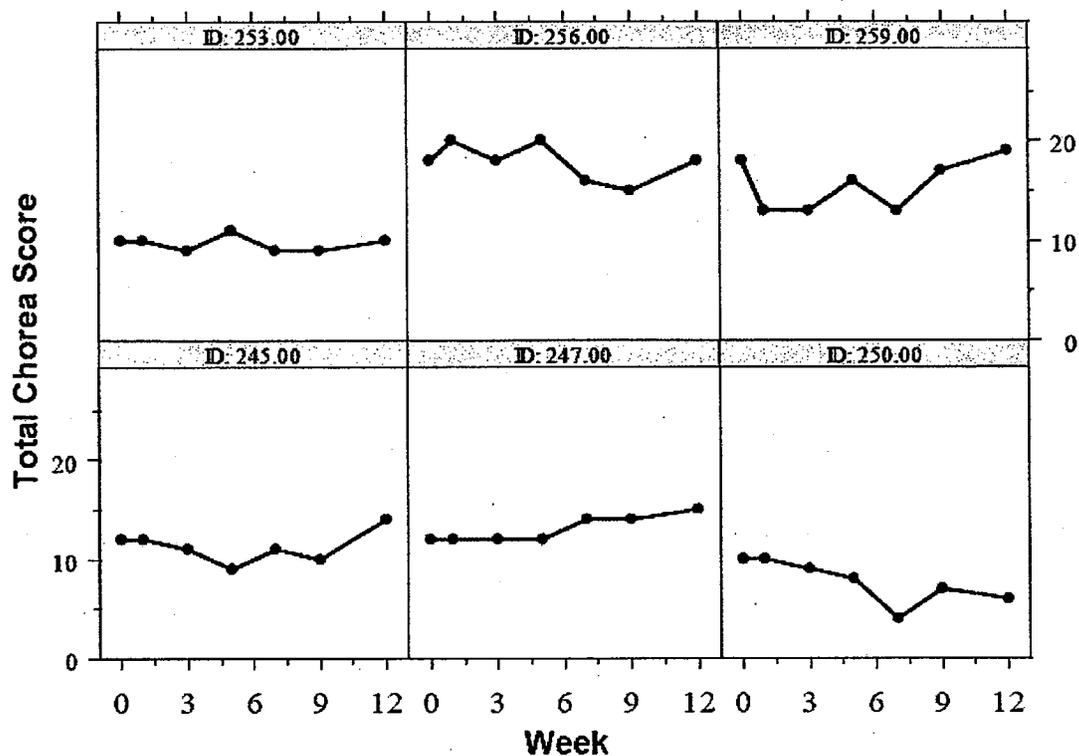


Figure 6. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by adding 447,000 to all ID numbers - Protocol TBZ 103,004.

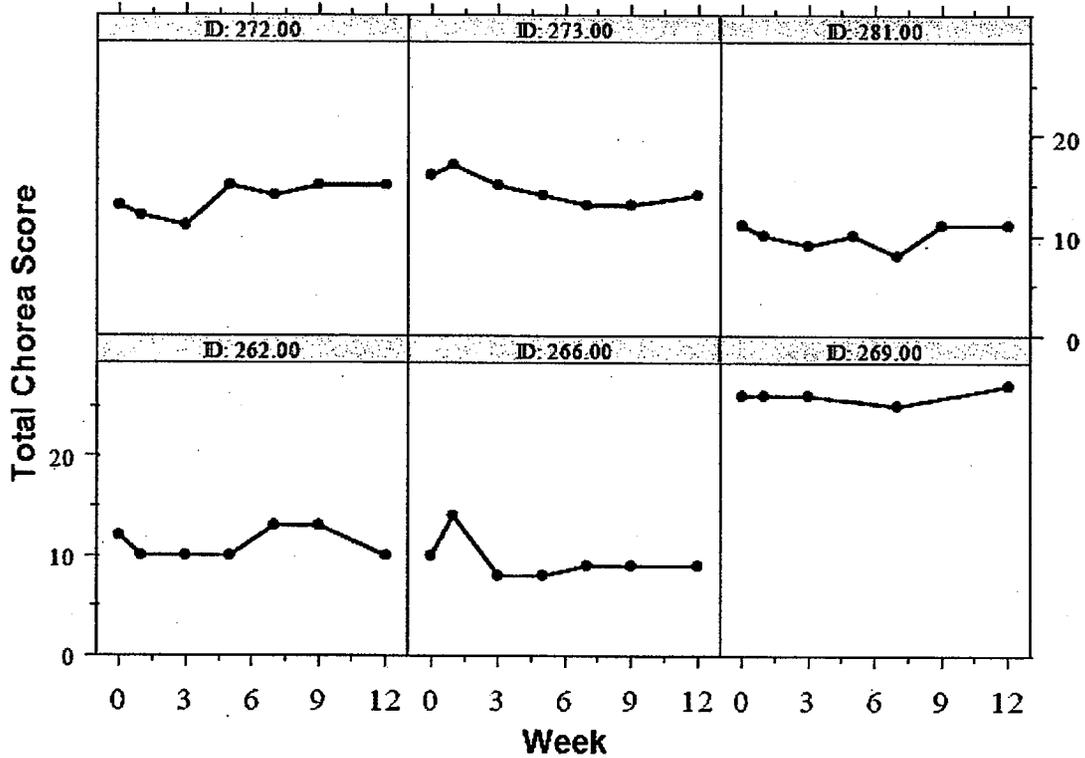
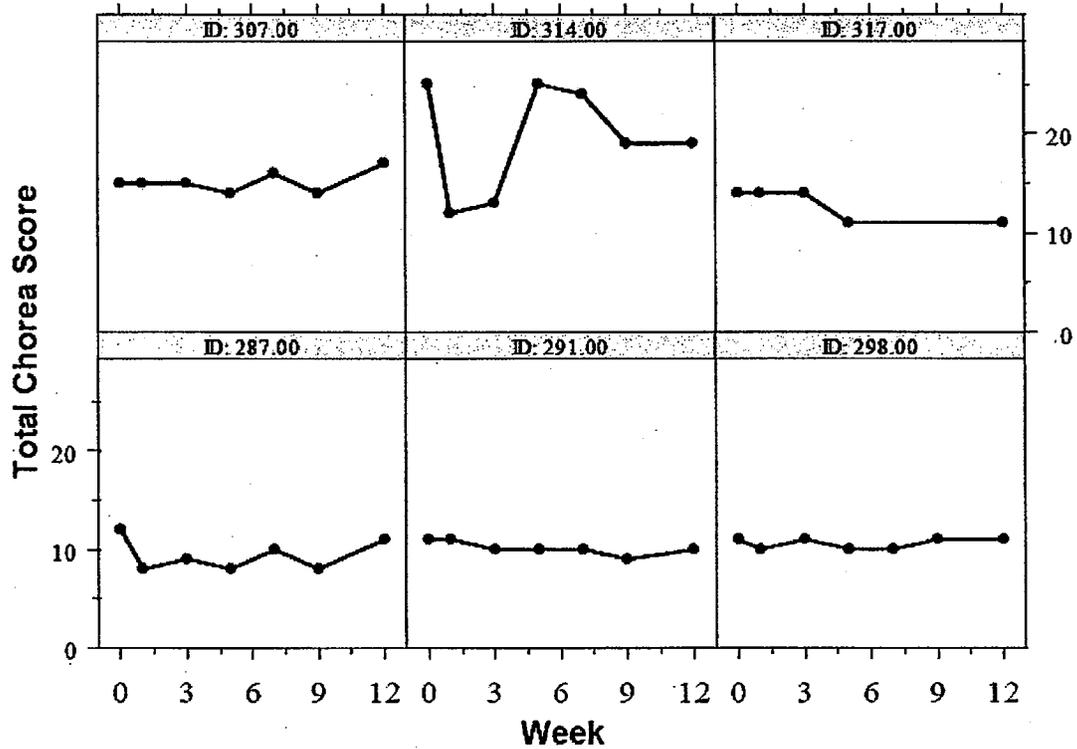


Figure 7. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by adding 447,000 to all ID numbers - Protocol TBZ 103,004.



There are three potential reasons that could cause delay between the drug administration and achievement of steady-state effect on Chorea scores. They are: 1) Pharmacokinetic half-life, 2) time-varying placebo response and/or 3) delayed drug response. For the following reasons we conclude that time does not confound with dosing during titration for the dose-Chorea analysis based on weekly visit data:

- Half-life of tetrabenazine is short (~6 hours). Pharmacokinetic steady state is achieved after a single dose,
- Most of the patients in placebo group have no changes in total chorea scores over time ; and
- Tetrabenazine elicits its effect on total chorea scores within one week post dose change. Chorea scores at every weekly visit demonstrate tetrabenazine's full effect at that dose.

Hence, the population average dose-response relationship without time being a factor was derived using mixed-effects analysis. Since the individual patients were titrated to their best response, the analysis methodology has to account for individual dose-response relationship before deriving the average dose-response. Analysis was conducted for Study TBZ103,004 and Study TBZ103,007 separately using various models (linear, Emax).

Overall, within the dose range studied, the effect on chorea scores increased linearly with dose. The estimates of the model parameters using a linear model for effects of dose are shown in Table 2. The diagnostic plots for assessing the adequacy of the model fit are shown in Figure 8.

Figure 8. A linear dose-response model describes the total chorea scores for the placebo and Tetrabenazine groups well. The symbols signify the observed Chorea scores in all patients and the solid line represents the line of identity. The predictions are distributed around the line of identity. Ideally, if the model were perfect the symbols and the line should be superimposed - Protocol TBZ 103,004.

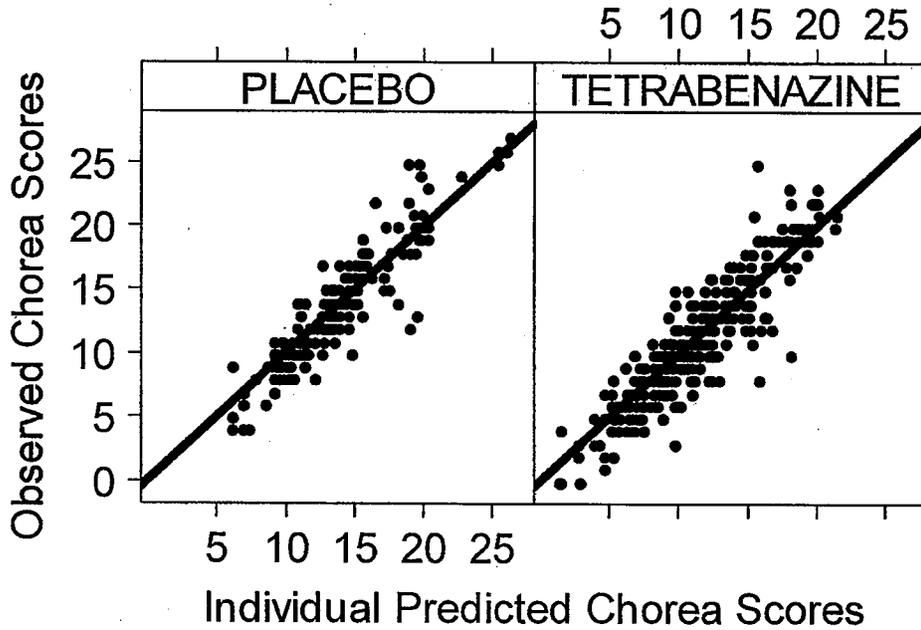
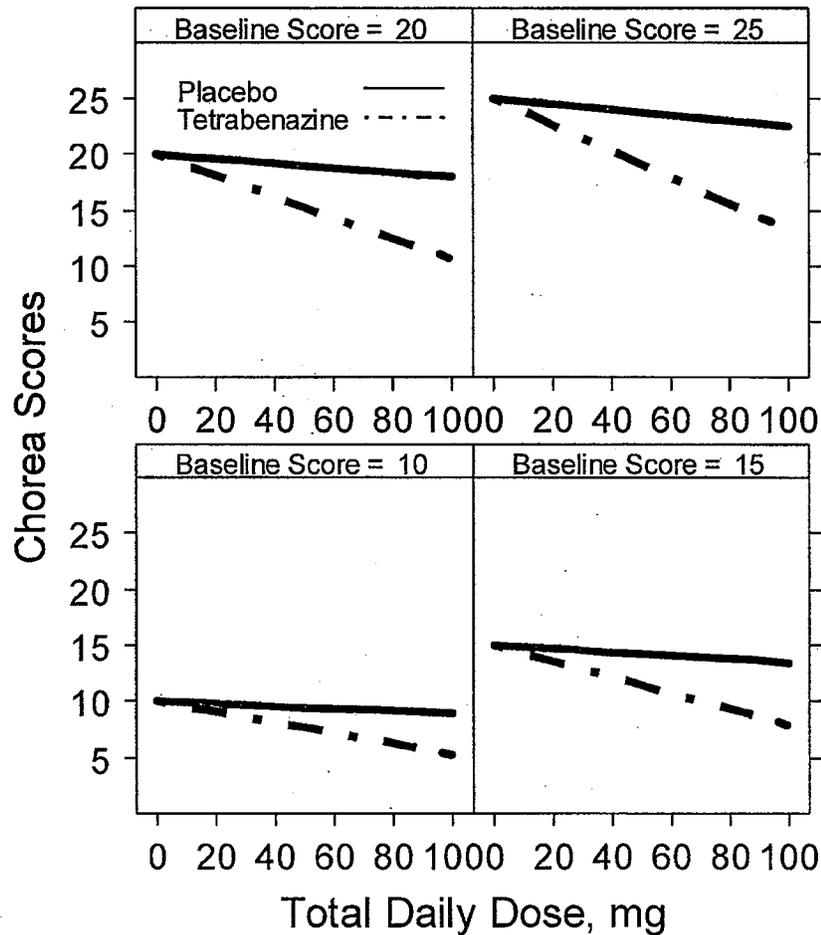


Table 2. Dose-response model parameter (mean and between-subject variability (BSV)) estimates and the 95% confidence intervals- Protocol TBZ 103,004. The slope of the dose-response is expressed as % change relative to baseline per mg of Tetrabenazine dose.

Parameter	Mean (CI)	BSV % (CI)
Baseline score for placebo group	14.3 (12.90, 15.69)	25 (18, 30)
Slope of Placebo effect, % per mg	-0.001 (-0.0018, -0.0017)	173 (101, 222)
Baseline score for dose group	13.7 (12.73, 14.66)	25 (20, 29)
Slope of dose-response, % per mg	-0.0047 (-0.0057, -0.0036)	70 (60, 88)
Residual Variability	2.17 (1.80, 2.49)	

Figure 9 shows the typical dose-response relationship in 4 patients whose baseline chorea scores are 10, 15, 20 and 25 units. Since the effects are proportional to baseline, greater effects are seen in patients with a baseline chorea score of 25. Also shown in the graph are responses if these patients are treated with placebo.

Figure 9. Typical dose-response curve based on parameters as shown in Table 2 in 4 patients whose baseline total chorea scores are 10, 15, 20 or 25.



Study TBZ 103, 004 Conclusions

1. The Tetrabenazine group beat placebo according to the pre-specified analysis ($p < 0.001$).
2. There is a significant dose-response relationship, which provides a strong

confirmatory evidence for the effectiveness of Tetrabenazine.

- 3. Chorea scores significantly increase, in fact reach baseline, within a week upon cessation of Tetrabenazine. This result also supports the effectiveness of Tetrabenazine.**

Study TBZ 103,005

This was a randomized placebo controlled study that recruited 30 patients who were stabilized on Tetrabenazine for at least 2 months. Tetrabenazine in 12 patients was stopped on day 1; on day 3 in another 12 patients; and on day 5 in the remaining 6 patients. Until stopped patients received their 'best dose'. The sponsor claims that the investigators instructed their patients to stop taking Tetrabenazine on the previous evening. That is, if patients were supposed to receive their last dose on day 3, in reality the patients received their last dose on the evening of day 2. So, at least 12 hours have elapsed since the last dose.

The primary analysis was Group 1 (Tetrabenazine withdrawn on Day 1) versus Groups 2 (Tetrabenazine withdrawn on Day 3) and 3 (Tetrabenazine withdrawn on Day 5). This endpoint was not met. The sponsor attributed this failure to their belief that in all the groups Tetrabenazine treatment was 'completely' washed out. However, there is one useful piece of information from this trial that supports the effectiveness of Tetrabenazine. Table 3 shows the mean total chorea scores in the all the 3 groups and Table 4 presents the comparison between the different groups. Clearly, in Group 1 in which patients withdrew from Tetrabenazine on Day 1, the scores increased significantly ($p < 0.001$). The mean increase is 5.3, which is consistent with the effect size seen in Study 103, 004. This is further supported by the sustained increase on Day 5. The results are similar for Group 2 also.

Table 3. Mean (\pm SD) Total chorea Scores throughout the Study by Withdrawal Group and by Study Day -- Protocol TBZ 103,005.

Withdrawal Group	Day 1	Day3		Day 5
	On Tetrabenazine	Off Tetrabenazine	On Tetrabenazine	Off Tetrabenazine
Group 1 (N=12)	9.4 \pm 4.9	14.8 \pm 5.4		14.8 \pm 7.1
Group 2 (N=12)	9.1 \pm 6.2	12.7 \pm 5.3		14.6 \pm 5.4
Group 3 (N=6)	11.2 \pm 4.4		12.8 \pm 6.0	15.2 \pm 6.0

Table 4. Mean (\pm SD) Change Scores with p-Value (By T-Test) of Total chorea Scores By Treatment Group from Day 5 to Day 3 and Day 3 to Day 1 for 30 HD Participants - Protocol TBZ 103,005.

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

Study TBZ 103, 005 Conclusions

1. The fact that the total chorea scores have increased significantly upon withdrawal of Tetrabenazine is a strong evidence of its effectiveness. The increase in total chorea scores is about 5.3 in patients who stopped drug intake either on Days 1 or 3. This effect size is consistent with that reported in TBZ 103, 004.

Study TBZ 103,007

Patients who completed study TBZ 103, 004 (placebo controlled study, which was positive), were included in the study TBZ 103,007. This was an open-label study with titration allowed for 11 weeks and the total chorea score data up to 36 weeks were available. Total chorea scores were measured in all patients at baseline (post wash-out period of Study TBZ 103, 004) and subsequently at weeks 2, 6, 12, 24, 25 and 36.

Figure 5 clearly shows that the mean Tetrabenazine effects observed in Study 004 and 007 are in close agreement. Of particular interest is the sustained effect of Tetrabenazine over 24 weeks on maintenance dose. A concern with open-label studies is their vulnerability to influence the investigator assessments and patient response. However, for the following reasons the results are internally consistent. First, there are two well-controlled studies (Study 004 and 005) which unequivocally showed that Tetrabenazine lowers chorea scores. Second, the patients who participated in Study 004 exhibited identical effects (on an average) in this extension study (007) as shown in Figure 10. Third, in 10 patients in whom Tetrabenazine was withdrawn at week 24, the chorea scores increased and reached baseline by week 25. This observation is in congruence with the results from Study 005. Fourth, patients who received placebo in

Study 004 had lower chorea scores when they received Tetrabenazine in Study 007 as show in Figure 11.

Dose-response analysis for Study 007 indicated that the estimate of the slope was 0.0050 % per mg, which is in close proximity to 0.0042 % per mg for the Study 004 data alone. Further, in 10 patients who withdrew from Tetrabenazine treatment (planned) on week 24, the total chorea scores reached baseline by week 25 (mean change at week 24 was 6 versus zero at week 25).

Figure 10. Mean total chorea scores in Studies TBZ 103,004 and TBZ 103,007 for placebo and Tetrabenazine groups. Effects of Tetrabenazine in study TBZ 103,004 and TBZ 103,007 are identical. Titration schemes in both the studies were similar. Study 007 supports the durability of response over 36 weeks, specifically for about 24 weeks on maintenance.

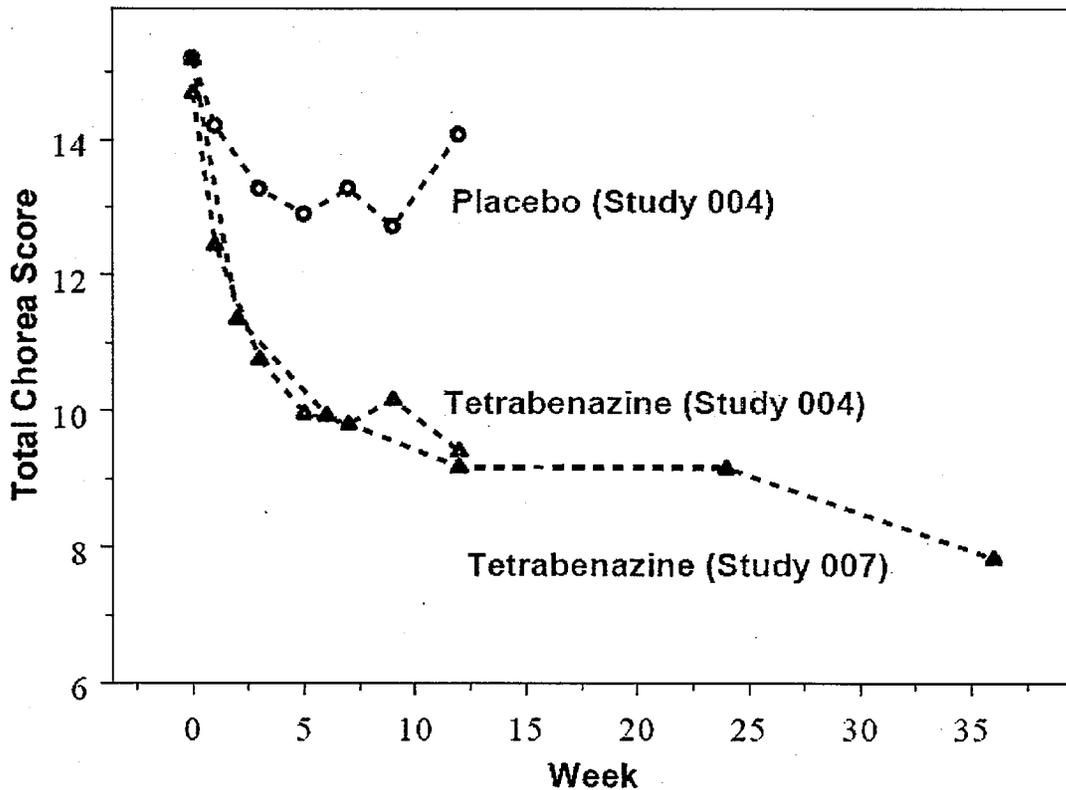


Figure 11. Mean total chorea scores of patients who received placebo in study TBZ 103,004 and then received Tetrabenazine in study TBZ 103,007. The total chorea scores are lower in patients when they received Tetrabenazine (TBZ).

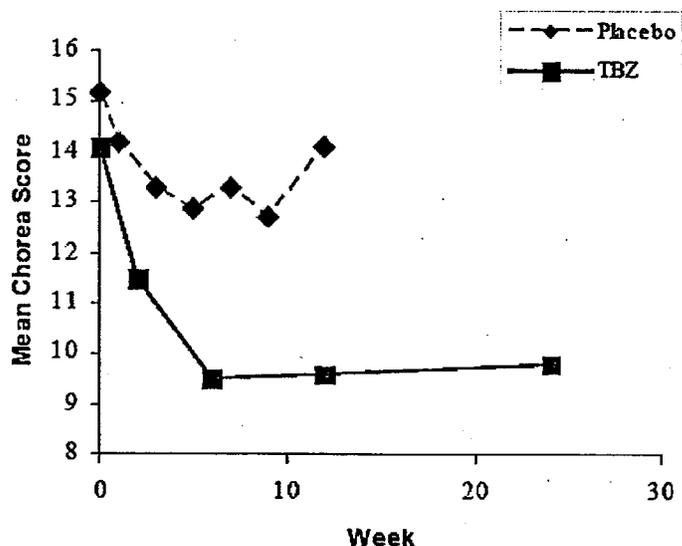


Table 5. Dose-response model parameter (mean and between-subject variability (BSV)) estimates and the 95% confidence intervals- TBZ 103,007. The slope of the dose-response is expressed as %change relative to baseline per mg of Tetrabenazine dose. These estimates are consistent with those reported in Table 2 for TBZ 103,004.

Parameter	Mean (CI)	BSV % (CI)
Baseline score for dose group	14.1 (13.22, 14.97)	24 (18, 30)
Slope of dose-response, % per mg	-0.0050 (-0.0058, -0.0042)	59 (60, 75)
Residual Variability	2.57 (2.17, 3.92)	

Study TBZ 103, 007 Conclusions

1. The changes in chorea scores from this study and TBZ 103,004 are super-imposable.
2. There is a significant dose-response relationship, which provides evidence for the effectiveness of Tetrabenazine. This relationship is consistent with that observed in TBZ 103,004.
3. Choreia scores significantly increase, in fact reach baseline, within a week upon cessation of Tetrabenazine. This result also supports the effectiveness of

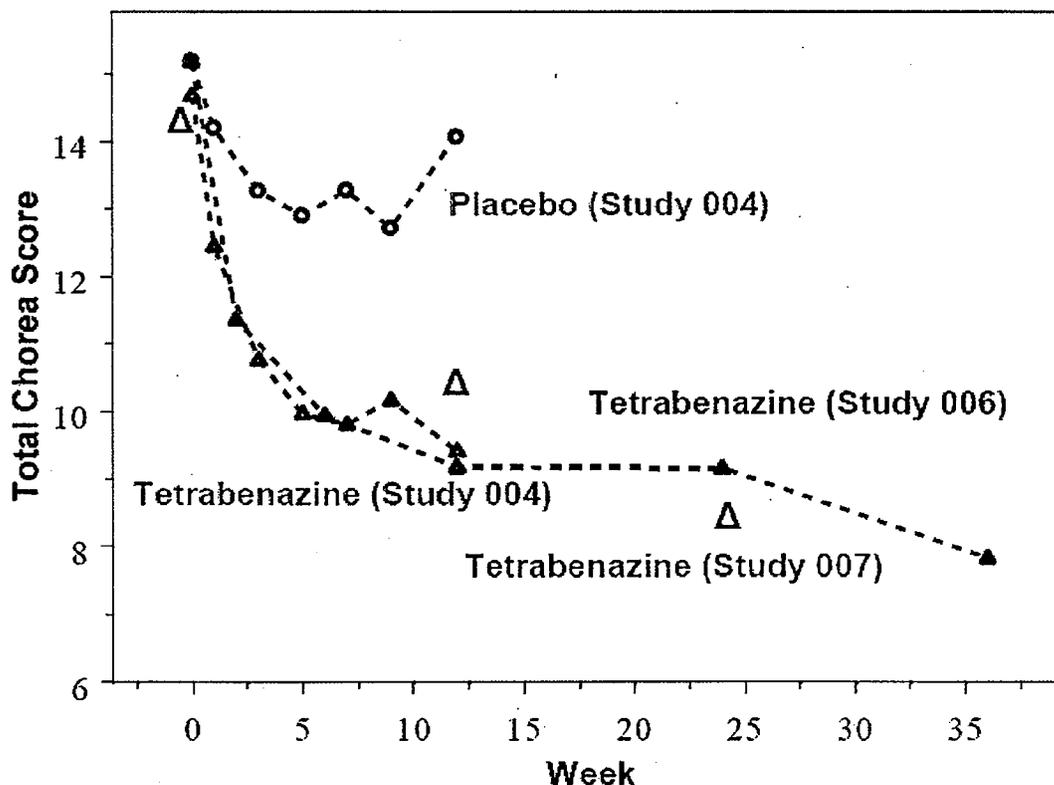
Tetrabenazine.

4. The lowering of chorea scores is shown to be sustained over 24 weeks, but more importantly between week 11 and week 24 (maintenance phase).

Study TBZ 103,006

This study enrolled patients who completed TBZ 103,005. In TBZ 103,005 thirty patients were off Tetrabenazine by Day 5. These patients were previously stabilized on 'best dose' of Tetrabenazine. In TBZ 103,006, these patients were resumed on the 'best dose' instead of upward titration again. Chorea measurements were performed on weeks 12 and 24. The mean total chorea scores for 3 studies are shown in Figure 12.

Figure 12. Mean total chorea scores in Studies TBZ 103,004, TBZ 103,007 and TBZ 103,006 for placebo and Tetrabenazine groups. Effects of Tetrabenazine in all studies are similar. Titration schemes in both TBZ 103,004 and TBZ 103,007 were similar. Study TBZ 103,006 did not employ titration for the first 12 weeks, but dose was increased in 53% (9 of 17) patients after week 12. Study 007 and 006 supports the durability of response over 36 weeks, specifically for about 24 weeks on maintenance.



As shown in Figure 12, the chorea score changes for Study TBZ 103,006 are reasonably consistent with the Study TBZ 103,004 and TBZ 103,007. The mean change in chorea score at week 12 in this study was -3.7. More measurements between week

0 and 12 would have allowed appreciation of the time course of drug effects better. But the claim is that the maximal changes in chorea scores occur shortly after giving the 'best dose'. Also, there is a further decrease in chorea scores upon increasing doses after week 12. It is not again clear why patients needed higher doses than their previously established 'best dose'. The differences, if any, between the investigator assessment and that of the patients' previous physician could lead to the need for further titration. Nevertheless, there is a decrease in chorea scores by week 12 and further decrease upon upward titration at week 24.

Study TBZ 103, 006 Conclusions

- 1. The mean chorea score changes in Study 006 are similar to those reported in Study 004, 005 and 007.**
- 2. Patients resuming their 'best dose' had a lower chorea scores at week 12. This period can be treated as maintenance period as the doses were not changed (unless an AE happens).**
- 3. The need for further increase from their previously established 'best dose' after week 12 is not clear. But this could be due to differences between investigators.**

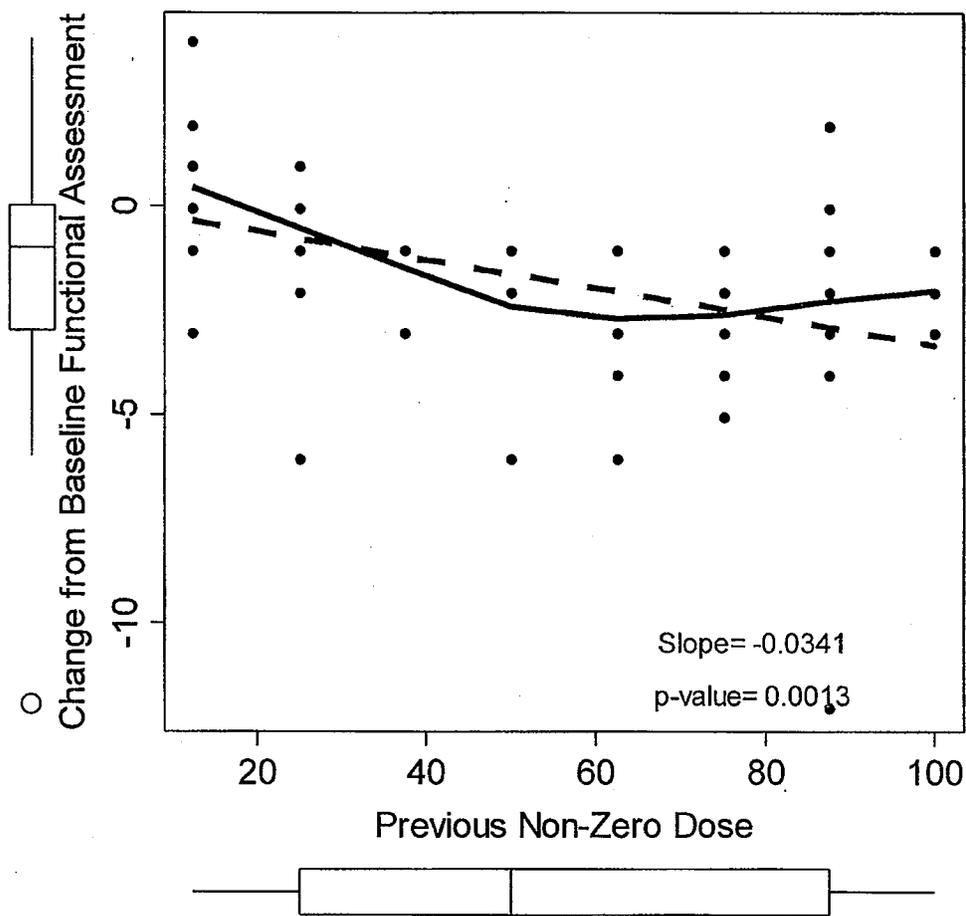
2. *Is the worsening of Functional Scores, Cognitive Scores, Sedative Scores related to dose?*

The trend in Changes in the Functional Assessment, Cognitive Scores, Sedative Scores with dose, if any, is not obvious.

The FDA pharmacometrics reviewer analyzed these data using regression techniques and the results are similar to those reported by the sponsor. Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, Figure 19 do not support any clear relationship between dose or previous dose or previous non-zero dose and the worst functional status, sedative or cognitive scores.

There was, however, a trend towards lower functional assessment scores in relation to non-zero dose taken prior to worst score in Study TBZ 103,004, but no clear interpretation can be derived.

Figure 13. Relationship between change from baseline functional assessment score and previous non-zero dose in Study TBZ 103,004. Shown in the graph are observed data representing worst score in a patient (symbols) with local smoothing curve (solid line) and linear model fitted line (dotted). Also shown below each axis are the box plots showing the range of values on x and y axis.



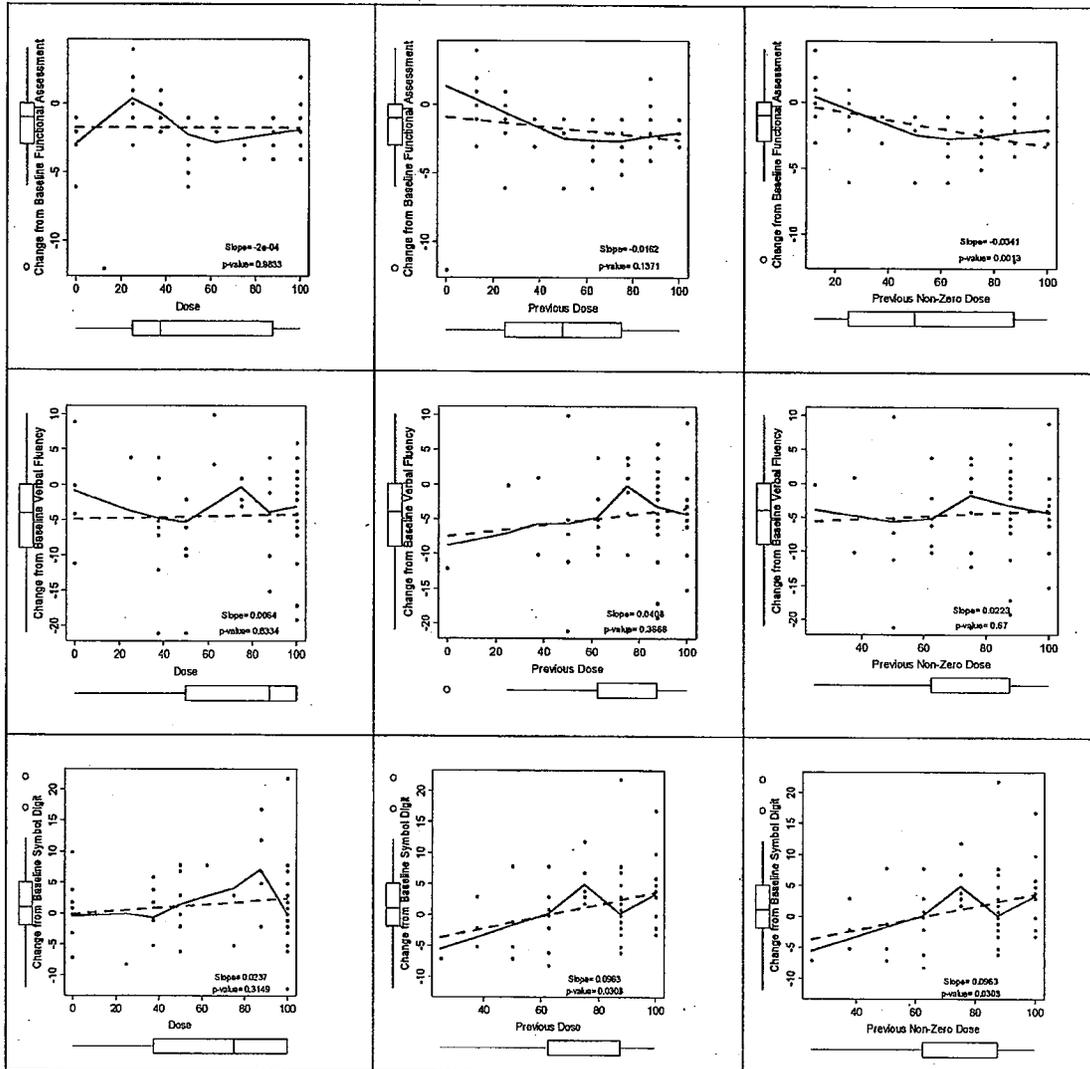


Figure 14. Relationship between change from baseline scores (worst score) for functional status, verbal fluency, symbol digit and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,004.

Tetrabenazine Pharmacometrics Review

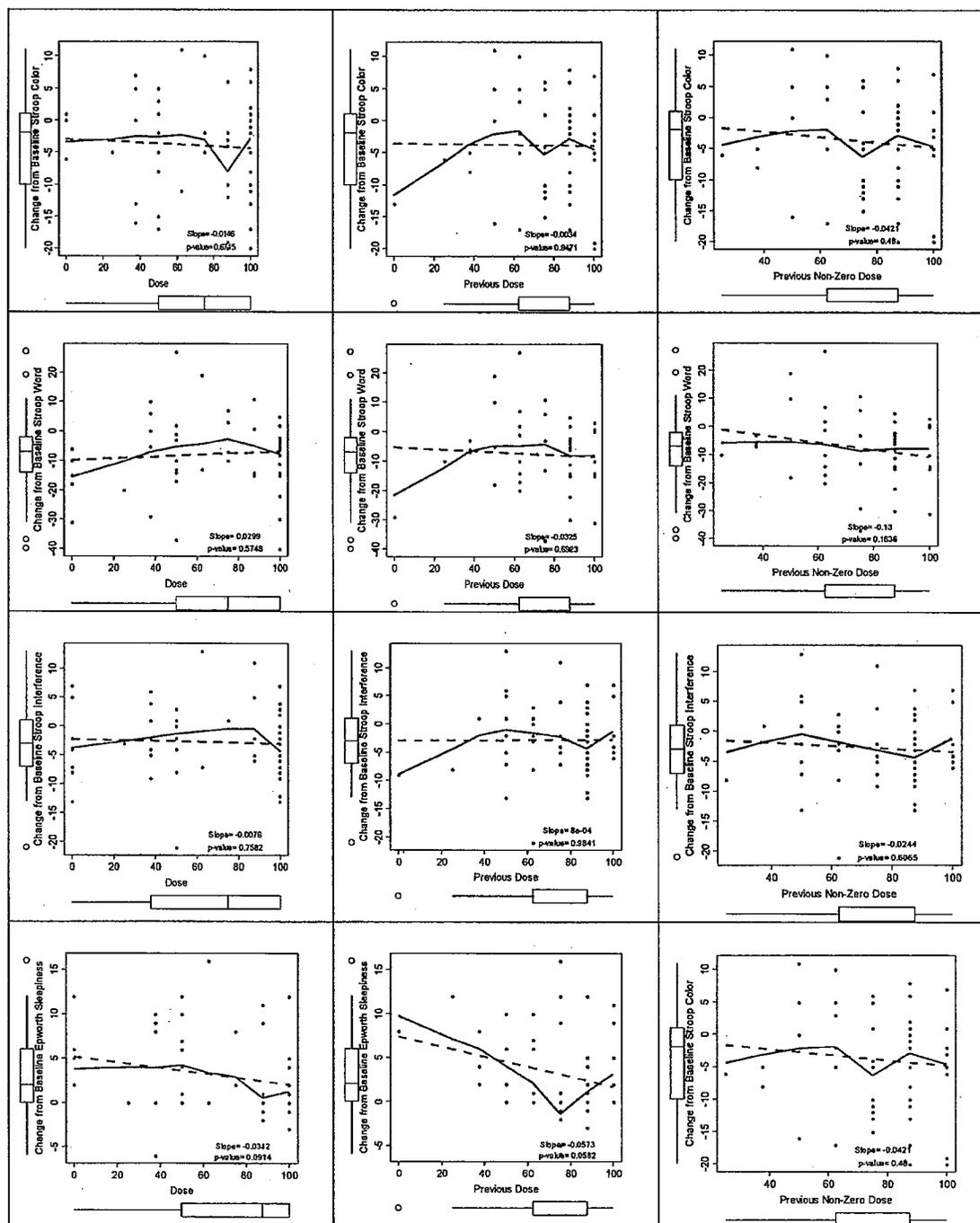


Figure 15. Relationship between change from baseline scores (worst score) for stroop color, stroop word, stroop interference, epworth sleepiness and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,004.

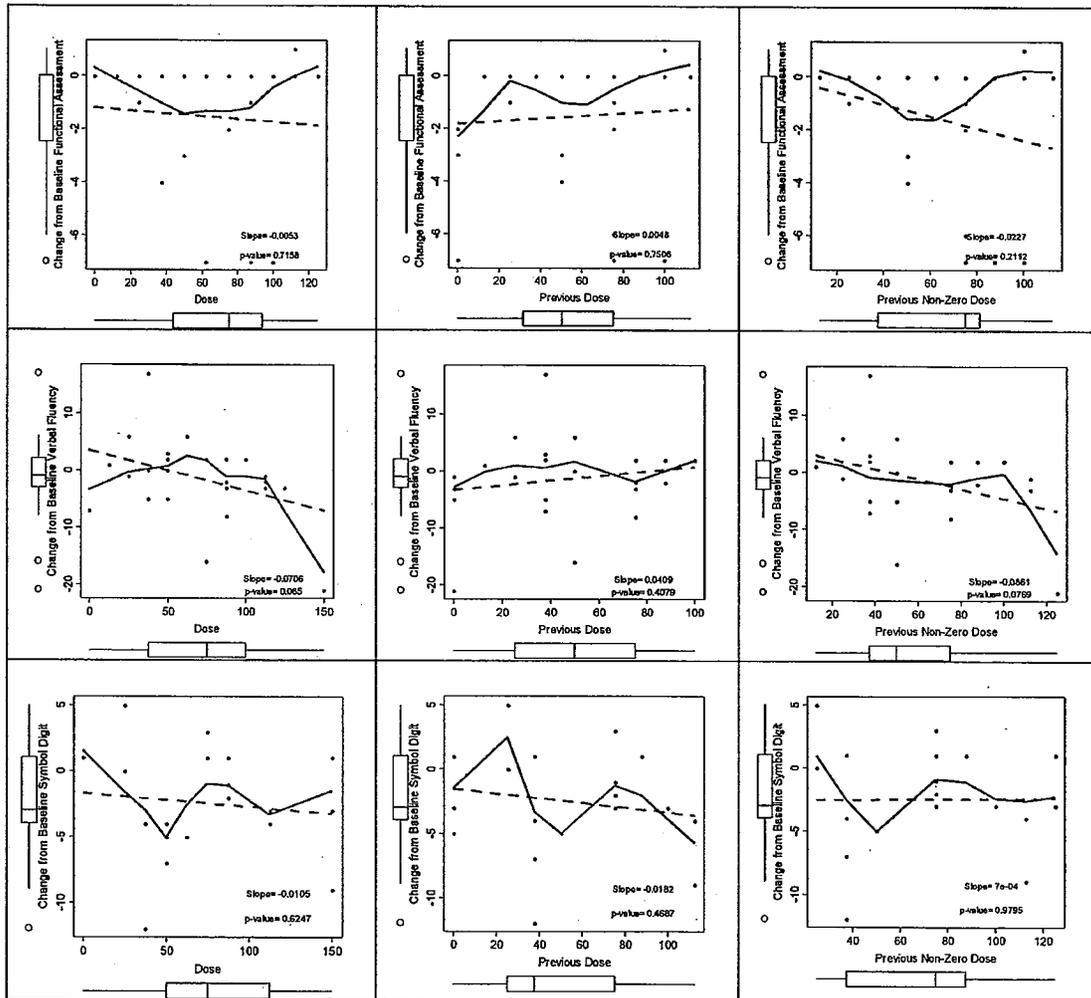


Figure 16. Relationship between change from baseline scores (worst score) for functional status, verbal fluency, symbol digit and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,006.

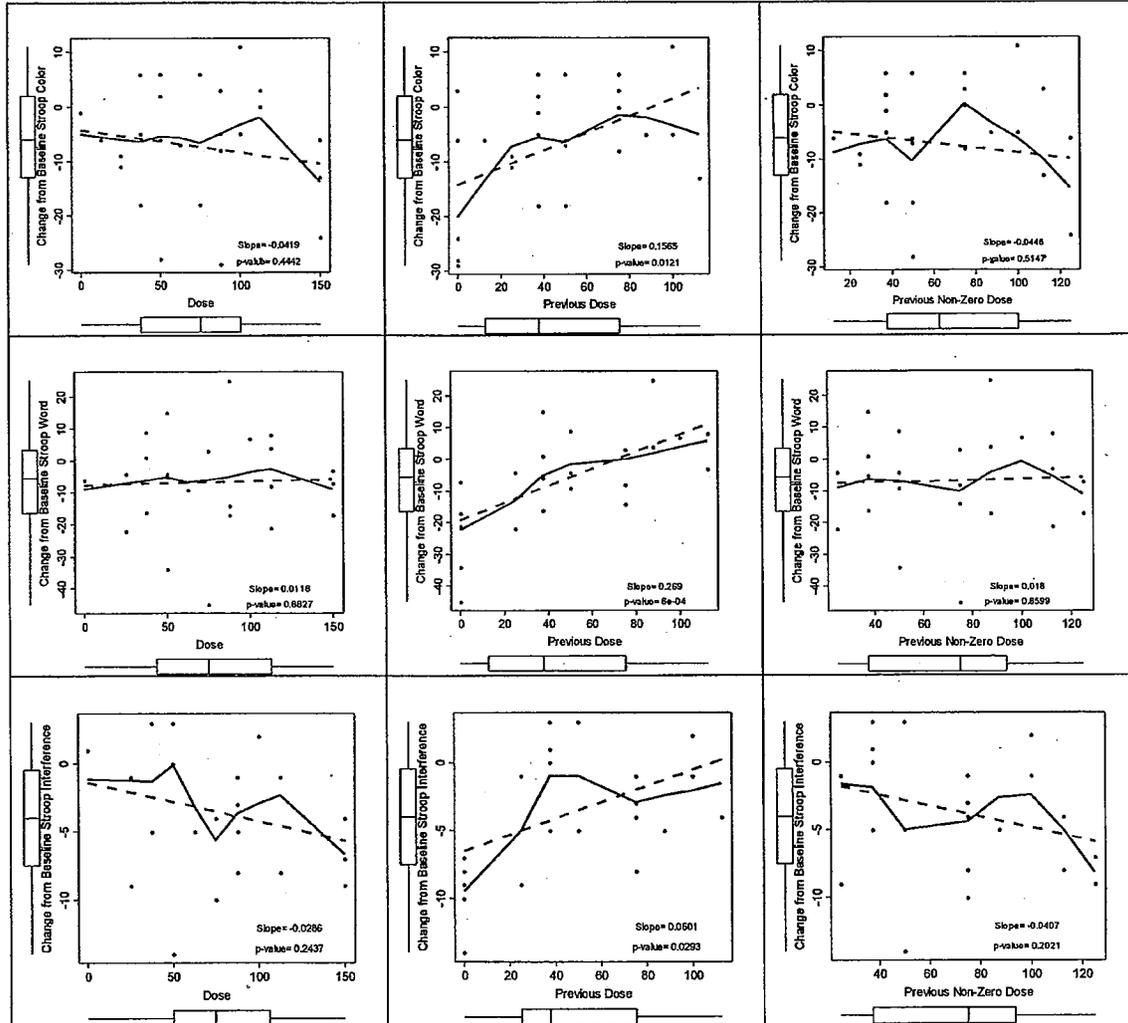


Figure 17. Relationship between change from baseline scores (worst score) for stroop color, stroop word, stroop interference, epworth sleepiness and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,006.

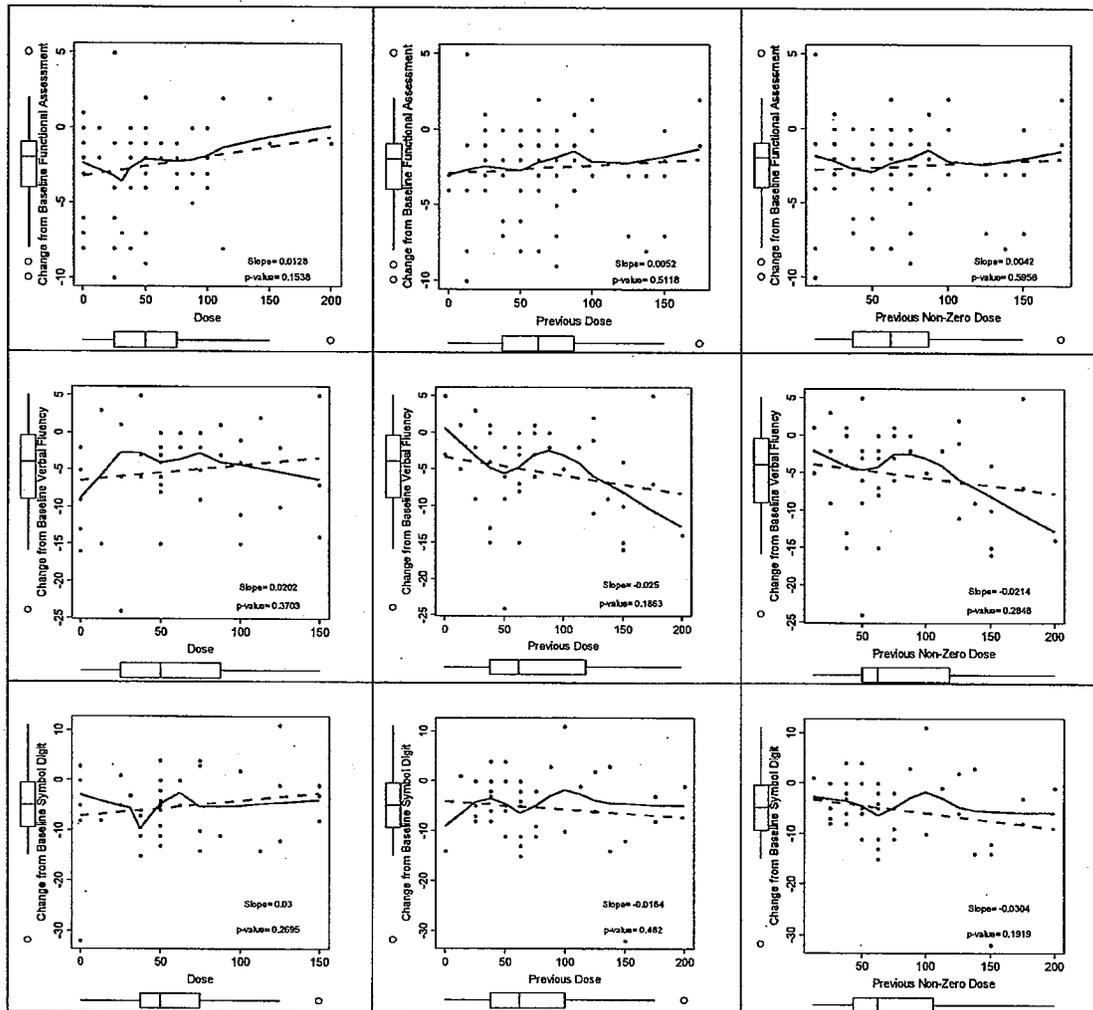


Figure 18. Relationship between change from baseline scores (worst score) for functional status, verbal fluency, symbol digit and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,007.

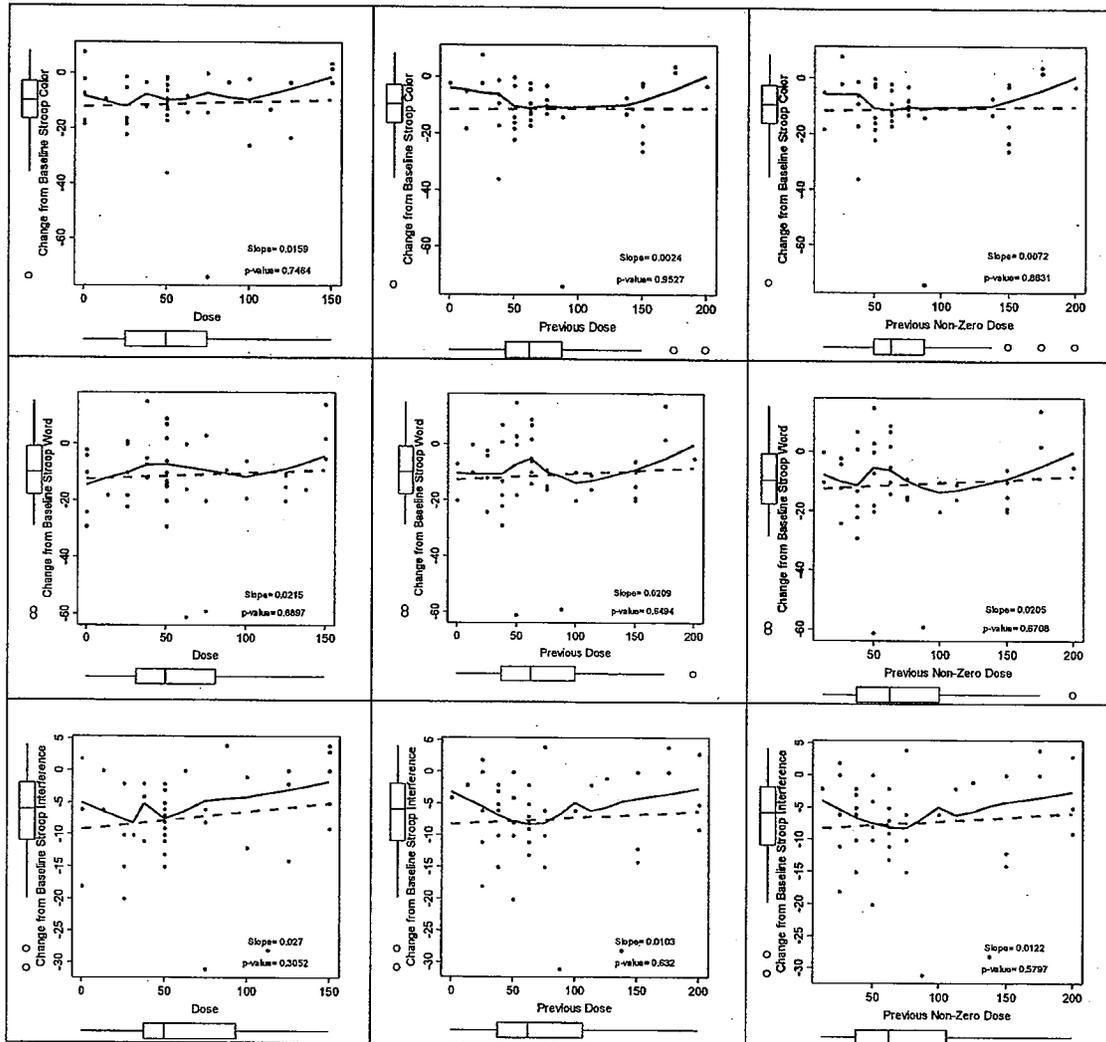


Figure 19. Relationship between change from baseline scores (worst score) for stroop color, stroop word, stroop interference, epworth sleepiness and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,007.

3. Will lowering of tetrabenazine dose for management of safety events result in total loss of reduction in chorea scores?

Unlikely in a majority of patients. Due to the linear relationship between dose and improvement in chorea scores, changes in dose from 100 mg to 50 mg for example to manage safety events will not result in total loss of effect on chorea scores. To explore this further the reviewer identified clinical diagnosis situations such as sedation, parkinsonism, depression, akathisia that would warrant dose adjustments. For details on dose adjustments in other studies (Study 007, Study 006) please refer to the reviews by clinical division. This review only focused on the placebo controlled clinical trial Study 004.

Error! Reference source not found. shows the distribution of tetrabenazine doses at the end of study 004 (Week 12). About 40% of the patients were treated with 100 mg dose of tetrabenazine.

Total Daily Dose (mg)	Percentage of patients
0	7.5
25	3.7
37.5	13.2
50	22.6
62.5	3.7
75	3.7
87.5	5.6
100	39

Table 6. Distribution of tetrabenazine dose levels received by patients at week 12 in Study TBZ 103,004 (Double-Blind).

In tetrabenazine group, 28 patients out of 54 discontinued upward titration because of an adverse event. Out of these 28 patients, 24 of them responded to treatment prior to the adverse event. A patient was judged to have responded to treatment if a 3 point decrease in chorea scores was observed.

Sedation, akathisia, depression and parkinsonism are the main reasons for discontinuation of dose titration and/or reduction in daily dose. Figure 20 shows the time of occurrence of the safety events that necessitated dosage adjustment in Study 004. Most of the adverse events appear to occur after 20 days of treatment. The patients at this visit are at a doses of 50 mg and higher. However, it is not clear if the occurrence of the event is as a results of cumulative exposure to several doses of tetrabenazine.

Figure 20. Time of occurrence of adverse events that resulted in dose adjustment in Study TBZ103,004. Each symbol in Tetrabenazine or placebo group represents a unique patient. If a patient had more than one adverse event the symbol is shown more than once.

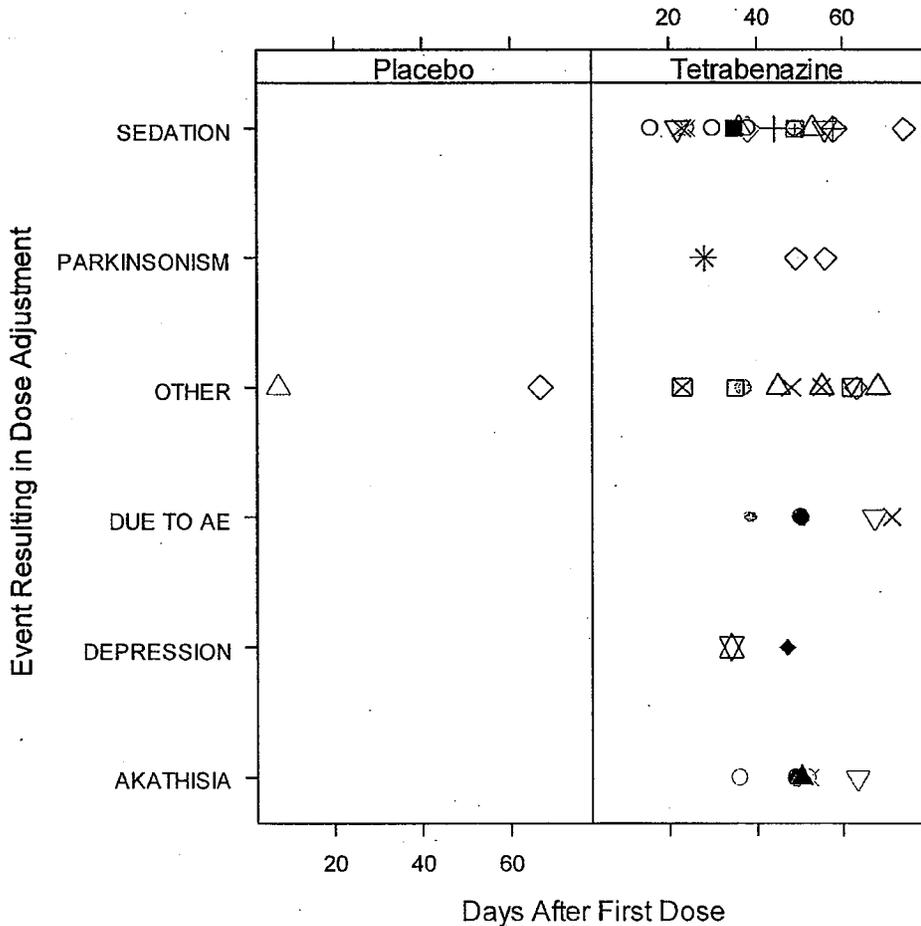


Figure 21 shows the longitudinal time course of mean (functional status score, parkinson score and HAMD scores in Study TBZ103,004. The changes in parkinson's scores are similar in placebo and tetrabenazine groups. For HAMD scores, it appears that patients in placebo group have improvement in HAMD scores. There is a trend towards a worsening in functional status score after visit 3 (Week 5). Overall, the mean changes do not reflect dramatic worsening on tetrabenazine in comparison to placebo.

Figure 21. Change in mean (± 1 standard error) parkinson score, functional status score and HAMD score in placebo and tetrabenazine treatment groups. Note that HAMD score data was available till 12 weeks (Visit 6) only while parkinson score data was available at 13 weeks (Visit 7) (1 week after patients were withdrawn from treatment at 12 weeks).

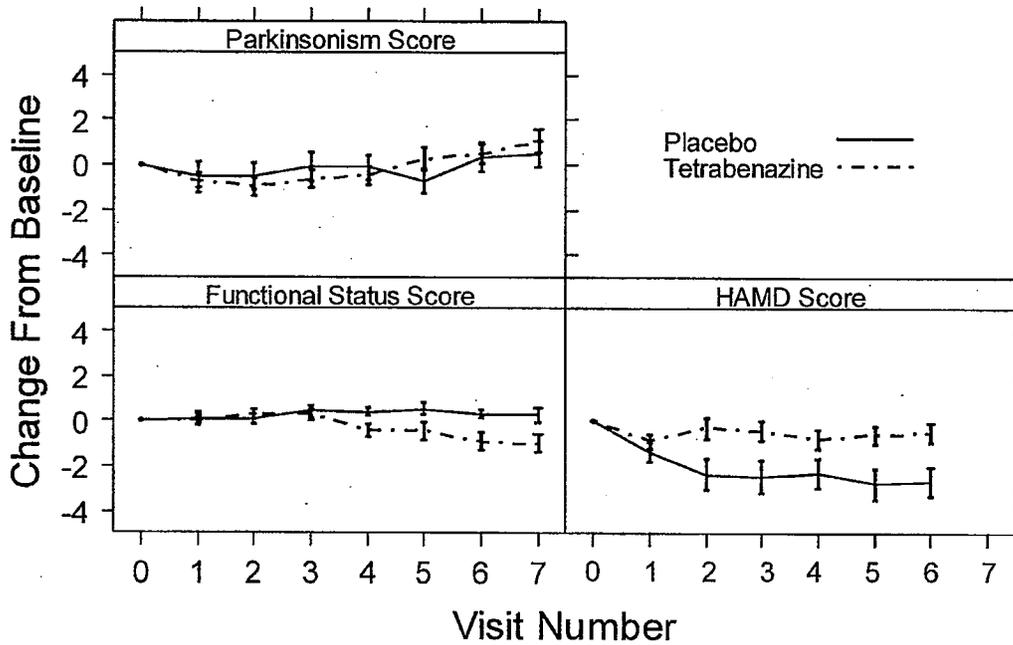
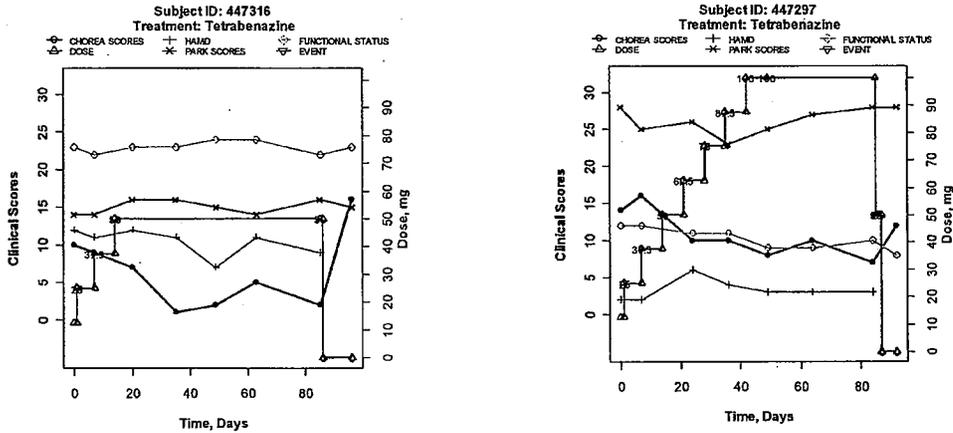


Figure 23, Figure 24, Figure 25, Figure 26, Figure 27 show the time course of clinical scores (Chorea, Parkinsonism, HAMD, Functional Status) along with dose in selected patients whose doses were either adjusted for management of sedation, akathisia, parkinsonism or depression. Also shown for reference are two patients in Figure 22 in whom no dose adjustments were performed for safety issues.

Dose Adjustment For Maximizing Reduction in Chorea Scores in Study TBZ103,004

Patient 447316 and 447287: The dose was adjusted for maximizing reduction in chorea scores. In patient 447316, desired effect on chorea scores was achieved with 50 mg. In patient 447287 doses upto 100 mg were required to achieve the desired effect. No safety events warranted dose adjustment in these patients. No clear changes in the functional status or HAMD scores or parkinsonism (PARK) scores are observed.

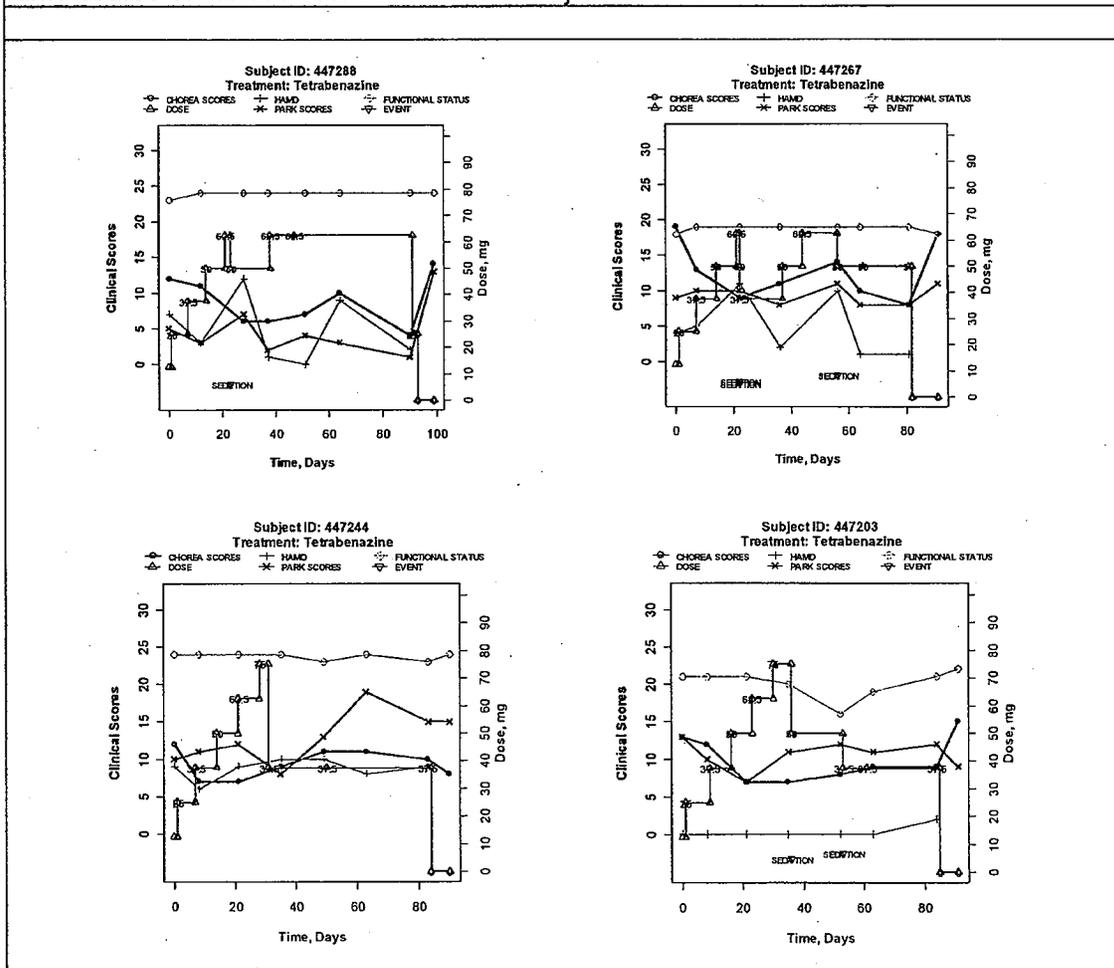
Figure 22. Changes in clinical scores (Chorea, HAMD, Parkinson (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when no dose adjustments are made for safety issues.



Dose Adjustment Due to Sedation in Study TBZ103,004

The dose of tetrabenazine was adjusted in 15 patients due to sedation. In 10 out of 15 patients, a reduction of atleast 3 units in chorea score was preserved inspite of dose reductions. 4 out of 15 patients did not respond to treatment (no change in chorea scores at any dose level) while 1 out of 15 patients did not have preserve 3 units reduction in chorea scores due to dose reduction. Shown in Figure 23 is the time course of chorea scores, functional status, HAMD scores and parkinsonism score (PARK) in patients whose dose was adjusted for sedation.

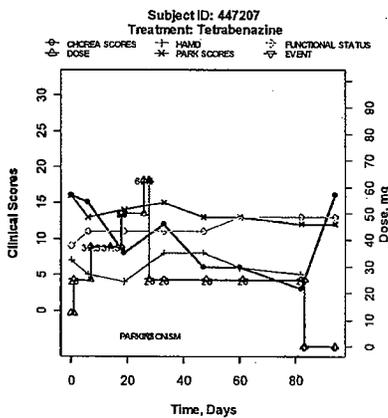
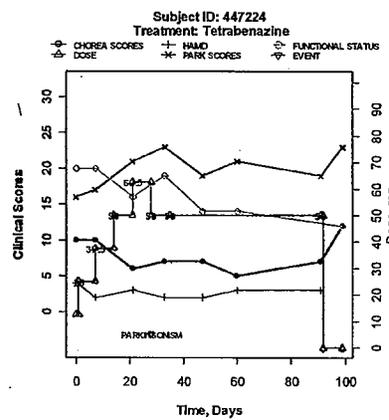
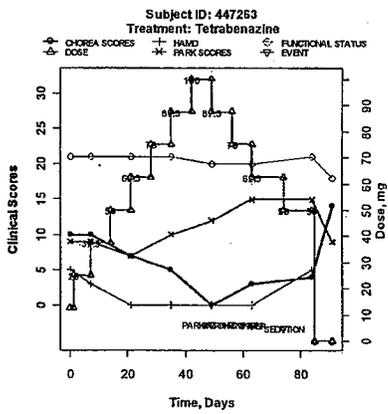
Figure 23. Changes in clinical scores (Chorea, HAMD, Parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for sedation.



Dose Adjustment Due to Parkinsonism in Study TBZ103,004

The dose of tetrabenazine was adjusted in 3 patients due to parkinsonism. In 3 out of 3 patients, a reduction of atleast 3 units in chorea score from baseline was preserved inspite of dose reductions. Shown in Figure 24 is the time course of chorea scores, functional status, HAMD and parkinsonism (PARK) scores in patients whose dose was adjusted for parkinsonism. In patient 447263, dose reduction did not result in decrease of parkinsonism scores till the last day of treatment.

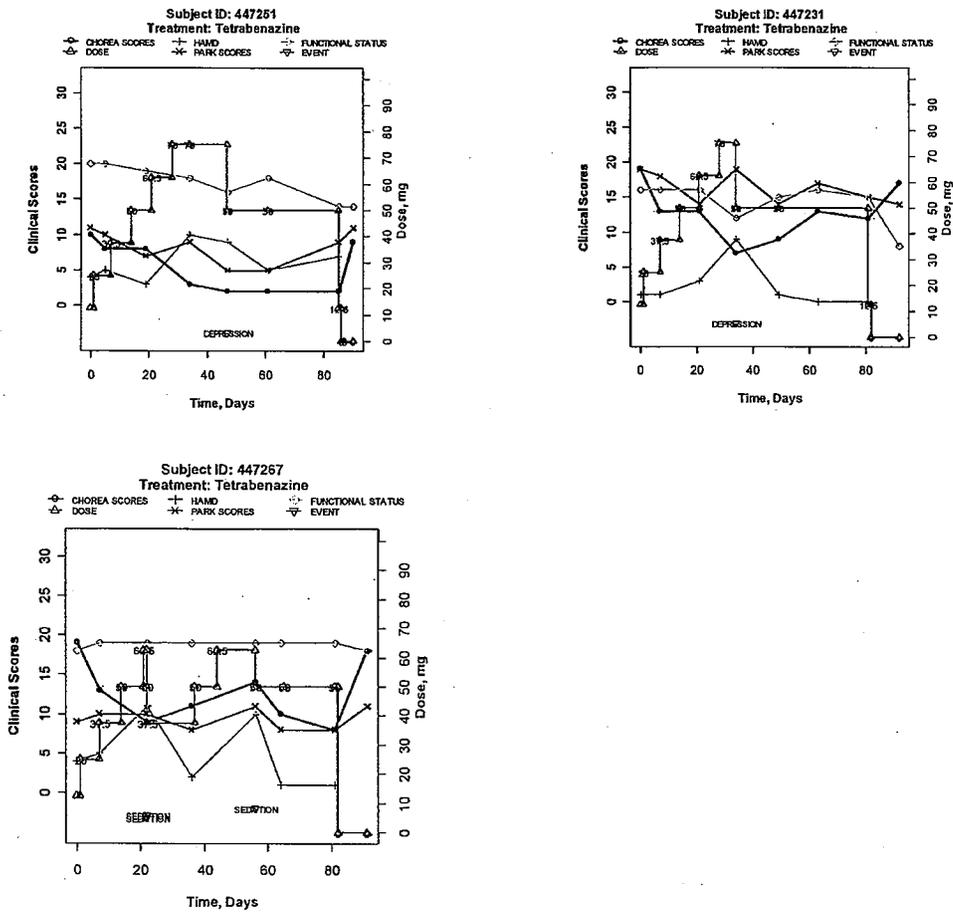
Figure 24. Changes in clinical scores (Chorea, HAMD, Parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for parkinsonism.



Dose Adjustment Due to Depression in Study TBZ103,004

The dose of tetrabenazine was adjusted in 3 patients due to depression. In 3 out of 3 patients, a reduction of atleast 3 units in chorea score from baseline was preserved inspite of dose reductions. Shown in Figure 25 is the time course of chorea scores, functional status, HAMD and parkinsonism (PARK) scores in patients whose dose was adjusted for depression. The dose reductions result in lowering of the HAMD scores.

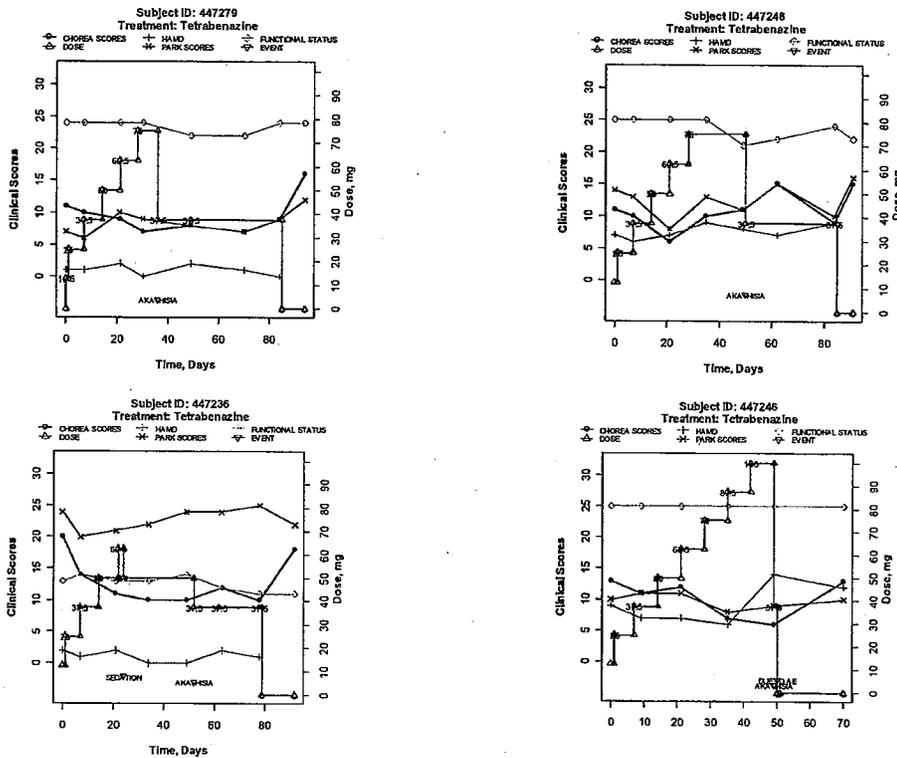
Figure 25. Changes in clinical scores (Chorea, HAMD, parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for depression (increase (worsening) in HAMD scores).



Dose Adjustment Due to Akathisia in Study TBZ103,004

The dose of tetrabenazine was adjusted in 3 patients due to akathisia according to sponsor. FDA medical officer identified a total of 5 patients in whom the dose of tetrabenazine was adjusted. In 2 out of 5 patients, a reduction of atleast 3 units in chorea score from baseline was preserved inspite of dose reductions. Shown in Figure 26 is the time course of chorea scores, parkinsonism (PARK), functional status, HAMD scores in patients whose dose was adjusted for akathisia.

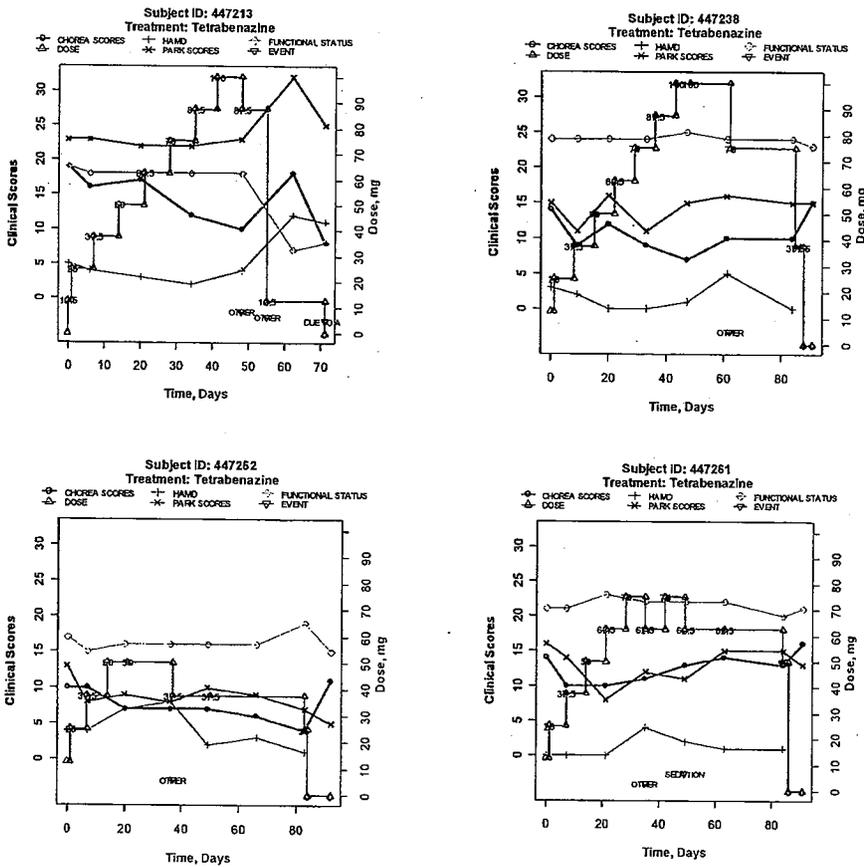
Figure 26. Changes in clinical scores (Chorea, HAMD, Parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for akathisia.



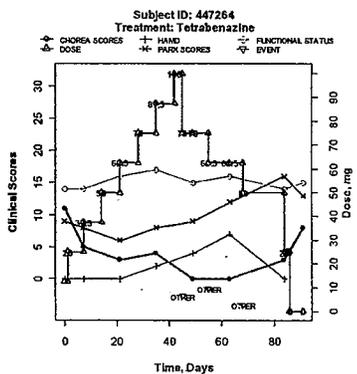
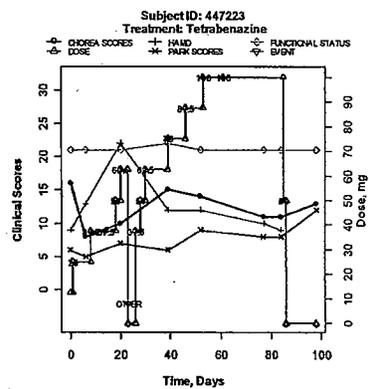
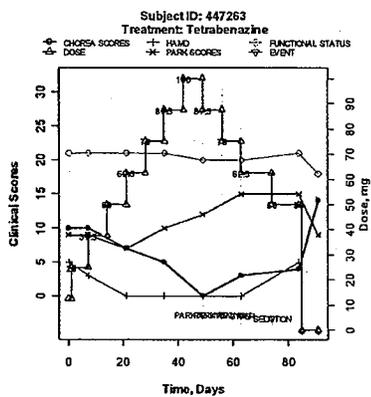
Dose Adjustment Due to Other Events in Study004

The dose of tetrabenazine was adjusted in 7 patients due to other adverse events such as agitation, anorexia, restlessness, fatigue, diarrhea, anxiety attack. In 5 out of 7 patients, a reduction of atleast 3 units in chorea score was preserved inspite of dose reductions. 1 out of 7 patients did not respond to treatment (no change in chorea scores at any dose level) while 1 out of 7 patients did not have preserve 3 units reduction in chorea scores due to dose reduction. Shown in Figure 27 is the time course of chorea scores, parkinsonism (PARK), functional status, HAMD scores in patients whose dose was adjusted for other reasons.

Figure 27. Changes in clinical scores (Chorea, HAMD, Parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for other adverse events.



Tetrabenazine Pharmacometrics Review



4. How should the dose of Tetrabenazine be adjusted in patients initiating treatment with CYP2D6 Inhibitors?

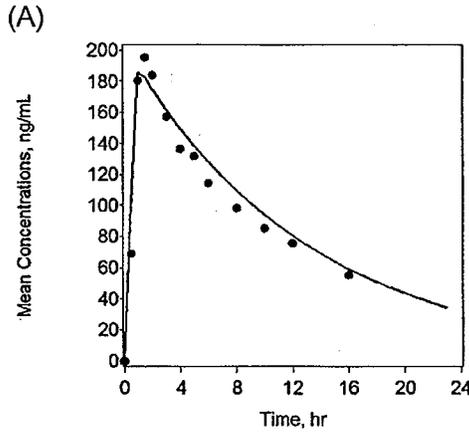
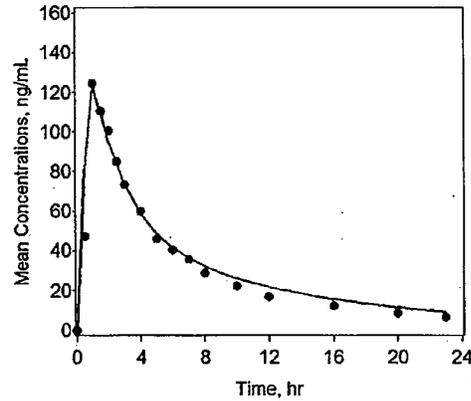
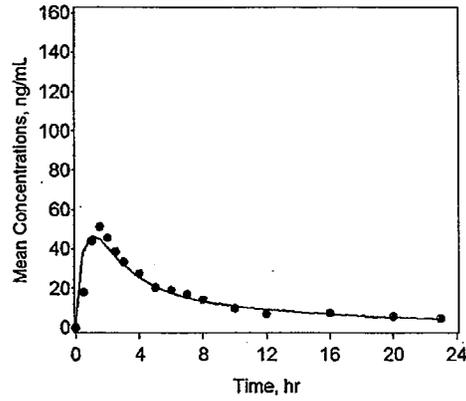
Tetrabenazine is metabolized by reductase enzymes to α -dihydro-tetrabenazine (α -HTBZ) and β -dihydro-tetrabenazine (β -HTBZ). Both α -HTBZ and β -HTBZ are further metabolized predominantly by CYP2D6 enzyme. Patients with Huntington's disease who are likely to be administered strong CYP2D6 inhibitors such as Paroxetine for management of depression will accumulate both α -HTBZ and β -HTBZ. Since it is not known whether the observed pharmacological adverse effects (sedation, somnolence, akathisia, depression, parkinsonism) are related to either α -HTBZ or β -HTBZ, dosing recommendations are being provided which would result in plasma concentrations of total HTBZ (α -HTBZ + β -HTBZ) similar to the patients not taking any CYP2D6 inhibitors. The aim is to match the concentrations of total HTBZ as close as possible with the simplest dosing regimen which would minimize dosing errors. Simulations were conducted using Pharsight Clinical Trial Simulator.

Figure 28 shows the observed and simulated mean concentrations of total HTBZ in patients after a single oral dose of 25 and 50 mg in Study TBZ 104,015. Figure 28 shows the simulated mean concentrations of total HTBZ in patients taking a single 50 mg dose after treatment with multiple oral doses of Paroxetine in Study TBZ 107,018. These graphs confirm the validity of the chosen models as the observed and simulated data are similar.

Based on these models, simulations were conducted to determine the plasma concentrations of total HTBZ after multiple total daily doses of (A) 100 mg with Paroxetine (B) 50 mg with Paroxetine (C) 25 mg with Paroxetine (D) 100 mg without Paroxetine.

Based on the mean predicted concentrations as shown in Figure 29, if the dose in a patient who is currently taking a total daily dose of 100 mg (A) is reduced by 50% to 50 mg which is split to be administered every 12 hours (B) will provide adequate concentrations. These concentrations are higher in comparison to a patient who is not taking Paroxetine (D). Also it should be noted that in Study TBZ 107,018 the AUC of alpha-tetrabenazine (active metabolite) increases by 3 fold. The AUC of beta-tetrabenazine (inactive metabolite) increases by 9 fold. This dosing regimen might ensure that patients will still have retained adequate exposure to alpha-tetrabenazine and ultimately the effects of Tetrabenazine on chorea.

Figure 28. Mean observed (●) and simulated (solid line) total HTBZ concentrations after (A) Single oral dose of 25 mg (B) Single oral dose of 50 mg in Study TBZ 104,015 (C) Single oral dose of 50 mg in Study TBZ 107,018.



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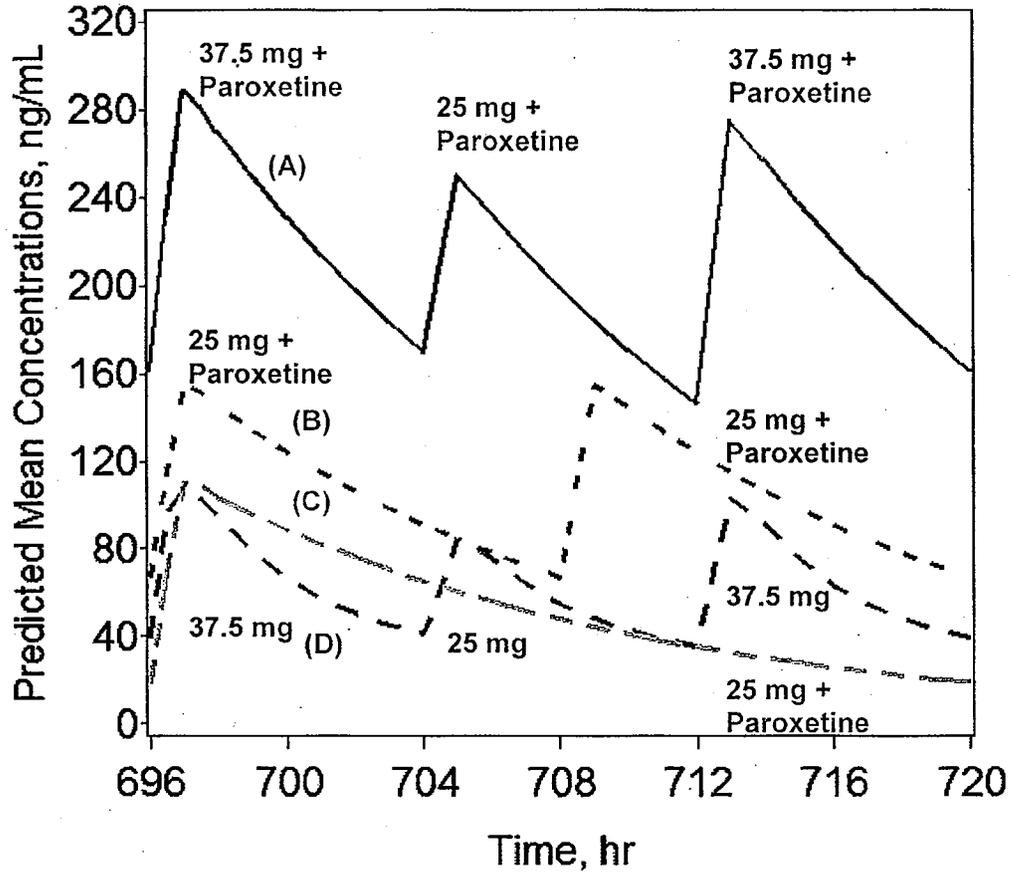
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Figure 29. Predicted mean concentrations of alpha+beta Tetrabenazine at steady state after multiple total daily doses of (A) 100 mg with Paroxetine (B) 50 mg with Paroxetine (C) 25 mg with Paroxetine (D) 100 mg without Paroxetine.

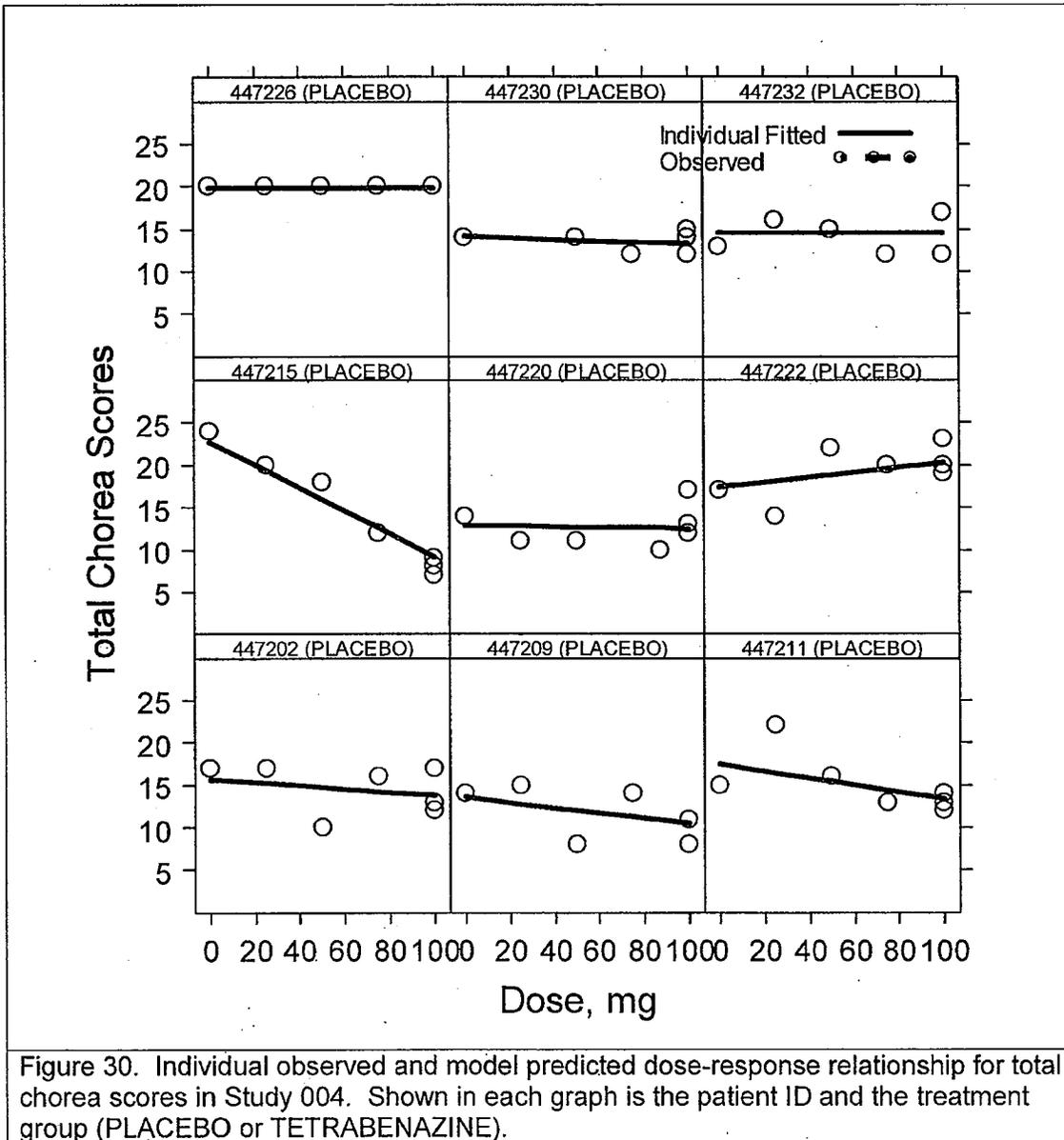


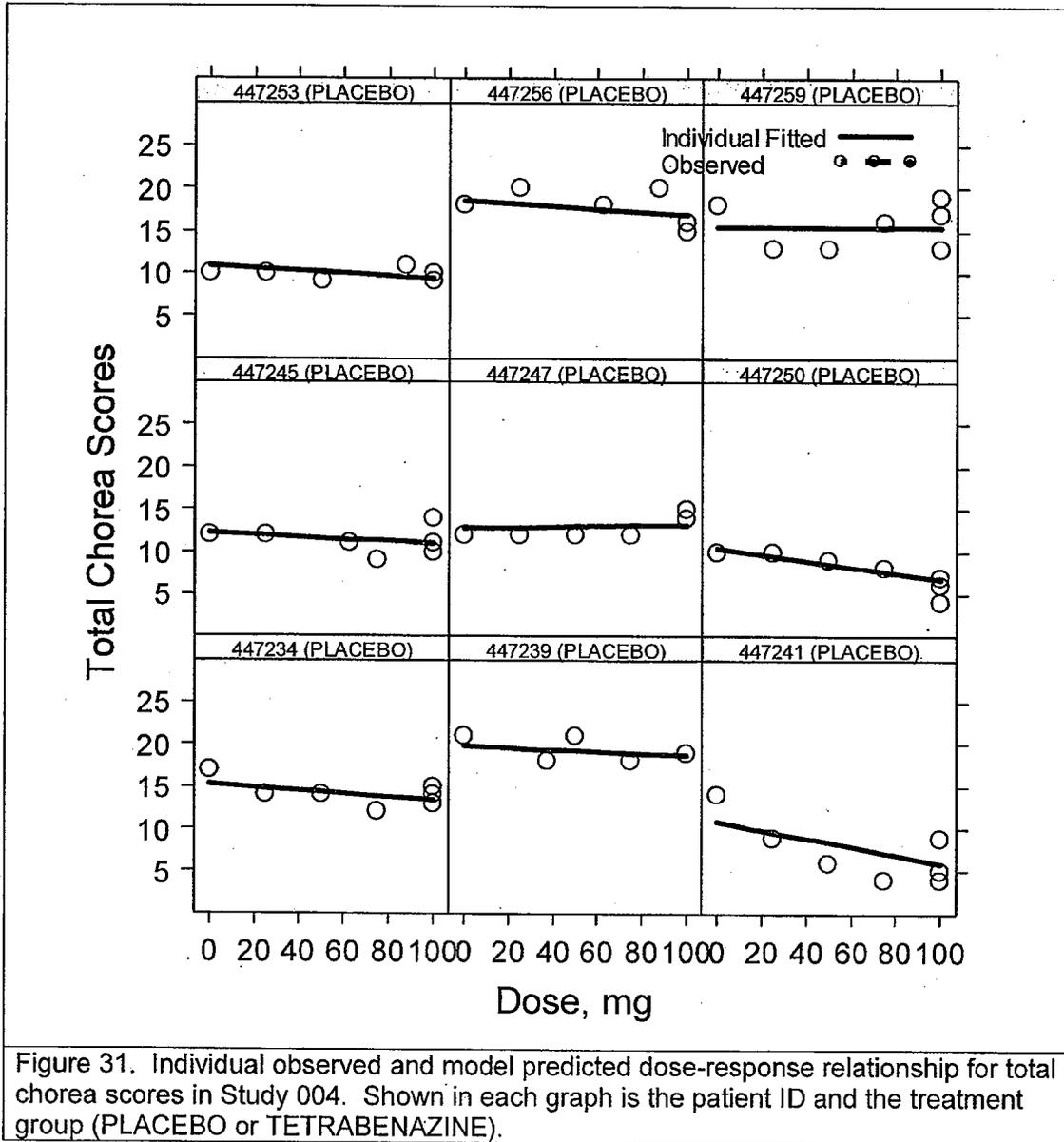
Conclusions

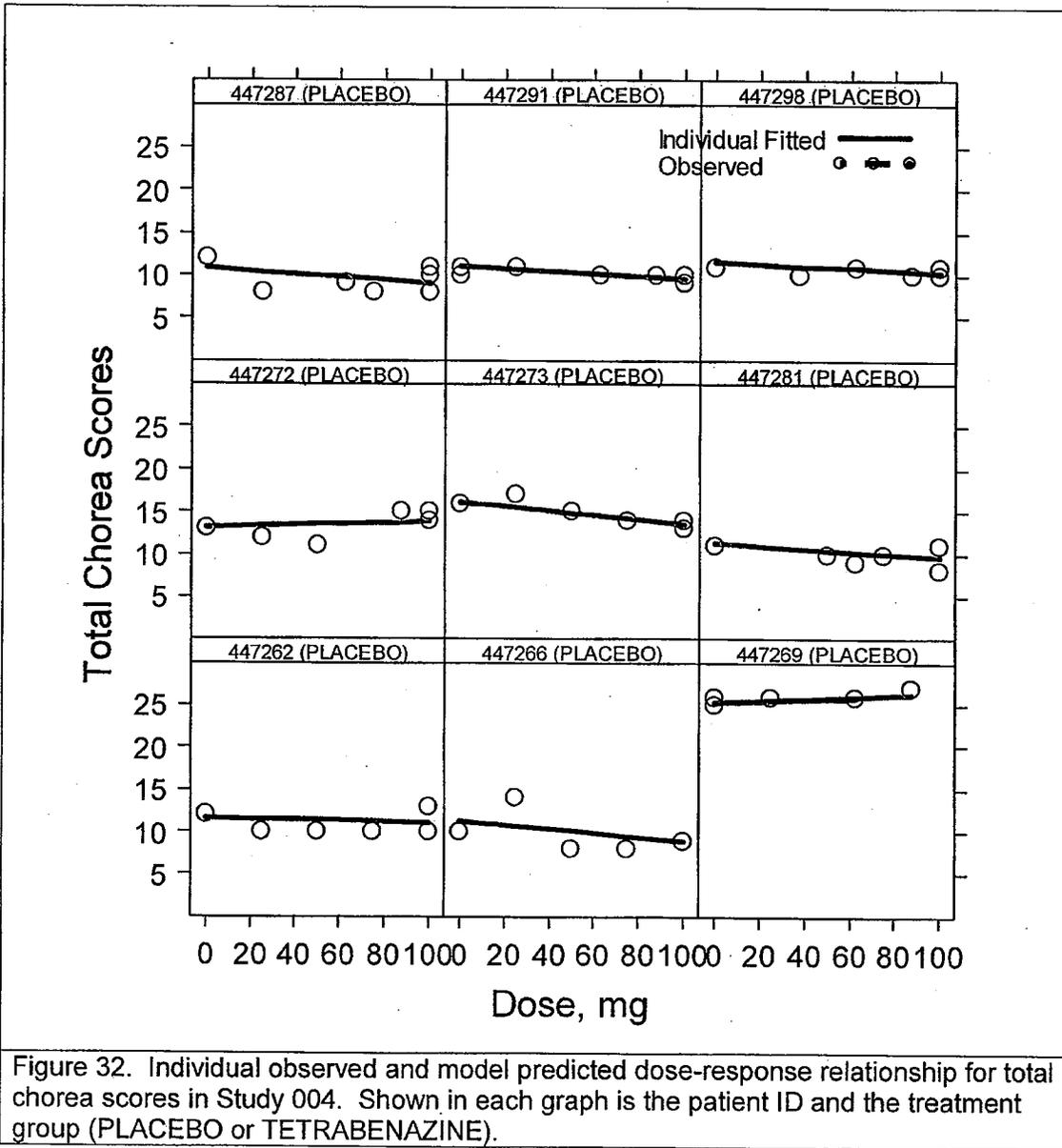
- In TBZ 103, 004 the primary endpoint is met and the trial is positive. In addition, there is a clear dose-response relationship for the Chorea scores confirming that Tetrabenazine significantly affects Chorea scores.
- About 40% of patients required 100 mg dose by week 12 for optimal benefit, in Study TBZ 103,004.
- Patients with higher baseline symptoms had greater lowering of Chorea score. The drug effect was found to be proportional to baseline Chorea scores.
- The trend in Changes in the Functional Assessment, Cognitive Scores, Sedative Scores with dose, if any, is not obvious.
- The dose of tetrabenazine should be reduced by 50% and administered as twice daily dosing regimen in patients who are currently taking Tetrabenazine and will be initiating treatment with strong CYP2D6 inhibitors.

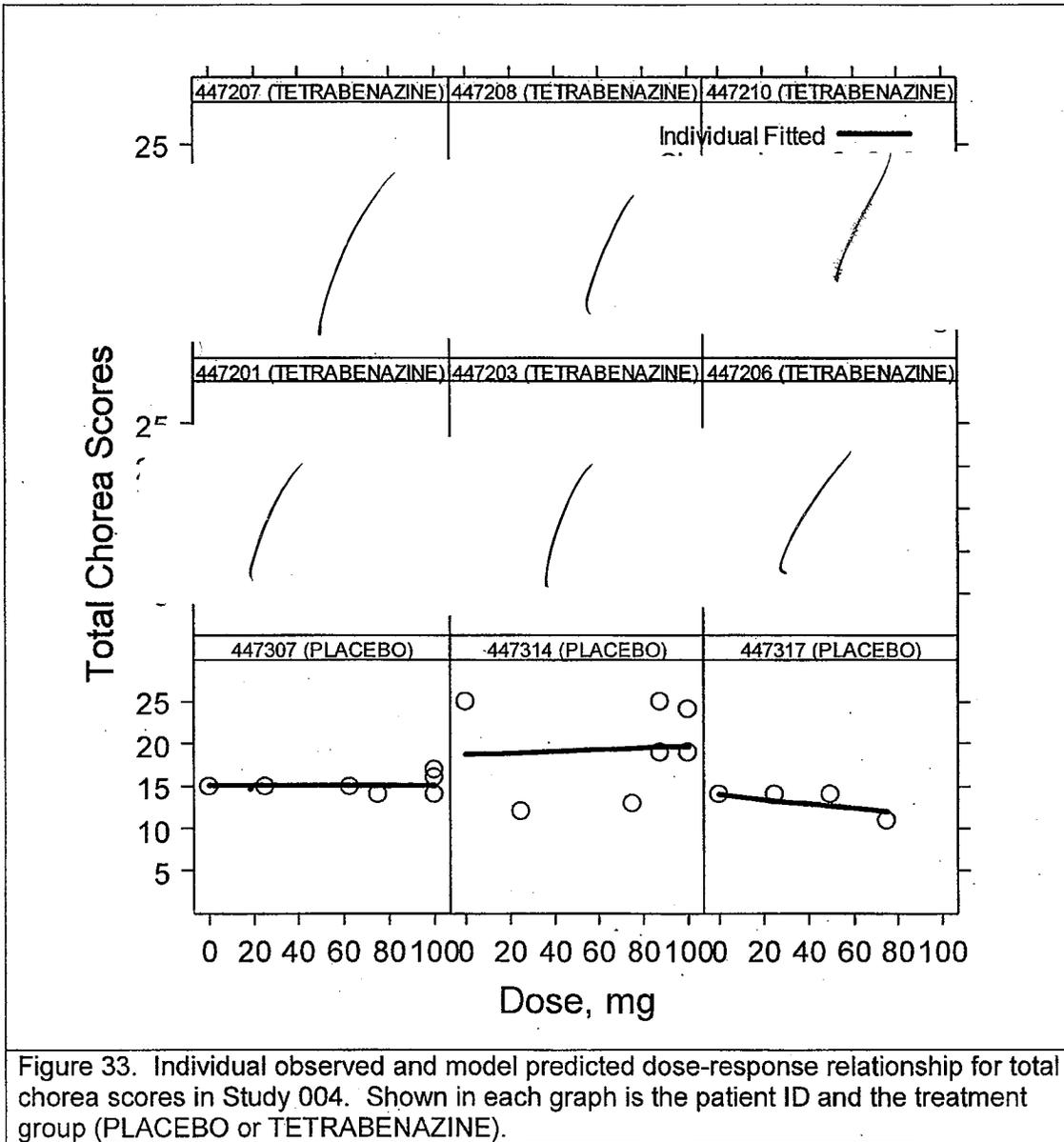
APPENDIX I

Individual dose-response fits based on linear dose-response model









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Atul Bhattaram
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12/26/2007 02:20:32 PM
BIOPHARMACEUTICS

NDA 21,894
Tetrabenazine

Clinical Pharmacology Review

NDA:	21-894	
Brand Name:	Xenazine	
Generic Name:	Tetrabenazine	
Type of Dosage Form:	Tablet	
Strengths:	12.5 mg, 50 mg	
Indications:	Chorea of Huntington's Disease	
Type of Submission:	Response to Approvable Letter	
Sponsor:	Prestwick Pharmaceuticals, Inc.	
Submission Date:	2/20/07	8/15/07
	4/4/07	8/17/07
	4/10/07	8/20/07
	6/12/07	8/31/07
	6/13/07	9/11/07
	6/26/07	9/26/07
	6/28/07	10/3/07
	7/19/07	10/5/07
	8/12/07	10/12/07
	8/6/07	10/23/07
	8/5/07	11/27/07
OCP Division:	DCP-I	
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1 Executive Summary

1.1 Recommendations

The clinical pharmacology information submitted to NDA 21-894 is acceptable provided that the following are addressed prior to approval:

- 1) An *in vitro* metabolism study should be performed to characterize the inhibitory effect of TBZ, α -HTBZ and β -HTBZ on CYP2B6. The results of this study will guide the need for further *in vivo* drug interaction studies.
- 2) Agreement is reached between the Sponsor and the Agency regarding labeling (Please refer to **Section 3** of this review).

The Clinical Pharmacology requests for Phase 4 Commitments in the original NDA have been resolved and are no longer applicable.

1.2 Phase 4 Commitments

If it is determined that NDA 21-894 can be approved in this cycle, the recommendation above for an *in vitro* study of CYP2B6 can be addressed as a Phase IV commitment.

**APPEARS THIS WAY
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1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The present submission is a Response to the Approvable Letter for NDA 21894 to support the approval of XENAZINE (tetrabenazine) for the treatment of chorea associated with Huntington's disease. The strengths of tetrabenazine (TBZ) are 12.5 mg and 25 mg. The proposed starting dose is 25 mg daily (12.5 mg in the morning and 12.5 mg in the evening) with upward titration as follows. One week later the dose should be increased to 37.5 mg per day (12.5 mg in the morning, 12.5 mg at noon, and 12.5 mg in the evening) and then continue to be increased weekly by 12.5 mg increments until satisfactory control of chorea is achieved or until side effects occur or until a maximal dose of 100 mg per day (given in divided doses, generally tid) is reached.

Clinical Pharmacology Comments in the Approvable Letter:

The following Clinical Pharmacology and Biopharmaceutics comments were included in the approvable letter:

1. Clarify the rotation speed at which the dissolution method was generated (previously requested on 1/2/06). If you have data to support the proposed rotation speed and agreement is reached between us regarding dissolution specifications, the method and agreed upon specifications can be accepted as interim method and specifications. The recommended dissolution method and specifications are as follows:

Apparatus: USP Apparatus 2 (Paddles)

Medium: 0.1 M HCl

Volume: 900 ml

Rotation Speed: 50 rpm

Specification: \geq $\frac{Q}{Q}$ in 30 minutes

2. Since the 25 mg tablet is scored, you should demonstrate dissolution similarity (with f2 testing and using the interim dissolution method above) between 2 half-tablets and 1 whole 25 mg tablet.

3. The P16 component, identified as the largest circulating component in the mass balance study, should be characterized. In addition, the extent to which the mono- and bis-dealkyl tetrabenazine metabolites (and other individual metabolites) are circulating should be clarified.

4. You should submit adequately performed *in vitro* metabolism studies to address the potential for inhibition or induction of P450s by TBZ and its metabolites. You should also characterize the *in vitro* metabolism of TBZ and its metabolites as well as the role of Pgp in TBZ disposition. Finally, you should adequately address the role for TBZ as a Pgp inhibitor *in vitro*. There is currently insufficient information to allow for adequate labeling regarding the potential for drug interactions. Please see our comments below about performing the *in vitro* drug metabolism studies (communicated to you in an email of 12/21/05).

i. You have not taken a step-wise approach to understanding the metabolism of TBZ or its metabolites. The preferred first approach would be to directly identify metabolites after incubation with hepatocytes or liver slices. Subsequent studies can also eliminate non CYP oxidative pathways.

ii. The studies to evaluate CYP pathways of TBZ and HTBZ metabolism are methodologically deficient. It is recommended that recombinant enzymes not be used alone, but in combination

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with other methods (such as use of inhibitors) for identifying drug metabolizing P450 isozymes. In addition, the probes used as controls in the submitted studies are not classical, preferred probes, and you have not provided justification, so it is difficult to understand the acceptability of the results.

iii. Studies characterizing the metabolism of TBZ *in vitro* should include measurement of the formation of metabolites (including the oxidative metabolites of TBZ and the oxidative metabolites of HTBZ) to identify the pathways by which they are formed.

iv. You should follow-up the results of the submitted studies with *in vitro* inhibition studies that use well accepted methodology and preferred substrates to confirm lack of involvement of TBZ and its metabolites in inhibition of P450s.

v. The *in vitro* study of TBZ inhibition of Pgp provided from the literature was not conducted with methods that are in agreement with current Agency thinking. The *in vivo* TBZ-digoxin interaction study was performed with a low dose of TBZ, and does not allow for conclusions about higher doses that will be used clinically. You should perform an adequate *in vitro* inhibition study using preferred methodology to determine the need for further *in vivo* study.

vi. The results of adequate *in vitro* drug metabolism studies will guide the need for further *in vivo* drug interaction studies.

vii. Since CYP2D6 appears to be involved in the metabolism of TBZ and HTBZ, we recommend genotyping for CYP2D6 in future TBZ clinical trials.

viii. The thorough QT study did not assess exposure to TBZ or metabolites outside of the ranges that might be normally observed after administration. The results of the *in vitro* drug metabolism studies may help guide decisions regarding the need and approach for further metabolically based evaluation of QT.

In addition, the following were identified as Phase 4 commitments:

1. Perform an *in vivo* study of the effect of CYP2D6 inhibition on TBZ disposition using a strong CYP2D6 inhibitor since CYP2D6 inhibition may increase the exposure to the inactive β -HTBZ relative to the active moiety α -HTBZ (based on evaluation of plasma concentrations in Phase III studies).
2. Evaluate the clinical relevance of CYP2D6 inhibition after administration of TBZ *in vivo* using a sensitive CYP2D6 substrate (such as desipramine) since *in vitro* studies suggest involvement of CYP2D6.
3. Other *in vivo* drug interaction studies should be guided by the results of the *in vitro* drug metabolism studies, in agreement with the Agency.
4. The discriminatory ability of the interim dissolution method should be determined in order to determine the final dissolution specifications.

Present Submission: In the present submission the Sponsor has responded to the 4 Clinical Pharmacology Comments.

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- Responses to comments 1 and 2 regarding dissolution of this immediate release product were reviewed by Office of New Drug Chemistry (please see Dr. Tele's review) and will not be reviewed here. The CMC review concludes that the proposed dissolution method is acceptable and can be the final regulatory method for this product.
- Responses to Comment 3 regarding the P16 component and other circulating metabolites and to Comment 4 regarding in vitro drug metabolism study will be reviewed in the present review (Section 2.1).

The initial Clinical Pharmacology request for Phase 4 commitments can be resolved as follows:

- The Sponsor has conducted an *in vivo* study of the effect of CYP2D6 inhibition on TBZ disposition and that study is reviewed in the present review (Section 2.1).
- Following review of *in vitro* data, it does not appear that TBZ or its α - or β -HTBZ metabolites are inhibitors of CYP2D6. Therefore, it is no longer necessary to perform a clinical study to evaluate the potential for this type of interaction.
- The results of *in vitro* drug metabolism studies do not suggest the need for further *in vivo* drug interaction studies.
- The Office of New Drug Chemistry has reviewed the dissolution method, and the Clinical Pharmacology recommendation to determine discriminatory ability is no longer relevant.

The following clinical pharmacology studies have been submitted and reviewed:

- | | |
|--|-------------|
| • Mass Balance Study (Metabolite Characterization) | CAM/06 |
| • In Vitro TBZ Metabolism Study | CAM/16 |
| • In Vitro TBZ Metabolism in Several Species | CAM/26 |
| • In Vitro α -HTBZ Metabolism Study | CAM/19 |
| • In Vitro β -HTBZ Metabolism Study | CAM/20 |
| • In Vitro Study of TBZ and Metabolites as P450 Inducers | — 063015 |
| • In Vitro Study of TBZ and Metabolites as P450 Inhibitors | — 065005 |
| • In Vitro Study of TBZ and Metabolites as Pgp Substrates and Inhibitors | 6PRESF |
| • Paroxetine Interaction Study | TBZ 107,018 |

A final study report for Hepatic Impairment Study TBZ 203,010 (completed in August 2007) was submitted and reviewed. (The interim study report was reviewed with the original NDA submission). The conclusions of the present review have not changed since the original review, and contraindication of TBZ in patients with hepatic impairment is recommended.

The Sponsor has submitted the final study report for thorough QT study 104,015 that is under review by the IRT. The Sponsor has submitted studies 107,017 and 107,018 that include additional QT information. These data will be evaluated by Pharmacometrics with respect to the exposure response relationship.

In addition, the following study report was submitted but not reviewed:

The key findings with respect to the Clinical Pharmacology of TBZ as identified in the Response to Approvable Letter are as follows:

- The P16 component has been identified as O-dealkylated HTBZ. This is further metabolized to sulfate conjugates. These 3 metabolites contribute to a significant portion of the circulating moieties following administration of TBZ in humans.
- The primary pathway for metabolism of TBZ is reductase (non-P450)-mediated formation of HTBZ.
- The primary pathway for metabolism of α - and β -HTBZ is CYP2D6. Paroxetine, a strong inhibitor of CYP2D6, resulted in an approximate 3-fold increase in exposure to α -HTBZ and a 9-fold increase in exposure to β -HTBZ after a single dose of TBZ in healthy volunteers. The elimination half-life of α -HTBZ and β -HTBZ was prolonged from approximately 4-7 hours to approximately 14 hours. OCP recommends consideration of dosage adjustment (e.g. _____) in patients taking strong CYP2D6 inhibitors, and this recommendation is extended to patients known to be poor metabolizers of drugs metabolized by CYP2D6.
- Neither TBZ nor its α - or β -HTBZ metabolites are predicted to result in inhibition of CYP2D6, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A at clinically relevant exposures, based on results of *in vitro* studies. Effects on CYP2B6 have not been evaluated.
- Neither TBZ nor its α - or β -HTBZ metabolites are predicted to result in induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 based on results of *in vitro* studies. No further study of induction is necessary.
- Neither TBZ nor its α - or β -HTBZ metabolites are predicted to be substrates or inhibitors of P-glycoprotein at clinically relevant exposures.
- The final study report for the hepatic impairment study TBZ 202,010 confirms that exposure to TBZ is significantly increased in subjects with mild-moderate hepatic impairment. Without an understanding of the contribution of elevated levels of TBZ to safety, it is not possible to recommend a dosage adjustment in hepatic impairment. OCP recommends that TBZ should be contraindicated in patients with hepatic impairment.

Recommendations:

The clinical pharmacology information submitted to NDA 21-894 is acceptable provided that the following are addressed prior to approval:

- 1) An *in vitro* metabolism study should be performed to characterize the effect of inhibitory effect of TBZ, α -HTBZ and β -HTBZ on CYP2B6. The results of this study will guide the need for further *in vivo* drug interaction studies.
- 2) Agreement is reached between the Sponsor and the Agency regarding labeling (Please refer to Section 3 of this review).

NDA 21,894
Tetrabenazine

**APPEARS THIS WAY
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Office of Clinical Pharmacology

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CSO/S. Daugherty
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor

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2 Question-Based Review

Note: the primary metabolites of tetrabenazine were previously referred to by the Sponsor as α - and β -dihydro-tetrabenazine (HTBZ). In the revised labeling submitted with the Response to the Approvable Letter, the Sponsor has now designated these metabolites as — This review refers to the metabolites as HTBZ.

2.1 Background

Tetrabenazine (TBZ) has been developed for treatment of chorea associated with Huntington's disease (HD). It was discovered in the 1950s-1960s and the Sponsor states that TBZ was first introduced for treatment of chorea in the United Kingdom in 1971. It is currently registered in Europe, Canada, Australia, and New Zealand where it is available as 25 mg immediate release tablets.

TBZ is rapidly metabolized to more than 19 metabolites. At the time of the initial NDA submission, the circulating metabolites that had been characterized were α - and β -dihydro-tetrabenazine (HTBZ). Clinical Pharmacology information, as summarized in the OCP review of the original NDA is as follows. TBZ normally does not circulate to a significant extent (in healthy volunteers it is usually not detectable or is seen at concentrations approximately 5-fold lower than α -HTBZ, with an estimated half-life of approximately 0.4 hrs, according to the original OCP review). The active moiety is thought to be α -HTBZ. On average, exposure to α -HTBZ is greater than exposure to β -HTBZ, although the ratio ranges from approximately 0.4 to 6.8. (The ratio is generally at the low end with CYP2D6 inhibition). The elimination half-life is approximately 4-8 hours for α -HTBZ and approximately 2.4-5.2 hours for β -HTBZ.

The strengths of tetrabenazine (TBZ) are 12.5 mg and 25 mg. The proposed starting dose is 25 mg daily (12.5 mg in the morning and 12.5 mg in the evening) with upward titration as follows. One week later the dose should be increased to 37.5 mg per day (12.5 mg in the morning, 12.5 mg at noon, and 12.5 mg in the evening) and then continue to be increased weekly by 12.5 mg increments until satisfactory control of chorea is achieved or until side effects occur or until a maximal dose of 100 mg per day (given in divided doses, generally tid) is reached. The proposed maximum dose at any given administration is 37.5 mg.

The original NDA was submitted on 9/23/05 and an approvable letter was sent to the Sponsor on 3/24/06. Clinical concerns focused on considerations of risk. The following Clinical Pharmacology and Biopharmaceutics comments were included in the approvable letter:

1. Clarify the rotation speed at which the dissolution method was generated (previously requested on 1/2/06). If you have data to support the proposed rotation speed and agreement is reached between us regarding dissolution specifications, the method and agreed upon specifications can be accepted as interim method and specifications. The recommended dissolution method and specifications are as follows:

Apparatus: USP Apparatus 2 (Paddles)
Medium: 0.1 M HCl
Volume: 900 ml

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Tetrabenazine

Rotation Speed: 50 rpm
Specification: \geq $\frac{1}{Q}$ in 30 minutes

2. Since the 25 mg tablet is scored, you should demonstrate dissolution similarity (with f_2 testing and using the interim dissolution method above) between 2 half-tablets and 1 whole 25 mg tablet.
3. The P16 component, identified as the largest circulating component in the mass balance study, should be characterized. In addition, the extent to which the mono- and bis-dealkyl tetrabenazine metabolites (and other individual metabolites) are circulating should be clarified.
4. You should submit adequately performed *in vitro* metabolism studies to address the potential for inhibition or induction of P450s by TBZ and its metabolites. You should also characterize the *in vitro* metabolism of TBZ and its metabolites as well as the role of Pgp in TBZ disposition. Finally, you should adequately address the role for TBZ as a Pgp inhibitor *in vitro*. There is currently insufficient information to allow for adequate labeling regarding the potential for drug interactions. Please see our comments below about performing the *in vitro* drug metabolism studies (communicated to you in an email of 12/21/05).
 - i. You have not taken a step-wise approach to understanding the metabolism of TBZ or its metabolites. The preferred first approach would be to directly identify metabolites after incubation with hepatocytes or liver slices. Subsequent studies can also eliminate non CYP oxidative pathways.
 - ii. The studies to evaluate CYP pathways of TBZ and HTBZ metabolism are methodologically deficient. It is recommended that recombinant enzymes not be used alone, but in combination with other methods (such as use of inhibitors) for identifying drug metabolizing P450 isozymes. In addition, the probes used as controls in the submitted studies are not classical, preferred probes, and you have not provided justification, so it is difficult to understand the acceptability of the results.
 - iii. Studies characterizing the metabolism of TBZ *in vitro* should include measurement of the formation of metabolites (including the oxidative metabolites of TBZ and the oxidative metabolites of HTBZ) to identify the pathways by which they are formed.
 - iv. You should follow-up the results of the submitted studies with *in vitro* inhibition studies that use well accepted methodology and preferred substrates to confirm lack of involvement of TBZ and its metabolites in inhibition of P450s.
 - v. The *in vitro* study of TBZ inhibition of Pgp provided from the literature was not conducted with methods that are in agreement with current Agency thinking. The *in vivo* TBZ-digoxin interaction study was performed with a low dose of TBZ, and does not allow for conclusions about higher doses that will be used clinically. You should perform an adequate *in vitro* inhibition study using preferred methodology to determine the need for further *in vivo* study.
 - vi. The results of adequate *in vitro* drug metabolism studies will guide the need for further *in vivo* drug interaction studies.
 - vii. Since CYP2D6 appears to be involved in the metabolism of TBZ and HTBZ, we recommend genotyping for CYP2D6 in future TBZ clinical trials.

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viii. The thorough QT study did not assess exposure to TBZ or metabolites outside of the ranges that might be normally observed after administration. The results of the *in vitro* drug metabolism studies may help guide decisions regarding the need and approach for further metabolically based evaluation of QT.

In addition, the following were identified as Phase 4 commitments:

1. Perform an *in vivo* study of the effect of CYP2D6 inhibition on TBZ disposition using a strong CYP2D6 inhibitor since CYP2D6 inhibition may increase the exposure to the inactive β -HTBZ relative to the active moiety α -HTBZ (based on evaluation of plasma concentrations in Phase III studies).
2. Evaluate the clinical relevance of CYP2D6 inhibition after administration of TBZ *in vivo* using a sensitive CYP2D6 substrate (such as desipramine) since *in vitro* studies suggest involvement of CYP2D6.
3. Other *in vivo* drug interaction studies should be guided by the results of the *in vitro* drug metabolism studies, in agreement with the Agency.
4. The discriminatory ability of the interim dissolution method should be determined in order to determine the final dissolution specifications.

Present Submission: In the present submission the Sponsor has responded to the 4 Clinical Pharmacology Comments.

- Responses to comments 1 and 2 regarding dissolution of this immediate release product were reviewed by Office of New Drug Chemistry and will not be reviewed here.
- Responses to Comment 3 regarding the P16 component and other circulating metabolites and to Comment 4 regarding *in vitro* drug metabolism study will be reviewed in the present review (Section 2.1).

The initial Clinical Pharmacology request for Phase 4 commitments can be resolved as follows:

- The Sponsor has conducted an *in vivo* study of the effect of CYP2D6 inhibition on TBZ disposition and that study is reviewed in the present review (Section 2.1).
- Following review of *in vitro* data, it does not appear that TBZ or its α - or β -HTBZ metabolites are inhibitors of CYP2D6. Therefore, it is no longer necessary to perform a clinical study to evaluate the potential for this type of interaction.
- The results of *in vitro* drug metabolism studies do not suggest the need for further *in vivo* drug interaction studies.
- The Office of New Drug Chemistry has reviewed the dissolution method, and the Clinical Pharmacology recommendation to determine discriminatory ability is no longer relevant.

The following clinical pharmacology studies have been submitted and reviewed:

- | | |
|--|-------------|
| • Mass Balance Study (Metabolite Characterization) | CAM/06 |
| • In Vitro TBZ Metabolism Study | CAM/16 |
| • In Vitro TBZ Metabolism in Several Species | CAM/26 |
| • In Vitro α -HTBZ Metabolism Study | CAM/19 |
| • In Vitro β -HTBZ Metabolism Study | CAM/20 |
| • In Vitro Study of TBZ and Metabolites as P450 Inducers | — 063015 |
| • In Vitro Study of TBZ and Metabolites as P450 Inhibitors | — 065005 |
| • In Vitro Study of TBZ and Metabolites as Pgp Substrates and Inhibitors | 6PRES |
| • Paroxetine Interaction Study | TBZ 107,018 |

A final study report for Hepatic Impairment Study TBZ 203,010 (completed in August 2007) was submitted and reviewed. (The interim study report was reviewed with the original NDA submission). The conclusions of the present review have not changed since the original review, and contraindication of TBZ in patients with hepatic impairment is recommended.

The Sponsor has submitted the final study report for thorough QT study 104,015 that is under review by the IRT. The Sponsor has submitted studies 107,017 and 107,018 that include additional QT information. These data will be evaluated by Pharmacometrics with respect to the exposure response relationship.

In addition, the following study report was submitted but not reviewed:

2.1 Sponsor's Response to Approvable Letter and Additional Clinical Pharmacology Information

2.1.1 Does this drug prolong the QT or QTc interval?

Thorough QT Study 104,105 is under review by the IRT. As reported in the original OCP review, TBZ caused an approximate 7 msec increase in QTc (F or I) and a 10 msec increase could not be excluded. Additional evaluation of studies 104,105 and drug interaction studies 107, 017 and 107, 018 is being conducted by Pharmacometrics.

2.1.2 Have the circulating moieties been characterized following administration of tetrabenazine?

In the response to the approvable letter, the Sponsor has identified, as requested, the P16 component that was previously identified as the largest circulating component in the previously conducted mass balance study (RD 204/24124) and characterized the remainder of the circulating components through 8 hours after administration. This information can be found in the study report for CAM/06. P16 has been identified as O-dealkylated-HTBZ. As seen in the

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table below, provided by the Sponsor, this metabolite (for which the enantiomers were not separately characterized) accounts for approximately 35% of the circulating radioactivity up to 1.5 hours following a single oral dose of [¹⁴C]-tetrabenazine in 6 healthy male subjects, and represents a mean of approximately 31% of the circulating radioactivity for the first 8 hours following a single oral dose of TBZ. In addition, the P11 and P13 components are the sulfate conjugates of O-dealkylated HTBZ and account for a significant portion of the circulating radioactivity in the mass balance study. Bis-O-dealkylated metabolites of TBZ, α-HTBZ, or β-HTBZ were not identified as major metabolites in human plasma, urine, or feces in the evaluation of the mass balance study (although they are observed *in vitro*). Sulfate conjugates of O-dealkylated HTBZ account for approximately 45% of the urinary metabolites, and glucuronide conjugates of O-dealkylated HTBZ are also observed. The components of the plasma that account for > 10% of the circulating radioactivity are shown in the table below, as provided by the Sponsor in the Efficacy Information Amendment (031) from 2/16/07.

Table 3 Metabolites Greater Than 10% in Plasma Following Single Oral Dosing of [¹⁴C]-Tetrabenazine to Six Male Human Subjects

Component	Identity	Metabolite Type	0.25 – 1.5 hours	2 – 3 hours	4 – 8 hours	Mean
P11	Sulfate conjugate of O-dealkylated-HTBZ	tertiary	23.44 (16.67)	29.52 (20.41)	15.23 (16.90)	22.73 (17.99)
P13	Sulfate conjugate of O-dealkylated-HTBZ	tertiary	26.73 (19.01)	41.77 (28.88)	24.22 (26.88)	30.91 (24.92)
P16	O-dealkylated-HTBZ	secondary	49.54 (35.24)	50.11 (34.65)	19.77 (21.95)	39.81 (30.61)
P17	β-HTBZ	primary	13.65 (9.71)	6.54 (4.52)	4.48 (4.97)	8.22 (6.40)
P18	α-HTBZ	primary	25.73 (18.30)	16.70 (11.55)	14.05 (15.60)	18.83 (15.15)

Source: Modified from Table 15 in CAM/06 (5.3.1.1)

Results expressed as ng equivalents/mL. Values in () are % sample radioactivity

HTBZ = dihydrotetrabenazine

As reviewed by OCP in the original NDA submission, there is great variability in the pharmacokinetics of α- and β-HTBZ in humans, and great variability in the ratio of these metabolites. In the initial thorough QT study 104,015 the ratio of AUC for α: β ranged from 0.29-6.14, an approximate 20-fold range.

Of note, in a submission from October 3, 2007 the Sponsor has provided additional information to support the presence of circulating O-dealkylated HTBZ (desmethyl HTBZ) following a single 50 mg dose of TBZ in 6 healthy subjects. The results are shown in the table below, as provided by the Sponsor. (These results are considered by the reviewer to be preliminary because the supporting analytical method has not been provided).

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Table 1: Summary of pharmacokinetic parameters for α -HTBZ, β -HTBZ, 1-desmethyl HTBZ, and 3-desmethyl HTBZ after oral administration of a single 50 mg dose of tetrabenazine to healthy volunteers.

Parameter ¹	α -HTBZ	β -HTBZ	1-Desmethyl ² HTBZ	3-Desmethyl ² HTBZ
C _{max} (ng/mL)	87.3 ± 21.7 (6)	46.8 ± 30.6 (6)	26.9 ± 8.41 (6)	9.53 ± 3.28 (5)
T _{max} (h)	1.25 (6)	1.50 (6)	2.00 (6)	2.00 (5)
AUC(0-t) (h·ng/mL)	491 ± 269 (6)	219 ± 251 (6)	313 ± 113 (6)	59.3 ± 19.7 (4)
AUC(∞) (h·ng/mL)	506 ± 276 (6)	234 ± 253 (6)	466 ± 161 (6)	73.8 (1)
λz (h ⁻¹)	0.1017 ± 0.0340 (6)	0.1710 ± 0.0592 (6)	0.0631 ± 0.0209 (6)	0.1260 (1)
t½ (h)	7.33 ± 1.94 (6)	4.58 ± 1.86 (6)	12.3 ± 4.65 (6)	5.50 (1)

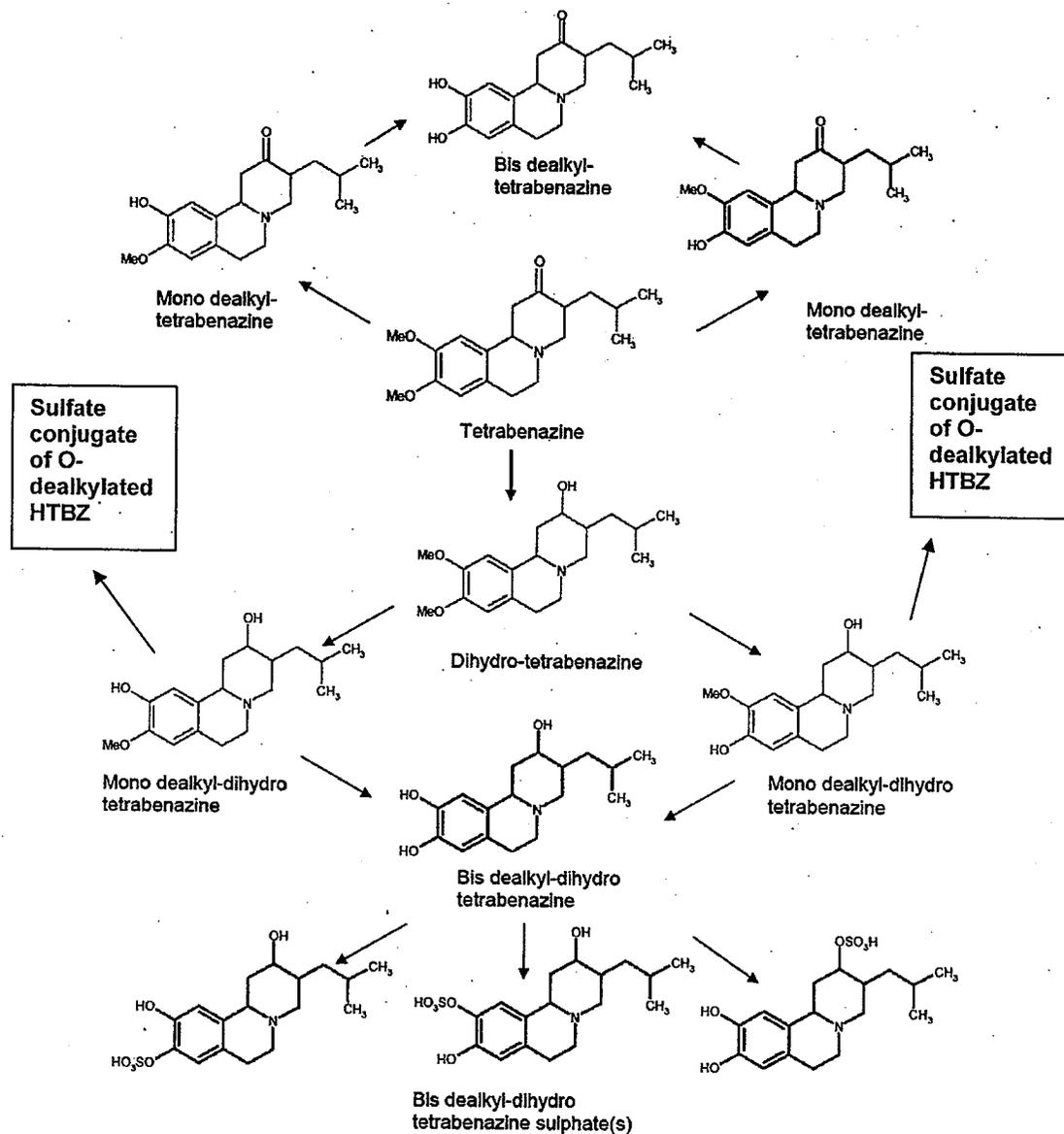
¹Mean ± standard deviation (N) except for T_{max} for which the median (N) is reported.

²The numbers correspond to the order of elution.

The Sponsor has proposed the following metabolic scheme (with sulfated metabolites added by the reviewer):

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Dihydro-tetrabenazine is the same as HTBZ. Mono dealkyl-dihydro-tetrabenazine is the same as O-dealkylated HTBZ.

2.1.3 Have the metabolic pathways of TBZ, α -HTBZ, and β -HTBZ been characterized?

In the response to the approvable letter, the Sponsor has evaluated the metabolism of TBZ and of α - and β -HTBZ using several different *in vitro* approaches.

P450-mediated metabolism of TBZ:

Study CAM/16 used 1) individual recombinant human P450s and 2) chemical inhibitors of P450s in human liver microsomes and cytosol. In addition to the finding that TBZ is metabolized (by carbonyl reductases) to α - and β -HTBZ, it was also found that TBZ is metabolized by P450 to the following metabolites:

- Monohydroxy-TBZ (This is not to be confused with HTBZ. It was not identified as a circulating moiety in the mass balance study and is not found on the chart on page 15 of this review).
 - Possible role of CYP2D6 unclear
- O-dealkylated-TBZ
 - CYP1A2 accounts for approximately 66% of the formation in this study; CYP2D6, CYP2C9, and CYP2C19 may also be involved
- Bis-O-dealkylated-TBZ
 - Responsible P450s not identified

It is noted, however, that these 3 primary metabolites of TBZ were not identified as the circulating metabolites in the mass balance study (CAM/06).

P450-mediated metabolism of α -HTBZ:

Study CAM/19 used human liver microsomes to identify the P450 isoenzymes responsible for metabolism of α -HTBZ *in vitro* in correlation studies and in studies with chemical inhibitors. Expressed P450s were used as well. The results suggested that α -HTBZ metabolism is mediated primarily by CYP2D6, CYP3A, and CYP1A2. CYP2B6 was not evaluated. The following are the major metabolites formed *in vitro*:

- Monohydroxy α -HTBZ (Note, this was reportedly not circulating in the mass balance study and has not been included in the chart on page 15 of this review).
 - Mediated by CYP3A
- O-dealkylated α -HTBZ
 - Mediated primarily by CYP2D6 (>78% in chemical inhibition studies) and by CYP1A2 (> 25% in chemical inhibition studies)

Monohydroxy α -HTBZ was not substantially detected in the plasma in the mass balance study (P1-9 and P10 in CAM/060). However, O-dealkylated-HTBZ was identified as a major circulating component in the plasma (the P16 component was O-dealkylated HTBZ, without distinguishing between α - and β). The formation of O-dealkylated HTBZ is also confirmed in results of a Phase 1 study 107,018.

P450-mediated metabolism of β -HTBZ:

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Study CAM/20 used human liver microsomes to identify the P450 isoenzymes responsible for metabolism of β -HTBZ *in vitro* in correlation studies and in studies with chemical inhibitors. Expressed P450s were used as well. The results suggested that β -HTBZ metabolism is mediated primarily by CYP2D6 and CYP3A. CYP2B6 was not evaluated. The following are the major metabolites formed *in vitro*:

- Monohydroxy β -HTBZ (Note, this was reportedly not circulating in the mass balance study and has not been included in the chart on page 15 of this review).
 - Minor metabolite *in vitro*
 - Mediated primarily by CYP3A; CYP2D6 plays a role
- O-dealkylated β -HTBZ
 - Major metabolite
 - Mediated primarily by CYP2D6

Monohydroxy β -HTBZ was not substantially detected in the plasma in the mass balance study (P1-9 and P10 in CAM/060). However, O-dealkylated-HTBZ was identified as a major circulating component in the plasma (the P16 component was O-dealkylated HTBZ, without distinguishing between α - and β). The formation of O-dealkylated HTBZ is also confirmed in results of a Phase 1 study 107,018.

In summary, the formation of the predominant metabolites of α - and β -HTBZ (O-dealkylated HTBZ) is mediated primarily by CYP2D6. The Sponsor depicts in the response to the approvable letter a role for CYP3A in the oxidative metabolism of α -HTBZ, although the review of *in vitro* data suggests that CYP3A is involved primarily in the formation of the minor metabolite of α -HTBZ (monohydroxy α -HTBZ). Thus the reviewer does not consider this to be a major enzymatic pathway.

2.1.4 Are further *in vitro* studies recommended to characterize the metabolism of TBZ?

Although the role of CYP2B6 was not evaluated in the present submission, the major pathways involved in the formation of the predominant circulating metabolites have been identified. Therefore, *in vitro* studies to characterize the role of CYP2B6 in the metabolism of TBZ are not necessary.

2.1.5 What is the potential for *in vivo* inhibition of TBZ metabolism?

Inhibition of CYP2D6 increases exposure to both α - and β -HTBZ.

Because of the predominant role for CYP2D6 in the metabolism of HTBZ *in vitro*, the Sponsor has carried out a study to investigate the effect of the potent CYP2D6 inhibitor, paroxetine, on the pharmacokinetics of TBZ and its metabolites in 25 healthy subjects. TBZ 50 mg was given as a single dose on Day 1 and again on Day 10 after administration of paroxetine 20 mg daily on Days 3-11. Plasma concentrations for TBZ were generally below the limit of quantification after the 2 hour time point and generally did not increase on Day 10 vs Day 1. No further analysis of TBZ PK was performed. PK parameters for α -HTBZ and β -HTBZ are shown in the table below.

Table 5. Pharmacokinetic parameters (arithmetic mean, %CV) for Study TBZ 107,018

		Day 1	Day 10
α -HTBZ	t_{max} (h) ^a	1.00 (1.0-3.1)	1.5 (1.0-6.0)
	C_{max} (ng/mL)	77.3 (34)	107 (25)
	AUC ₀₋₄ (ng*h/mL)	419 (52)	1235 (39)
	AUC _{0-inf} (ng*h/mL)	422 (53)	1365 (53)
	$t_{1/2}$ (h)	7.0 (29)	13.8 (32)
β -HTBZ	t_{max} (h) ^a	1.5 (1.0-3.1)	1.5 (1.0-4.0)
	C_{max} (ng/mL)	42.9 (56)	105 (31)
	AUC ₀₋₄ (ng*h/mL)	183 (94)	1368 (54)
	AUC _{0-inf} (ng*h/mL)	184 (95)	1638 (58)
	$t_{1/2}$ (h)	4.5 (57)	13.5 (40)

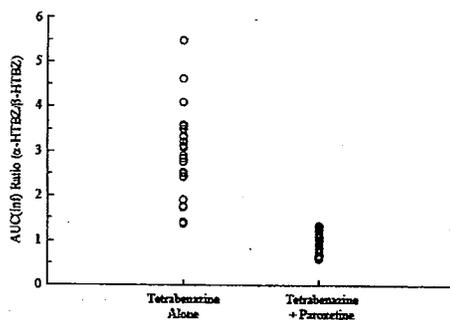
^a median (range)

For α -HTBZ there was an approximate 1.3x increase in C_{max} and an approximate 3.2x increase in AUC_{inf} after administration of repeated doses of paroxetine. In addition, there was an approximate 2x increase in the elimination half-life in the presence of a strong CYP2D6 inhibitor. For β -HTBZ the C_{max} was approximately 2.4x greater and the AUC_{inf} was approximately 9x greater after administration of paroxetine compared to no CYP2D6 inhibitor. The β -HTBZ elimination half-life was approximately 3x greater after CYP2D6 inhibition than when TBZ was given alone.

As observed in the OCP review of the original NDA, in the pivotal efficacy study 103,004, patients who were taking CYP2D6 inhibitors had a lower ratio of α : β HTBZ than did patients who were not taking CYP2D6 inhibitors. α : β ratios ranged from 0.43 to 6.4 in that study. For α : β ratios > 1.6, there was no concomitant medication identified by the Reviewer as being a CYP2D6 inhibitor. For ratios < 1.6, 26 of 47 samples were from subjects taking CYP2D6 inhibitors, and for ratios of < 1, twenty-one of 25 samples were from subjects taking CYP2D6 inhibitors.

Similarly, in study 107018 in the absence of CYP2D6 inhibition, exposure to α -HTBZ is generally greater than to β -HTBZ (median ratio of 3). Following CYP2D6 inhibition with paroxetine, the median ratio is 1. These results are shown in the figure below. This, along with the PK data above, suggests the importance of CYP2D6, especially in the metabolism of β -HTBZ.

Figure 7. Individual Subject Ratios of α -HTBZ to β -HTBZ AUC₀₋₄ After Single Dose Administration of Tetrabenzazine 50 mg Under Fasting Conditions Before and After 8 Days of Dosing with Paroxetine 20 mg QD to Healthy Volunteers



- Based on the PK changes in exposure to α - and β -HTBZ in subjects taking strong CYP2D6 inhibitors, OCP recommends that consideration be given to _____ of tetrabenazine in patients taking strong CYP2D6 inhibitors. (This would be expected to result in an accumulation of approximately 1.4, and that is similar to the approximate 1.6-1.7-fold increase in C_{max} seen after twice daily dosing in healthy volunteers in Study 203,008 reviewed in the original NDA).
- The recommendation for consideration of _____ should be extended to patients who are known to be poor metabolizers of CYP2D6.

2.1.6 Is P450 inhibited after exposure to TBZ, α -HTBZ, or β -HTBZ?

As outlined in the approvable letter, the Sponsor conducted studies to evaluate *in vitro* CYP inhibition by TBZ and its metabolites α -HTBZ and β -HTBZ. The isozymes evaluated were CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A. The results of *in vitro* Study 065005 do not suggest inhibition of P450s except for CYP2D6. In the case of CYP2D6, based on I/K_i (from PK data submitted in the original NDA submission) there is only a remote chance of CYP2D6 inhibition by either α -HTBZ and β -HTBZ, with I/K_i values of 0.02-0.03 for β -HTBZ and < 0.02 for α -HTBZ.

- No subsequent *in vivo* study for inhibition of CYP2D6 (or CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A) after administration of TBZ is necessary.
- The Sponsor has not evaluated the effect of TBZ or its metabolites on CYP2B6. It is recommended that this *in vitro* evaluation be performed for TBZ and for α -HTBZ and β -HTBZ.

2.1.7 Is P450 induced after exposure to TBZ, α -HTBZ, or β -HTBZ?

The Sponsor conducted studies to evaluate *in vitro* CYP induction by TBZ and its metabolites α -HTBZ and β -HTBZ in response to the recommendation outlined in the approvable letter. Study 063015 was adequately conducted to evaluate *in vitro* induction of P450s. The positive controls resulted in the expected induction of CYP1A2, CYP3A4, and CYP2B6. Neither tetrabenazine nor its metabolites α -OH-TBZ or β -OH-TBZ induced CYP1A2, CYP3A4, or CYP2B6 *in vitro*; it can be concluded that these are also not inducers of CYP2C8, CYP2C9, or CYP2C19.

- No further study of P450 induction is required.

2.1.8 Are TBZ or its metabolites substrates of P-glycoprotein?

Study 6PRESPI evaluated the role of TBZ, α -HTBZ, and β -HTBZ as substrates of P-glycoprotein (Pgp) *in vitro* using transfected MDRQ1-MDCK cells in an acceptable bidirectional

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permeability assay. Neither TBZ nor α -HTBZ are Pgp substrates *in vitro*. β -HTBZ 5 μ M (but not 10 μ M or 50 μ M) had a net efflux ratio of 2 and efflux was inhibited by the Pgp inhibitors cyclosporine and ketoconazole, suggesting that it is a substrate *in vitro*. However, due to its extensive metabolism *in vivo* that is not primarily mediated by CYP3A, no further evaluation for potential drug interaction with a Pgp inhibitor is necessary.

2.1.9 Are TBZ or its metabolites inhibitors of P-glycoprotein?

Study 6PRESPI evaluated the role of TBZ, α -HTBZ, and β -HTBZ as inhibitors of P-glycoprotein (Pgp) *in vitro* using digoxin efflux in Caco-2 cells as a model. At clinically relevant exposures, neither TBZ nor its α - and β -HTBZ metabolites are considered Pgp inhibitors. (In the original NDA, study TBZ 203,009 found no interaction between 25 mg TBZ and digoxin *in vivo*).

For inhibition in the GI tract, a worst case scenario would use a projected GI concentration of dose/250 ml as the inhibitor concentration for TBZ. In that case, [I] for a 37.5 mg dose would be approximately 472 μ M, and this would result in I/K_i of approximately 19. In this case, further *in vivo* interaction study with digoxin is also recommended. However, since TBZ is rapidly and extensively metabolized (primarily by a non-P450 mediated pathway) after oral administration in humans, it would be difficult to achieve a worst case scenario in the setting of an *in vivo* evaluation.

- Further *in vivo* study to investigate the potential for inhibition of Pgp after administration of TBZ is not recommended, and the potential for inhibition ~~is not recommended~~

2.1.10 How does hepatic impairment influence exposure to TBZ or its metabolites?

Hepatic impairment reduces the metabolism of TBZ resulting in substantial exposures relative to normal subjects in which minimal exposure to TBZ occurs. The increase in TBZ exposure is not entirely accounted for by changes in exposure to α - and β -HTBZ.

The Sponsor has completed Study TBZ 202,010 to compare PK characteristics of TBZ and α - and β -HTBZ in subjects with mild or moderate liver impairment to those of age-matched healthy subjects after administration of a single 12.5 mg dose of TBZ. An interim report was reviewed in the OCP review of the original submission. The final results, reported in the October 12, 2007 submission (055) are as follows. The overall conclusions have not changed.

Twenty-four male subjects have completed the study to date (12 healthy, 12 liver impaired). Nine subjects were considered to be mildly hepatically impaired and 3 subjects moderately hepatically impaired based on Child-Pugh classification. Plasma concentrations of TBZ are shown in the figure below and the PK parameters are shown in the table below.