Memorandum

DATE: November 7, 2007

FROM: Director
Division of Neurology Products/HFD-120

TO: Members, Peripheral and Central Nervous Systems Advisory Committee (PCNS AC)

SUBJECT: Briefing Memo for December 6, 2007 PCNS AC meeting to discuss NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease (HD)

As you know, the Division of Neurology Products (DNP) has scheduled a PCNS AC meeting, to be held on 12/6/07, to discuss NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease (HD), submitted by Prestwick Pharmaceuticals on 4/22/05. The application was subsequently withdrawn and re-submitted on 9/26/05.

The application contains reports of two randomized controlled trials, Studies 004 and 005, as well as safety data. The safety database is quite small, and much of the data were obtained by the sponsor from Dr. Jankovic, an HD expert at Baylor College of Medicine in Texas, who has been treating patients with tetrabenazine for years under his own IND.

The Agency issued an Approvable letter on 3/24/06. Although the Agency had determined that tetrabenazine was considered effective in the treatment of the chorea of HD, we noted several issues that raised significant concern about the ultimate approvability of the application.

Specifically, although analyses of the primary outcomes (measures of chorea) yielded statistically significant between-treatment differences favoring drug, analyses of numerous other secondary outcomes (including measures of functionality and cognition) tended to favor placebo, some reaching nominal statistical significance. In addition to the obvious concerns raised, we were concerned that if the drug actually caused deterioration in these domains, it would be difficult for the practitioner to recognize these clinical changes as being drug-related, given that deterioration of function and cognition are symptoms of HD itself.

Further, we noted the clear drug-related increase in significant adverse events, including parkinsonism, akathisia, depression, and dysphagia, the latter possibly being associated with aspiration pneumonia. Here, too, we were concerned that practitioners might not be able to identify some of these events as being drug

related, again because several of these are symptoms of HD. In particular, if these events were drug related, but were not considered as such, it is possible that they could continue to increase in severity, perhaps becoming irreversible and resulting in significant clinical sequelae. For these reasons, we informed that sponsor that we were unsure that the potential benefit of tetrabenazine on chorea could be justified, and it is this overarching issue that has motivated the division to bring the application to the PCNS.

In this package, we are including this cover memo, the statistical review of the effectiveness data, performed by Dr. Tristan Massie, statistician, reviews of the sponsor's response to the 3/24/06 Approvable letter performed by Drs. Carol Davis and Lourdes Villalba, of DNP, a review of the dose-response data (for both effectiveness and safety data) performed by Dr. Atul Bhattaram of the Office of Clinical Pharmacology, a copy of the Approvable letter of 3/24/06, and several articles from the literature that discuss various aspects of HD. In addition, a copy of the specific questions we would like the committee to vote on is included, as well as the agenda for the meeting.

At this point, I will give a relatively brief description of the effectiveness and safety data submitted in the original application, and a summary of the sponsor's response to the Approvable letter. As noted above, detailed reviews of the sponsor's responses, performed by DNP staff, are included.

Effectiveness

Study 004

This was a randomized, parallel group, double-blind trial in which patients not previously treated with tetrabenzine were randomized to receive either active drug or placebo in a 2:1 ratio, respectively. The study involved a 7 week titration phase, followed by a 5 week maintenance phase. Treatment was initiated at 12.5 mg once a day, then titrated by 12.5 mg/day increments per week to a maximum dose of 100 mg/day (the 12.5 and 50 mg/day doses were given qd and bid, respectively; higher doses were given in a qid regimen). Patients were to be titrated to the dose felt to offer the best control of their chorea and adverse events. Patients were to be seen after a one week period off of drug at the end of the trial, on week 13.

The primary measure of efficacy was the difference between drug and placebo on the mean change from baseline in the Chorea Score for the average of Weeks 9 and 12. The Chorea Score is a subset of the Motor Assessment Scale of the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS consists of 6 subscales:

1) Motor Assessment
2) Cognitive Assessment
3) Behavioral Assessment
4) Functional Assessment Checklist
5) Independence Scale
6) Functional Capacity (TFC)

Part 1 consists of 15 items, 7 of which constitute the Chorea Score; these 7 items are each graded 0 (chorea absent)-4 (marked/prolonged), for a maximum score of 28.

Part 2 consists of 5 timed items: verbal fluency, digit symbol substitution test, Stroop color naming test, Stroop word reading test, and the Stroop interference test.

Part 3 consists of 11 behavioral items, rated each for frequency and severity.

Part 4 consists of a list of 25 activities, each rated as 0 (cannot perform activity) or 1 (can perform activity).

Part 5 is an examiner rated assessment of the patient's level of independence, ranging from 10 (tube feeding, total bed care) to 100 (no special care needed).

Part 6 consists of 5 items (occupation, finances, domestic chores, ADL, and care level). Zero represents the lowest level of functioning, 13 represents normal functioning.

The following measures were secondary outcomes that were to be analyzed in the following order:

CGI, part 2: A 7 point scale, ranging from 1 (Very Much Improved) to 7 (Very Much Worse)

Mean Change from Baseline in the total Motor Score (UHDRS, Part 1)

Mean Change from Baseline in the Functional Assessment (UHDRS, Part 4)

Mean Change from Baseline in the Gait Score (UHDRS, Part 1, Item 13)

Results

A total of 84 patients were enrolled at 16 centers in the US. The following chart displays patient flow in the study:

	Drug	Placebo
Randomized	54	30
Completed	49	29
Withdrew AEs	5	0
Withdrew consent	0	0

The following chart displays the results of the primary analysis for the intent-to-treat population (ITT):

	Baseline Chorea	Change	P-value
Tetrabenzine (N=54)	14.7	-5.04	
Placebo (N=30)	15.2	-1.52	0.0001

The following results were seen for the secondary outcomes:

	Change From Baseline	P-value
CGI		
Tetrabenzine	2.99	
Placebo	3.73	0.0074
Total Motor Score		
Tetrabenazine	-6.84	
Placebo	-3.51	0.0752

	Change from Baseline	P-value
Functional Assessment		
Tetrabenzine	-0.81	
Placebo	0.37	0.0183*
Gait		
Tetrabenazine	0.0001	
Placebo	0.11	0.2410

*-favors placebo

Other endpoints were evaluated:

Behavioral Assessment (UHDRS Part 3)

Tetrabenazine	-0.96	
Placebo	-2.22	0.355*

In this subscale, one of 11 items, the Anxiety item, reached nominal significance (P=0.03) in favor of placebo.

Cognitive Assessment (UHDRS Part 2)

Tetrabenzine	-7	
Placebo	5	0.025*

All 5 items of this scale favored placebo numerically, with the Stroop Word and Interference items reaching nominal statistical significance (0.012 and 0.053, respectively).

Independence Scale (UHDRS Part 5)

Tetrabenazine	-1.98	
Placebo	0.55	0.135*

Functional Capacity (UHDRS Part 6)

Tetrabenazine	-0.43	
Placebo	-0.03	0.29*

Further examination of the effect on Chorea

Because the effect on chorea seemed so robust, the following additional analyses were performed.

As can be seen from Figure 1 in Dr. Massie's review (page 14), the between treatment comparisons on the mean chorea score becomes statistically significant at Week 3, and was also significant at Weeks 7 and 12.

Most patients in the tetrabenzine group received maintenance doses of either 50 or 100 mg.day (18.5% and 41%, respectively). In these groups, 90% and 64%, respectively, had a 3 point or more improvement in the chorea score. For the entire tetrabenazine group, a total of 69% of patients had an improvement of at least 3 points. In the placebo group, almost all patients received the maximum number of pills (94%), and a total of 21% of these had an improvement of at least 3 points (a total of 23% of placebo patients had an improvement of at least 3 points). The difference between the overall rates of improvement of at least 3 points (69% tetrabenazine vs 23% placebo) was highly statistically significant ($p<0.0001$).

The following distribution of improvements in chorea score between the treatment groups was seen:

	10 points	6-9	3-5	0-2	Worsening
Tetrabenazine	19%	31%	19%	20%	11%
Placebo	3%	3%	17%	50%	27%

Finally, an examination of the results by individual centers revealed a numerical difference in favor of tetrabenazine in 14/15 centers, with the difference at one center, Center 5 (Rush Presbyterian), reaching near nominal significance ($p=0.056$).

In addition, other analyses document the robustness of this finding.

Specifically, upon drug withdrawal at Week 12, patients' chorea scores returned to baseline levels by Week 13, confirming the drug effect seen over the previous 12 weeks. In addition, exploratory analyses document that the pattern of response of patients during the first 11 weeks of Study 007, the open-label extension to Study 004, during which all patients were re-titrated, were essentially identical to the responses seen in the drug treated patients during the titration period in Study 004. This effect in Study 007 was seen in both patients who had previously received active treatment in Study 004 as well as in those who had previously received placebo.

A similar effect was seen for patients enrolled in Study 006, the open-label extension to Study 005. That is, although patients (after their participation in Study 005) were placed back on their best dose in Study 006 (as opposed to being re-titrated, as were the patients in Study 007), their responses over the first 12 weeks in Study 006 were also essentially identical to those of the drug-treated patients in Study 004.

Further, the drug effect is relatively independent of the baseline degree of severity of the chorea.

Finally, although patients were not randomized to fixed dose in Study 004, PK/PD analyses strongly suggest a dose response relationship in this study.

Study 005

This was a study in which patients already receiving tetrabenazine for at least 2 months were randomized in a five day randomized phase to one of three groups in a 2:2:1 ratio:

Group 1-to receive placebo for all 5 days
Group 2-to receive tetrabenazine until after the assessment on Day 3
Group 3-to receive tetrabenazine for all 5 days

The primary outcome was to be a comparison of the mean change from baseline (Day 1 of the randomized phase) in the chorea score between Group 1 and the combined Groups 2 and 3 on Day 3.

A total of 24 patients were randomized into Groups 1 and 2 (12 patients in each group) and 6 patients were randomized into Group 3.

The mean daily dose of tetrabenzine in the three groups was 50 mg, 37.5 mg, and 62.5 mg, respectively.

The following chart displays the chorea scores for each group, and the results of the primary analysis:

	Baseline Chorea	Change Day 3	Change Day 5
Group 1	9.4	5.3	5.3
Group 2	9.1	3.6	5.5
Group 3	11.2	1.7	4.0
Group 2/3	9.8	2.9	

The p-value for the primary comparison (Group 1 vs Group 2/3 on Day 3) was 0.078.

After the study was completed and analyzed, the sponsor learned that the protocol had not been followed. Specifically, although the protocol stated that the Day 3 assessment was to be made after the morning dosing on Day 3, the investigator actually treated patients in Group 2 with placebo in the morning. As a result, presumably, the change in the scores for the Group 2 patients was smaller than expected. In an attempt to address this problem, the sponsor performed several post hoc analyses.

For example, given that the scores in Group 2 were intermediate between those for Groups 1 and 3 on Day 3 (again, presumably as a result of the specifics of the study conduct), the sponsor performed a trend test; this yielded a p-value of 0.048.

Another analysis combined Groups 1 and 2 and compared this combined group to Group 3. The rationale for this analysis was that Group 2 was, as the study was conducted, similar to Group 1, in that patients were off treatment for a reasonable duration (about 12-18 hours in Group 2) that would be expected to be sufficiently similar (pharmacodynamically) to the duration that Group 1 patients had been off treatment (about 3 days in this latter group).

Another analysis compared the results in Group 1 and Group 3 at Day 3. The rationale for this analysis was that Group 3 patients clearly were treated as per protocol (that is, they received drug on Day 3 prior to the assessment), and this keeps faith with the intent of the original protocol (that is, Groups 2 and 3 were to be combined because they both were to have been treated on Day 3 prior to the assessment).

The results of these two analyses are displayed below:

	Change at Day 3	P-value
Group 1 and 2 (N=24)	4.45	
Group 3 (N=6)	1.67	0.138
Group 1 (N=12)	5.33	
Group 3 (N=6)	1.67	0.11

SAFETY

The sponsor submitted safety data from several sources, which they denote as primary and secondary.

Primary

A total of 651 unique individuals received tetrabenazine in this database.

A total of 150 subjects received tetrabenazine in Phase 1 studies.

A total of 514 patients received tetrabenazine in controlled and open-label Phase 2/3 studies.

Specifically, in Study 004, the only study in which treatment-naïve patients were exposed to tetrabenazine in a controlled setting, 54 patients received drug.

An additional 27 unique patients (who had been randomized to placebo in the controlled phase) received tetrabenazine in the open-label extension (Study 007) to Study 004 (a total of 75 patients received tetrabenazine in Study 007).

Study 011 was an open-label titration study in patients with Chorea. A total of 123 patients received drug in this study; 76 had HD, 47 had chorea not associated with HD.

In Study 005, 30 patients received tetrabenazine; 29 of these continued drug in an open-label extension (Study 006).

Finally, in Study H-721, a total of 280 patients without chorea (but with hyperkinetic movement disorders) received drug in a “compassionate” use protocol at Baylor College of Medicine.

Secondary

Nitoman 003

This was an open-label study in 757 patients with hyperkinetic movement disorders conducted by Roche in Canada between 1989-1995. Records were available for 541 patients. Of these 541, 66 patients had HD.

Deaths

A total of 69 patients died in the studies described above.

Study 004

One 40 year old man committed suicide; he had been treated for 65 days, and was receiving a dose of 87.5 mg/day at the time of his death. This patient had a history of suicidal ideation.

Study 007

One 55 year old woman died of metastatic breast cancer after 451 days of treatment.

Study 011

A total of 18 patients died in this study. Very little documentation or description of these patients is available. The data submitted by the sponsor for this study were taken from patient records and transcribed onto CRFs years after the patient records had been created. Of these 18 deaths, 9 were considered due to "end-stage" HD (2 with aspiration pneumonia), 2 were due to MIs, 3 were related to either pneumonitis or pneumonia (one explicitly stated to be due to dysphagia and aspiration), 2 were related to "unknown" causes, and one each due to lung carcinoma and peptic ulcer with hemorrhage. Two of the pneumonia deaths occurred at 20 and 36 days of treatment. A total of 9 of the deaths occurred after at least 1000 days of treatment. Of the remaining 7 deaths, the duration of treatment in 6 varied from 193-884 days; duration of treatment was not available for one patient.

Of particular note, an inspection of this site by the Agency's Division of Scientific Investigations revealed that Dr.Jankovic, the investigator, did not record all cases of dysphagia, because he considered it related to the underlying HD; therefore, how many cases of dysphagia occurred (with resultant aspiration pneumonia) is unknown.

Study H-721

A total of 4 patients died in this study.

A man with Tourette's syndrome had a suicidal gesture consisting of an overdose of tetrabenazine. However, his death was related to a suicide more than a month after discontinuing the drug.

Three women died of cardiovascular disease from months to years after discontinuing treatment with tetrabenazine.

Nitoman 003

A total of 45 patients died in this study, 10 of whom had HD. Data are relatively incomplete for these patients as well.

Of the 10 patients with HD who died, 6 died of aspiration pneumonia secondary to dysphagia, 3 died of “end-stage” HD, and 1 died of a subarachnoid hemorrhage.

Of the 35 deaths in patients with other movement disorders, 10 were related to dysphagia/aspiration pneumonia, 4 each were related to CVA and MIs, and the cause for 11 was unknown.

Serious Adverse Events (SAEs)

The following were the SAEs that led to discontinuations.

A total of 12 patients suffered SAEs that led to discontinuation of treatment with tetrabenazine.

Study 004

One patient, described above, committed suicide. Another patient fell with a resultant subarachnoid hemorrhage. A third experienced restlessness (which decreased after a decrease in dose) and suicidal ideation (presumably secondary to the resultant increase in chorea related to the decrease in dose), and a fourth patient discontinued due to a diagnosis of breast cancer.

No placebo patients reported an SAE.

Study 006

One woman discontinued secondary to nausea and dehydration.

Study 007

One woman died from breast cancer. One man discontinued because of depression, agitation, anxiety, and akathisia.

Nitoman 003

A total of five patients discontinued secondary to an SAE.

The one patient with HD had aspiration pneumonia, GI hemorrhage, and dehydration. The other four patients had dystonia, confusion, depression, and “intercurrent illness”.

A total of 41 patients experienced SAEs that did not result in discontinuation.

Study 006

A total of 6 patients experienced SAEs that did not lead to discontinuation of treatment.

One woman had a fall, one woman had diarrhea and depression, two men had infections (pneumonia; UTI), one man had chest pain (presumably non-cardiac), and one woman developed hallucinations and suicidal ideation (she had a history of depression, and in this case had discontinued her antidepressants).

Study 007

A total of 6 patients had SAEs that did not lead to discontinuations.

Three (3) patients suffered falls that led to hospitalization. Two were noted to have pneumonia (one was noted to have dysphagia). Two other patients were diagnosed with cancer. One other patient had an elective hip replacement.

Study 011

A total of 23 patients experienced SAEs without discontinuing treatment.

A total of 7 patients had pneumonia (6 described either as aspiration pneumonia or associated with dysphagia), 5 patients had dehydration, 3 had suicidal ideation. No other specific event was present in more than one patient.

Nitoman 003

A total of 8 patients had an SAE that did not lead to discontinuation. The one patient in this group with HD experienced “over sedation”. One patient had pancreatitis and renal and hepatic failure. The other events listed were insomnia, sedation, and dysphagia.

Discontinuations

Several patients discontinued from Phase 1 studies, none related to drug treatment, almost all for protocol violations.

Study 004

One placebo patient discontinued. A total of 5 drug-treated patients discontinued treatment. The patient who died and the patient who fell and suffered a subarachnoid hemorrhage have been described.

Another patient discontinued after 71 days of treatment (final dose 12.5 mg) due to psychosis and paranoia. Another patient discontinued after a breast mass was found, and another developed akathisia after 50 days of treatment (final dose was 37.5 mg).

Studies 006,007

One patient from Study 005 did not continue into open-label because of inability to travel to the investigational site.

One patient discontinued because of nausea and dehydration 27 days after initiating treatment in Study 006, and another discontinued from the same study upon placement in a nursing home.

A total of 2 placebo patients from Study 004 did not enter Study 007, and 2 patients who received tetrabenazine in Study 004 did not enter Study 007; no reasons were given.

A total of 19 patients discontinued treatment with tetrabenazine in Study 007.

Two of these patients have previously been described (death from breast cancer; depression, anxiety, akathisia [this last patient was listed as “consent withdrawn”]).

One other patient developed suicidal ideation after 145 days of treatment. Two patients developed akathisia (one after 175 days of treatment [this patient also developed depression that did not remit with discontinuation], one after 153 days [this latter patient was described earlier]). One patient developed unsteady gait, two others were lost to follow-up, 6 patients were listed as “consent withdrawn” (see above; one other in this group experienced severe anxiety at the time of discontinuation).

One patient had abnormal liver function tests (maximum ALT of 289 IU/L, AST of 76 IU/L, GGT 131 IU/L about 2 months after enrollment in Study 007; ALT was 83 [2X ULN] at the end of Study 004). Three weeks after discontinuation of treatment, his ALT was normal, with a residual GGT of 131 IU/L.

One had an abnormal bilirubin (1.42 mmol/ml at the end of 004; bilirubin of 1.75 mmol/ml after 6 months in Study 007 [ULN 1.2], one met an exclusion criterion, one was considered to have had disease progression, and one patient had vocal tics (after 140 days of treatment; the tics did not resolve when tetrabenazine was discontinued).

Study 011

Of the 145 patients in this study who were treated for chorea at Baylor, 27 are still being treated in Study H-721. Of the remaining 118, 22 went into Study 005. Fourteen of the remaining patients died and twelve discontinued due to financial/travel difficulties. A total of 10 patients discontinued because of inadequate symptom control.

A total of 33 other patients discontinued for "other" reasons (including placement in a nursing home, lost to follow-up [6], disease progression, and transfer to another physician). A total of 28 other patients discontinued for reasons that were not entirely clear, but who reported adverse events at the time of discontinuation. Some of these events included 8 patients with depression, 6 patients with somnolence, 2 with parkinsonism, 2 with akathisia, (2 others with "restlessness", and one other with "movement disorder").

Study H-721

For these patients who were treated at Baylor and who did not have chorea, the sponsor cannot confirm which specific adverse events were responsible for discontinuations. The following partial list describes the AEs in the 45 patients who discontinued, excluding deaths:

Drowsiness/fatigue:	20
Parkinsonism:	13
Depression:	10
Nausea/vomiting:	9
Akathisia:	6

The sponsor presented analyses of specific adverse events of interest in the initial submission. I will briefly describe these analyses.

Sedation

A total of 19 (15%) of the 125 subjects in Phase 1 studies reported sedation. In single dose studies, 11% reported sedation after 12.5 or 25 mg, and 25% of subjects receiving a 50 mg dose reported sedation. In repeat dose studies, over 50% of patients receiving 25 mg/day reported sedation.

In Study 004, a total of 15 (28%) of patients receiving tetrabenazine had to have their dose decreased or did not have a scheduled increase in dose because of sedation; in almost all patients, the sedation resolved. No placebo patients complained of sedation. In Study 006, 28 patients (37%) experienced sedation.

A total of 3 (10%) of patients in Study 007 reported sedation.

In Study 011, 37 (38%) of HD patients reported sedation, and 28 (60%) of patients with non-HD related chorea experienced sedation. A total of 74 (26%) of patients with other hyperkinetic movement disorders also complained of sedation.

Depression

Study 004

In this controlled trial, 56% of the tetrabenazine and 67% of the placebo patients were being treated with anti-depressants. During the study, an additional 3 drug and 1 placebo patient started anti-depressant therapy. There was a statistically significant difference in the mean HAM-D between placebo and drug (p=0.003), in favor of placebo. A total of 8 drug (15%) and 0 placebo patients reported depression as an adverse event.

Across all HD studies, 15-30% of patients reported depression as an adverse event. In patients with non-HD chorea, 21% reported depression as an adverse event, and in patients with movement disorders other than chorea, 9% reported depression as an adverse event. In Study 007 (the extension of Study 005), 24% of patients reported depression.

Suicide/suicidal ideation

In Study 004, two drug-treated patients were reported as having either suicidal ideation or suicide. The sponsor conducted an analysis using the “Columbia” classification developed for use with the anti-depressants (in which patient narratives are reviewed in a blinded manner and classified into categories that define potential suicidal thinking and/or behavior); they determined that these were the only patients in this study who could reasonably be considered to have had “real” events, although the initial screen revealed a total of 12 patients who were considered to have had possibly suicide related adverse events (the other 10 were classified as Code 8, Other [i.e., whether or not these events represented true suicidality could not be determined]).

Insomnia

In Study 004, 12 patients (22%) reported insomnia; no placebo patients reported this event. A similar number of patients (21%) reported insomnia in Study 007, the extension phase of Study 004, and in Study 011 (28%).

Parkinsonism

In Study 004, 1 patient (2%) reported parkinsonism as an adverse event, but 6 patients had their dose reduced or titration curtailed because of parkinsonism. A

total of 2 patients (3%) reported parkinsonism as an adverse event in Study 007, and 14% reported parkinsonism in Study 011.

In Study 004, a total of 5 patients (9%) experienced akathisia, compared to 0 placebo patients. In Study 007, 11 patients (15%) reported akathisia; a similar number (12%) reported akathisia in Study 011.

Dysphagia/Pneumonia

In Study 004, 1 patient (2%) reported dysphagia. In Study 007, 2 patients (3%) reported dysphagia. In Study 011, 15% of patients reported dysphagia.

Common Adverse Events

In Study 004, the only controlled trial in naïve patients, the following incidences of adverse events were seen in at least 2 patients on tetrabenazine and at a frequency greater than in the placebo group:

Event	Tetra (N=54)	Placebo (N=30)
Somnolence	31%	3%
Insomnia	26%	0%
Fatigue	24%	13%
Nausea	17%	0%
Fall	17%	13%
Agitation	15%	0%
Anxiety	15%	3%
Depression	15%	0%
URI	13%	7%
Irritability	9%	3%
Ataxia	9%	0%
Akathisia	9%	0%
Diarrhea	7%	10%
Cough	7%	10%
Headache	6%	3%
Bradykinesia	6%	0%
Abnormal gait	6%	0%
Apathy	6%	0%
Anorexia	6%	0%
Vomiting	6%	3%
Dizziness	4%	3%
Hypertonia	4%	0%
Abdominal pain	4%	0%
Aggression	4%	0%
Confusion	4%	0%

Dysuria	4%	0%
Bronchitis	4%	0%
Dyspnea	4%	0%
Back pain	4%	0%
Obsessive compulsive Behavior	4%	3%

Laboratory findings

There were no important changes in routine laboratory findings, save for a mean change from baseline in ALT of 12 compared to 2 in the placebo group. This change was largely accounted for by 3 patients whose maximum ALTs were 145, 447, and 174 IU/L.

Vital signs

There were no important changes in vital signs.

EKGs

In Study 004, there were no important EKG changes, including changes in the QT interval duration.

However, the sponsor also performed a "thorough" QT study in which the effects of single doses of 25 and 50 mg of tetrabenazine on the QT interval were compared to single doses of moxifloxacin 400 mg (active control) and placebo. Dr. Yasuda has performed a detailed review of this study. In brief, according to Dr. Yasuda, the maximum mean change from baseline drug-placebo difference occurred at 2.5 hours after dosing for all 3 active treatments; this difference was about 12 msec for moxifloxacin, and about 7.5 msec (upper bound of the 95% CI 10 or slightly greater, depending upon the correction used) for the tetrabenazine 50 mg single dose. As she notes, the 50 mg dose is greater than any single dose recommended for a 100 mg/daily dose (to be given in a tid regimen).

COMMENTS

The sponsor submitted the results of two randomized controlled trials that, as noted earlier, the Agency concluded establish the effectiveness of tetrabenazine in the treatment of the chorea of HD. The results of Study 004 are quite robust in this regard, with the primary analysis yielding an extraordinarily low p-value, with extraordinary consistency of the finding across 14/15 centers, and with other ancillary analyses (including an examination of response by dose, withdrawal data, and the pattern of response in patients re-treated in Studies 006 and 007) yielding very positive results.

Study 005, on the other hand, did not meet the usual standard (p=0.05) for being a “positive” study; the p-value for the between-treatment comparison was 0.078. The sponsor suggested that this result was related to a study conduct issue, specifically that patients inappropriately had their morning dose of active drug withheld on the morning of Day 3, making Group 2 patients more like placebo patients (Group 1) than like patients who were, by protocol, to be continued on treatment (although these patients were not identical to Group 1 patients, in that the latter were off drug for three days, and the Group 2 patients had been off drug for 12-18 hours). In order to address this issue, the sponsor performed numerous post hoc analyses, which are described above.

We concluded that the most reasonable way to analyze this study was to compare Group 1 patients to Group 3 patients at Day 3. Although this was clearly a post hoc analysis, this analysis keeps complete faith with the protocol specified analysis, which was to compare patients off drug for 3 days to patients still on drug. This analysis yielded a p-value of 0.1 (relatively close to 0.05, given the very small numbers of patients in the analysis), and, importantly, the estimate of the treatment effect in this study was essentially identical to that seen in Study 004; about 3.5 points on the Chorea items of the Motor scale of the UHDRS (although it is true that there were baseline differences in the mean Chorea scores between these 2 groups; 9.4 in Group 1 and 11.2 in Group 3).

Although we did not conclude that the sponsor had submitted data that established substantial evidence of effectiveness under the typical requirement of evidence from at least two independent adequate and well-controlled trials, we did conclude that the evidence was consistent with the statutory standard of substantial evidence derived from a single adequate and well controlled trial plus confirmatory evidence.

In particular, Agency guidance describes the elements that could serve to support the use of single trial as providing substantial evidence of effectives, and many of these elements are present here, including a very small p-value, equivalent effects in sub-groups of different disease severity, and numerical superiority of drug compared to placebo in 14/15 study sites. Further, there is evidence of dose response, and the data from the withdrawal week in this study, as well as the pattern of responses in patients whose treatment was re-initiated (or initiated) in Studies 006 and 007 provide powerful confirmatory evidence of effectiveness. Although this language (confirmatory evidence) is not used in the Agency guidance, these sorts of findings are described in that document to serve exactly the same ends as confirmatory evidence; that is, to support the use of a single adequate and well controlled trial as providing substantial evidence.

Further, we did consider the results of Study 005 as being confirmatory.

Specifically, as noted earlier, we concluded that the Group 1 vs Group 3 analysis was an appropriate analysis, given the error in the study conduct. The results of this analysis yielded an estimate of the treatment effect essentially identical to that seen in Study 004; further, although the between-treatment contrast did not achieve statistical significance, this is not unexpected, given the very small number of patients included. Ordinarily, it should be noted, a "failed" second study should not be considered to "confirm" another, "positive" study. However, for the reasons stated above, we concluded in this case that it was reasonable to consider the elements described above in Study 004, together with the results of Study 005, to constitute "confirmatory evidence". For these reasons, we concluded that the sponsor had provided substantial evidence of effectiveness for tetrabenazine as a treatment for the chorea of HD.

However, examination of several of the secondary outcomes in Study 004 revealed troubling results.

Specifically, on the components of the UHDRS other than the motor score (which numerically favors drug, largely related to the effect on chorea), patients receiving placebo performed better than those on tetrabenazine, with several of these differences achieving nominal statistical significance. Specifically, patients on placebo performed superiorly on the Functional Assessment, the Behavioral Assessment, the Independence Scale, the Functional capacity, and the Cognitive Assessment.

These sorts, and frequency, of differences favoring placebo are unusual (for an effective drug). These findings do not undermine the effects on chorea, but they did raise significant questions about the approvability of the application. Study 004 did not include a patient/caregiver assessment of the utility of the treatment; it is possible that the effects on the chorea did not compensate, in the patient's/caregiver's mind, for any of these potentially negative effects that the drug seems to be associated with (assuming any of these negative findings on these scales have detectable clinical consequences). Indeed, it may be difficult to assess in this population any (subtle) deleterious effects of the sorts suggested by these negative findings, although they may be present (and possibly progressive).

In addition to the (potentially adverse) findings described above, it appears that the use of tetrabenazine is associated with the occurrence of several significant safety issues, including parkinsonism, depression, EPS, somnolence, and dysphagia resulting in aspiration pneumonia (with potential significant underreporting of this event). Although the incidence of a number of these events was not greater in the drug-treated patients than in the placebo-treated patients in Study 004, in some cases they were (for example, depression 15% on drug, 0 on placebo; akathisia 9% vs 0), and these events were seen in considerable numbers in open-label experience.

It is important to point out that, with regard to these findings (both the findings on the UHDRS and the frank adverse events), their (potential) drug-relatedness may be confounded with the progression of HD. That is, with progressive disease, patients develop cognitive and behavioral changes, as well as parkinsonism, dysphagia, depression, etc. This raised the concern that, even if these findings may be drug-related in any given case, the prescriber might be likely to attribute them to progressive disease, and not drug treatment (especially if the chorea continues to be well-controlled). In such a case, it might further be likely that the drug will be continued, and, at least theoretically, these findings may convert from being reversible (there is some evidence that this might be true for some of these events with short term treatment) to becoming irreversible (again, we have no reliable information, given the open-label nature of the long-term experience, about either the incidence of these events, or their reversibility with long durations of exposure).

The interpretation of the safety data was also complicated by some methodological difficulties, as described above. For example, there is little information presented about the cause of death in many of these patients, and, as noted, the true incidence of dysphagia in the Baylor experience is unknown, given that Dr. Jankovic attributed this event to progressive disease, and therefore did not record it in all cases. Further, the results of the thorough QT study strongly suggest that, at least at a single 50 mg dose, there is the potential for a significant prolongation of the QT interval.

As noted above, Drs. Davis and Villalba have reviewed the sponsor's response to the Approvable letter, and these detailed reviews are included in the package. As Dr. Davis has noted, although it is true that most of the between-treatment comparisons favoring placebo were not statistically significant and the differences were small, there seem to be no compelling reasons to conclude that the original directionality of the differences (i.e., favoring placebo) was inaccurate, or as the result of inappropriate analyses.

As Dr. Villalba notes, most of the adverse events of concern (depression, parkinsonism, akathisia) appear to be dose related, and in most cases, when the dose was decreased, the symptom resolved, if not entirely, at least to a large degree. It appeared that after the decrease in dose in many cases, there was still an important beneficial effect on the chorea, albeit often a smaller effect than at the higher doses (Dr. Bhattaram's pharmacometrics review clearly establishes a dose response for the effect on chorea, although a dose response for the adverse effects was more difficult to show formally). Nonetheless, there were cases of adverse events (especially depression) that appeared to not resolve with drug discontinuation, or to resolve very slowly of time (of course, in any given case, it is difficult to discern if depression was drug related, given the high prevalence of depression in patients with HD). Whether or not tetrabenazine is associated with dysphagia is difficult to tell; there was no increased incidence in

Study 004 compared to placebo, but there were numerous cases in the open-label experience (again, dysphagia occurs spontaneously in patients with HD). As noted earlier, in a significant subset of the patient experience presented, not all cases of dysphagia were recorded, making an accurate assessment of the occurrence of this event problematic.

Questions

We would like the committee to vote on and discuss the following questions:

1) Do the findings on the secondary efficacy outcomes (lack of a beneficial effect of tetrabenazine on numerous measures of function and cognition and/or numerical superiority of placebo on some measures) by themselves raise sufficient concerns about the utility of tetrabenazine's effect on chorea to justify not approving the application?
2) If not, is the panoply of adverse effects associated with tetrabenazine use sufficient to justify not approving the application? When considering this question, we are particularly interested in hearing the committee's views about whether or not a dosing regimen can be identified that would provide a benefit on chorea without an unacceptable risk of adverse events. Failing this, we would be interested in hearing the committee's views about any maneuvers that might mitigate these risks sufficiently to justify approval (e.g., reducing the dose, discontinuing the drug, instituting concomitant treatments [e.g., antidepressant therapy]). Further, we are also interested in the committee's views of the aforementioned Agency concerns that it might be difficult for the practitioner to discern if clinical worsening in various areas (e.g., cognition, depression, etc.) is drug related or not, with the possibility that, if drug related, the adverse events could become severe and/or irreversible.
3) If the committee determines that, for any reason, the application should not be approved, what studies (if any) could the sponsor perform to establish the necessary substantial evidence of effectiveness and/or safety in use?
4) If the committee determines that the application should be approved, are there any studies that the Sponsor should perform post-approval?

Note that we have not asked the committee to formally consider the question of whether or not the sponsor has established that tetrabenazine has a beneficial effect on chorea. As noted earlier, the Agency has concluded that they have. However, we are, of course, interested in any views the committee would like to offer on this issue in particular, or on any other issue, mentioned above or not, you believe is relevant to the consideration of this NDA.

We thank you in advance for the work you will do in preparation for the meeting, and, of course, for your work at the meeting. We hope the meeting will be

interesting and stimulating, and I am looking forward to seeing you all in December.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21, 894 (N_000)

Drug Name: Tetrabenazine

Indication(s): Huntington's Disease Chorea

Applicant: Prestwick Pharmaceuticals

Date(s): Submission Date: September 23, 2005

Review Priority: Priority

Biometrics Division: Division of Biometrics I

Statistical Reviewer: Tristan Massie, Ph.D.

Concurring Reviewers: Kun Jin, Ph.D., Team Leader

Kooros Mahjoob, Ph.D., Deputy Director, Division of Biometrics 1

Medical Division: Neurologic Drugs (HFD-120)

Clinical Team: Carole Davis, M.D.

John Feeney, M.D., Team Leader

Russell Katz, M.D., Division Director

Project Manager: Teresa Wheelous

Keywords: Analysis of Covariance; Secondary variables; Standard of evidence; Staggered Withdrawal Study; Study Conduct Error

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In one study, a 12 week study of tetrabenazine for the acute treatment of chorea in patients with Huntington's disease, the primary endpoint data support the proposed indication ($p<0.0001$). The result on the clinical global improvement endpoint was also statistically significant in favor of tetrabenazine. However, results on two other secondary endpoints related to other aspects of Huntington's disease were nominally statistically significant in favor of placebo and this is the only acute study in the application. In this study there was also one suicide in the drug group but none in the placebo group. It should be noted that there is a high prevalence of suicide in Huntington's disease and twice as many patients were randomized to the drug. On the other hand, there were 8 (15%) depression adverse events in the drug group and 0 in the placebo group, which is a nominally significant difference. The other study was a very small 5 day randomized staggered withdrawal study. Although the group that had Tetrabenazine withdrawn first had a numerically higher mean chorea score than the other groups, suggesting a return of chorea upon withdrawal, the p-value was not significant ($p=0.078$).

1.2 Brief Overview of Clinical Studies

Two studies were undertaken to support this application. The first was Study 103,004 - A 12 week randomized, double-blind, placebo controlled, multi-center study of tetrabenazine for the treatment of Huntington's chorea (Tetra HD). The second was Study 103,005 - A 5 day randomized, double-blind, placebo-controlled, staggered withdrawal study in patients with Huntington's Disease treated with Tetrabenazine. Both of these studies were conducted in the United States. Study characteristics are shown in Table 1.

Table 1 Study Characteristics

STUDY	NUMBER RANDOMIZED	DURATION	DOSE	LOCATION/ CENTERS	DEMOGRAPHICS	PRIMARY ENDPOINT
TBZ 103, 004	30 Placebo 54 TBZ	12 weeks	25-100 mg/day flexible dose titration to patient's "best" dose up to 100 mg	U.S. 16 centers	62% Female 94% Caucasian mean age: 49 Mean Chorea scores at Baseline were 14.9 for TBZ 15.2 for placebo	Change from baseline in UHDRS item 12-Maximal Chorea

STUDY	NUMBER RANDOMIZED	DURATION	DOSE	LOCATION/ CENTERS	DEMOGRAPHICS	PRIMARY ENDPOINT
TBZ 103, 005	12 Plac/Plac 12 TBZ/Plac 6 TBZ/TBZ (staggered withdrawal: day 1, day 3, day 5, respectively)	5 days	patient specific stable dose prior to study entry range: 12.5-150 mg/day	U.S. 1 center	60% Female, and 93% Caucasian. mean Age: 57	Change from baseline in UHDRS item 12-Maximal Chorea at day 3

1.3 Statistical Issues and Findings

The 12 week acute treatment study, TBZ 103,004, was positive on the primary endpoint, the difference between the baseline and the average of the week 9 and week 12 scores on Unified Huntington's Disease Rating Scale (UHDRS) item 12 (maximal chorea), p=0.0001. Because the pre-specified primary analysis of the second study, the staggered withdrawal study, was not significant at the 0.05 level (p=0.078) it is important to check for internal replication in the positive, acute study. Within all individual sites except one group differences in the primary endpoint favored tetrabenazine. None were nominally significant but there was limited power since all sites had 9 patients or less.

The sponsor specified four secondary endpoints and proposed a prioritized order for testing each of them at 0.05 as long as all prior tests were significant at 0.05. The statistically significant treatment difference on the CGI-Improvement, the secondary endpoint that the sponsor considered the highest priority, provides some internal replication of the primary result. However, the sponsor's pre-specified analysis of the change from baseline to maintenance (average of week 9 and week 12 scores) in the UHDRS motor subscale did not reveal a statistically significant group difference. The difference was in the right direction but the p-value was greater than 0.05 (p=0.075). Because of this insignificant result and the sponsor's conditional sequential testing procedure any differences on the secondary endpoints of lower priority can only be considered exploratory. However, it should be noted that on the third secondary endpoint of priority, the functional assessment checklist (part IV of the UHDRS), a small but nominally statistically significant difference favoring placebo was seen. The fourth and final secondary endpoint in the prioritized list was the UHDRS gait score. No difference was observed in the UHDRS gait score.

Some of the other endpoints that were of lower priority than the four mentioned above had results that were somewhat unexpected. In particular, the placebo group was nominally significantly better than the tetrabenazine group on the change from baseline to week 12 in the sum of the cognitive items (UHDRS part II). Looking at the cognitive items individually, one finds that the group difference on the Stroop Interference Test –Words surpassed the nominal level of significance (p=0.012 < 0.05), the Stroop Interference Test-Interference nearly did (p=0.053), and placebo was numerically but not significantly better than tetrabenazine on the three other cognitive items. There was no significant group difference in mean change from

baseline through the maintenance period in the behavioral assessments (UHDRS part III), the independence scale (UHDRS part V), or the functional capacity scale (UHDRS part VI) but all three numerically favored the placebo group. Thus, the secondary endpoints provide limited internal replication and raise questions about the drug's effect on non-chorea aspects of Huntington's disease.

Patients with HAMD scores > 15, a benchmark for depression, were excluded from the study. The average baseline HAMD score was 5.1 for placebo and 4.5 for Tetrabenazine. Eight of 54 (15%) tetrabenazine patients reported depression as an adverse event as compared to 0 of 30 placebo patients (two-sided exact test p=0.046). Sadly, one of the eight tetrabenazine patients actually committed suicide. This reviewer could not locate the sponsor's HAMD analysis results, but the sponsor reported that there was no group difference between the baseline HAMD score and the average of the week 9 and week 12 HAMD scores. However, this reviewer estimated the group mean change by ANCOVA to be 1.6 (+/- 0.5 S.E.) points smaller for placebo than Tetrabenazine (p=0.003). A nonparametric test yielded the same conclusion. Despite the apparent group difference, the average week 12 score was still only about 2.5 for placebo and 3.9 for Tetrabenazine, so neither group was depressed on average. However, this may be because many patients (60%) were using antidepressants concomitantly. Thus, although the average week 12 HAMD scores did not suggest depression the nominally significant group difference this reviewer found in the change in HAMD scores corroborates the observed increase in depression related adverse events in the tetrabenazine group.

After the 103,004 study was underway a protocol was introduced for videotaping patients at the end of treatment (week 12) and one week after the cessation of treatment (week 13). An expert in Huntington's disease was to determine chorea scores for the videotapes without knowing the treatment group of the patient or to which visit the tape corresponded. This was done to support the primary analysis because it was felt that the investigators might be unblinded by the side effects of the drug. While the data from the videotapes seems to support the primary analysis result only 23 (27%) patients had videotapes made. Some patients who should have been videotaped were not, therefore, within the videotaped subgroup the treatment groups may not be balanced with respect to important baseline characteristics. For this reason it is not clear that the observed group difference within the subgroup with videos is due to the treatment alone. Therefore, the video rating results do not seem to have added much to the primary analysis result.

Although the group differences in chorea scores in the randomized staggered withdrawal study (TBZ 103,005) favored the combined group of those withdrawn on day 3 or day 5 over the group withdrawn at day 1 the primary analysis did not reach statistical significance (p=0.078). Fewer patients were enrolled than originally planned (30 vs. 45) reducing the power of the study after it was determined that a smaller sample size would be adequate because, apparently, patients were reluctant to agree to be taken off the drug. An ambiguity in the protocol resulted in patients that were supposed to be withdrawn on day 3 after the morning efficacy assessment, receiving placebo instead of tetrabenazine just prior to the day 3 morning assessment. The sponsor reasoned that since this made the 3 groups ordered at day 3 with respect to time of withdrawal a trend analysis would be more appropriate than the pre-specified comparison. A post hoc trend analysis yielded an unadjusted p-value of 0.048 but this would not be significant after adjusting

for the other tests that were conducted. In fact, a trend analysis was not specified in the protocol and would not have made sense for the day 3 data if the study had been conducted as planned because groups 2 and 3 would have been treated identically up to day 3. Thus, the trend analysis is an attempt to save the study from not only an insignificant primary result but also the error in study conduct and in this sense is a more of a stretch than a typical post hoc analysis. Note that four patients took protocol prohibited neuroleptics throughout the study and if these patients are excluded from the analyses neither the pre-specified primary comparison or the post-hoc trend analysis is nominally significant.

2 INTRODUCTION

2.1 Overview

Tetrabenazine, a selective centrally acting monoamine depletor, was initially developed by Hoffmann-La Roche in the mid -1950s as an antipsychotic drug. While the drug never gained wide usage as a tranquilizer, it was reported, in several small placebo controlled crossover studies, to be effective for the treatment of chorea, notably chorea associated with Huntington's disease (HD) with response rates reportedly ranging from 70 to 90%. Tetrabenazine was first approved in the UK for the treatment of chorea in 1971 and has been available in several European countries for over 30 years. In the US, patients have been receiving tetrabenazine for several years under physician INDs. Previous placebo controlled studies of tetrabenazine were primarily crossover studies conducted in small numbers of patients treated for only short periods of time (usually less than four weeks). The following two new studies were conducted to support this application.

Study 103,004 - A 12 week randomized, double-blind, placebo controlled, multi-center study of tetrabenazine for the treatment of Huntington's chorea (Tetra HD)
Study 103,005 - A 5 day randomized, double-blind, placebo-controlled, staggered withdrawal study in patients with Huntington's Disease treated with Tetrabenazine.

2.2 Data Sources

The data for study TBZ 103,004 can be found at the following location:
\\CDSESUB1\n21894\N_000\2005-09-23\m5\datasets\tbz103,004\listings

The UH.xpt dataset contains the Unified Huntington's disease rating scale scores including items 12a-12g, the maximal chorea scores, the sum of which constitutes the primary endpoint.

The data for the 5 day randomized staggered withdrawal study, TBZ 103,005, are located in the following directory.
\\CDSESUB1\n21894\N_000\2005-09-23\m5\datasets\tbz103,005\listings

The UH.xpt dataset contains the Unified Huntington's disease rating scale scores including items 12a-12g, the maximal chorea scores, the sum of which constitutes the primary endpoint.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study TBZ 103,004

The date of the first patient's enrollment was July 9, 2003 and the date the last patient completed the study was March 15, 2004.

3.1.1.1 Study Design

Objectives

Primary:

The primary objective of this study was to establish the absolute reduction in chorea on optimized doses of tetrabenazine and placebo.

Secondary:

The secondary objectives were to determine the mean and standard deviation of the optimal dose and the percentage of participants responding at each dose level.

Study Design

This was a multi-center, randomized, double-blind, placebo-controlled, study of the efficacy, tolerability, and safety of tetrabenazine (titrated to best dose) in two parallel unbalanced (2:1) groups of participants suffering from manifest Huntington's disease. Huntington's disease was to be confirmed by the characteristic movement disorder (chorea); a positive family history of HD; and blinded CAG analysis during the study. Data from any participant who proved to not have HD by genetic testing was to be censored for the purposes of the primary analyses (note: it turned out that all randomized patients were positive for HD on genetic testing). Duration of double-blind treatment was to be 12 weeks, preceded by a screening period of no more than 2 weeks, and followed by a visit one week after the end of double-blind treatment. A total of at least 72 participants were to be enrolled in the study, and randomized in a 2:1 ratio to tetrabenazine or placebo. Doses were to be titrated up in increments of 12.5 mg per week to the dose that was best in terms of the desired effect and the tolerability of side effects (sedation and/or parkinsonism were expected to be the dose-limiting side effects). The minimum daily dose was to be 12.5 mg. The maximum daily dose was to be 100 mg. Study drug was to be administered q.d. and b.i.d. at the lower dosages of 12.5 and 25 mg per day, respectively, and t.i.d. for all other dosages. By the end of 7 weeks patients were to be at their best dose and this dose was to be maintained for the final 5 weeks of the double blind treatment phase. During the double blind treatment period, participants were to return to the clinic for efficacy, tolerability, and safety evaluations at the ends of Weeks 1 (± 2 days), 3 (± 3 days), 5 (± 3 days), 7 (± 3 days), 9 (± 3 days), and 12 (± 3 days). In addition, participants were to be contacted by phone during weeks 2 and 11. Finally, participants were to return to the clinic for a follow-up visit one week (Week 13 ± 2 days) after stopping treatment.

3.1.1.2 Efficacy Measures

Unified Huntington's Disease Rating Scale (UHDRS)
The Maximal Chorea score which consists of the sum of UHDRS items 12a-12g is the primary endpoint. Each of items 12a-12g is scored between 0 (chorea absent) and 4 (marked/prolonged). Thus, the Maximal Chorea Total ranges from 0 to 28.
The protocol was amended after the study was partially completed to require videotaping of the patients at the final visit on study drug (visit 6/week12) and off study drug at visit 7 (week 13). The videotapes were to be blinded according to visit and an independent expert in Huntington's disease was to score the chorea. These data were to be used in support of the primary endpoint. Because the videotaping was not originally planned only 23 (27%) patients had it done.

Secondary Endpoints

- Clinical Global Impression of Change
- parts I, II, III, IV, V and VII of the UHDRS.

3.1.1.3 Statistical Methods and Sample size

In accordance with the intent-to-treat principle, all participants randomized were to be kept in their originally assigned treatment group for analysis. All participants with at least one post-treatment evaluation were to be included in the efficacy analysis.

The primary efficacy analysis was to use change scores from baseline in Total Maximal Chorea Score. Secondary efficacy analyses were to use change scores from baseline in CGI, item 1; categorical analysis for CGI, items 2 and 3; and total scores on the UHDRS Parts I, II, III, IV, V, and VII. Change scores were to be measured from baseline to the end of Week 12, i.e., before any participants began to washout. These change scores were to be analyzed by ANCOVA, adjusting for sites and baseline scores. Two sided tests were to be used in the efficacy analyses. Additional analysis was to be performed to adjust for any significant imbalance of baseline characteristics.

The statistical analysis plan stipulated that the primary outcome measure was the change in Total Maximal Chorea score from baseline to the maintenance period. The maintenance score is defined as the average of the Week 9 and Week 12 scores. If either of these scores was missing the maintenance score was defined as the available score. For patients with neither a week 9 nor a week 12 measurement, the last available assessment was to be used in place of the value during the maintenance phase. Sites with fewer than three patients were to be pooled into one "site" for the analysis.

For the objective of finding the most effective and tolerable dose (subsequently called best dose), and dose-related efficacy, the frequency distribution of the best doses for the treatment group

was to be tabulated. The mean and standard deviation for these doses was to be obtained. The change score in total chorea from baseline to the end of week 12 at these doses was to be examined, and any relationship between the best doses and the change scores was to be recorded. The best doses were also to be correlated to other variables such as plasma concentration and baseline severity of chorea.

Sample Size Calculation

In this study, participants were required to have a Total Maximal Chorea Score ≥ 10 at baseline. Power calculations are based on the results obtained in a previous HSG study (Intro-HD) in the subgroup of patients who had a baseline Total Maximal Chorea Score ≥ 10. Treatment duration in Intro-HD was 12 weeks, identical to treatment duration in this study. Based on this data a total of 24 placebo patients and 48 TBZ patients would provide 80% power to detect a group difference of 2.7 points in the Total Maximal Chorea change scores, assuming a standard deviation of 3.5 and allowing for a drop out rate of 15%.

A data and safety monitoring committee (DSMC) consisting of two physicians familiar with clinical research and a biostatistician, all of whom are otherwise not involved in the conduct of the study were to meet by conference call to review the protocol prior to the first randomization, after 20 participants had completed the study and finally after 40 participants had completed the study. The DSMC was to be unblinded and to have responsibility for reviewing AE occurrences and advising the PI, Steering Committee, and Sponsor in the event that the study should have been terminated for considerations of safety.

3.1.1.4 Disposition of Patients

A total of 84 patients were enrolled in this study; 54 patients were randomized to tetrabenazine and 30 to placebo. All enrolled participants were included in the primary efficacy analysis. Five (9%) tetrabenazine patients and one (3%) placebo patient did not complete the 12 week double blind treatment phase. The tetrabenazine withdrawals were due to the following adverse events: suicide; fall complicated by subarachnoid hemorrhage and confusion; suicidal ideation/psychosis/paranoia; pre-existing mass diagnosed as breast cancer; akathisia. The placebo patient withdrew consent.

3.1.1.5 Patient Demographics

Eighty-four HD subjects were randomized to tetrabenazine or placebo in two parallel, unbalanced (2:1) groups. The mean age was 49 years and ages ranged between 25 and 77 years. Sixty two percent of patients were female and 94% were white. Demographic characteristics and baseline disease characteristics were comparable between the groups.

Table 2 TBZ103, 004: Baseline Demographic Characteristics and Baseline Efficacy Measures

VARIABLE	STATISTIC/ LEVEL	TBZ	PLACEBO	ALL	P-VALUE
Age	Mean (SD)	49.4 (12.3)	48.7 (10.5)	49.2 (11.7)	0.807
Age Group	N(%) < 50	27. (50.0)	15 (50.0)	42 (50.0)	1.000
Age Group	N(%) ≥ 50	27. (50.0)	15 (50.0)	42 (50.0)	1.000
Race	N(%) Native Am	2. (3.7)	0 (0.0)	2 (2.4)	0.398
Race	N(%) Black	1. (1.9)	0 (0.0)	1 (1.2)	0.398
Race	N(%) White	50. (92.6)	29 (96.7)	79 (94.0)	0.398
Race	N(%) Multiple	1. (1.9)	0 (0.0)	1 (1.2)	0.398
Race	N(%) Unknown	0. (0.0)	1 (3.3)	1 (1.2)	0.398
Gender	N(%) Female	33. (61.1)	19 (63.3)	52 (61.9)	0.841
Gender	N(%) Male	21. (38.9)	11 (36.7)	32 (38.1)	0.841
UHDRS 12a-g Max Chorea	Mean (SD)	14.7 (3.8)	15.2 (4.4)	14.9 (4.0)	0.578
CGI-Sev	N(%) 3	12. (22.2)	10 (33.3)	22 (26.2)	0.614
CGI-Sev	N(%) 4	32. (59.3)	16 (53.3)	48 (57.1)	0.614
CGI-Sev	N(%) 5	9. (16.7)	3 (10.0)	12 (14.3)	0.614
CGI-Sev	N(%) 6	1. (1.8)	1 (3.3)	2 (2.4)	0.614
CGI-Sev	Mean (SD)	4.0 (0.7)	3.8 (0.7)	3.9 (0.7)	0.361
UHDRS Functional	Mean (SD)	18.8 (4.4)	19.6 (3.8)	19.1 (4.2)	0.381
UHDRS Gait	Mean (SD)	1.2 (0.6)	1.0 (0.5)	1.1 (0.6)	0.154
UHDRS Motor	Mean (SD)	47.0 (16.7)	44.8 (15.4)	46.2 (16.2)	0.548
CAG1	Mean (SD)	44.9 (3.4)	44.3 (3.7)	44.7 (3.5) Range: 39-54	0.490
CAG2	Mean (SD)	17.6 (3.6)	18.8 (2.8)	18.0 (3.3)	0.108
DiseaseDuration	Mean (SD)	8.6 (4.7)	7.4 (4.5)	8.2 (4.6)	0.254
Father HD	N(%) 0 No	30. (55.6)	12 (40.0)	42 (50.0)	0.432
	N(%) 1 Yes	21. (38.9)	12 (40.0)	33 (39.3)	0.432
	N(%) Unknown	3. (5.6)	6 (20.0)	9 (10.7)	0.432
Mother HD	N(%) 0 No	21. (38.9)	16 (53.3)	37 (44.1)	0.078
	N(%) 1 Yes	30. (55.6)	10 (33.3)	40 (47.6)	0.078
	N(%) Unknown	3. (5.6)	4 (13.3)	7 (8.3)	0.078
Prior-suicattempt	N(%) 0 No	53. (98.1)	29 (96.7)	82 (97.6)	0.670
Prior-suicattempt	N(%) 1 Yes	1. (1.9)	1 (3.3)	2 (2.4)	0.670
Prior-suic. ideation	N(%) 0 No	45. (83.3)	28 (93.3)	73 (86.9)	0.193
Prior-suic. ideation	N(%) 1 Yes	9. (16.7)	2 (6.7)	11 (13.1)	0.193

The tetrabenazine and placebo groups were generally comparable for baseline HD characteristics. Disease duration was comparable in both groups. Disease severity, as judged by the CGI part 1 was also comparable in both groups. More in the tetrabenazine group reported that their mother was affected than in the placebo group (56% vs. 33%) but more in the placebo group did not specify whether their mother was affected (13% vs. 6%) and if the unspecified ones in the placebo group were mostly mothers it could resolve the difference.

The treatment groups were comparable for baseline chorea and HD severity as measured by total scores on the primary and secondary efficacy measures at baseline.

The protocol specified that patients with a total 17-item HAM-D score greater than 15 were not to be enrolled in the study. The mean HAM-D at baseline was 4.5 for the Tetrabenazine group and 5.1 for the Placebo group. Thirty (56%) tetrabenazine patients and 20 (67%) placebo patients took an antidepressant concomitantly with the study treatment.

3.1.1.6 Sponsor's Results

Prior to unblinding it was decided in the data analysis plan (dated April 2, 2004) that centers with 3 patients or less would be pooled. This resulted in the pooling of centers 104, 123, and 151. The primary efficacy analysis was an ANCOVA of the difference between the average of the week 9 and week 12 total chorea scores (sum of UHDRS items 12a-12g) and the baseline total chorea score. The model was adjusted for centers and treatment groups, and baseline total chorea score was included as the covariate. If a subject was missing either the week 9 or week 12 chorea score then the available score was used for the maintenance score (i.e., the average of week 9 and week 12). If both week 9 and week 12 were missing the last available post-baseline assessment was used. All but six participants completed the 12-week treatment period.

As seen in Table 3, chorea scores for participants in the tetrabenazine group declined from baseline to the maintenance period by a mean of 5.0 units, while those in the placebo group declined by 1.5 units. The treatment effect of 3.5 units is highly significant ($p<0.0001$). A pre-specified sensitivity analysis imputed one plus the worst week 9 or week 12 chorea score (which happens to be 27+1=28) for the three participants with missing data, 2 in the tetrabenazine group and 1 in the placebo group. After this imputation the corresponding p-value was 0.0015 which is still significant and suggests that the three missing scores would likely have little impact on the results.

Table 3 TBZ 103,004: Primary Efficacy Analysis Adjusted Mean Change (± S.E.M) in Total Chorea Score

MEAN CHANGED TOTAL CHOREA SCORE (UHDRS ITEM 12)		
Tetrabenazine (N=54)	Placebo (N=30)	P-value based on ANCOVA
-5.04 ± 0.49	-1.52 ± 0.67	<0.0001

* Based on an ANCOVA model with effects for baseline chorea score, sites, and treatment group

Figure 1 shows the group mean changes in UHDRS Max Chorea score over time. A nominally significant group difference in the mean change in chorea scores was seen as early as week 3 but no claim on this time of first difference is possible since no such determination was planned or accounted for in the primary decision rule (i.e., no alpha was allocated for testing at times before week 12). Note that the placebo group worsened by about a point from week 9 to week 12, while the tetrabenazine group improved by about a point.

Figure 1 TBZ 103,004: Change in UHDRS Max Chorea Score over Time (FDA Reviewer's Analysis)

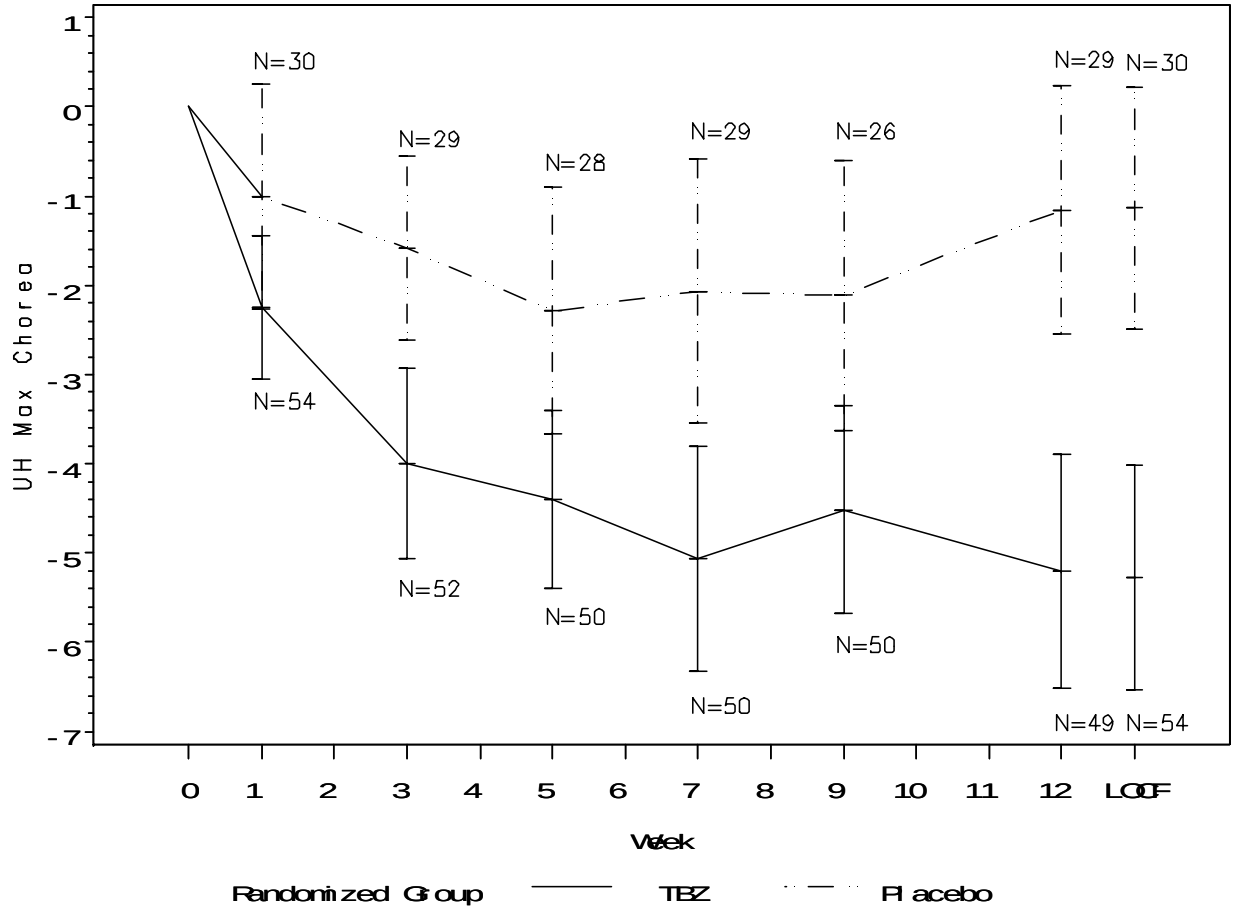


Table 4 shows the distribution of doses at week 7 (the end of titration) and the percent of patients at each dose that had a decrease in the chorea score of 3 points or more at the end of the study. Patients were not randomized to dose but rather titrated up to their "best dose". Doses of 50.0 and 100.0 were the most frequent in the tetrabenazine group. Ten of 11 (91%) at 50.0 mg had a 3 point decrease as compared to 13 of 22 (59%) at 100.0 mg. The highest dose might be expected to have a moderate proportion of non-responders because in the absence of AEs non-responders are titrated up in this study design.

In the placebo group almost all (93%) patients were taking the maximum number of placebo tablets (8). This suggests the possibility that if not all patients took the same number of tablets and one knew the number of tablets the patient was taking one could have guessed the treatment fairly accurately. Therefore, there could have been some unblinding of the investigators.

Table 4 TBZ 103,004: Dose at Week 7 and Percent with 3 point decrease from baseline in Total Chorea score

	Treatment Name											
	Placebo						Tetrabenazine					
	N	Pct	3pt Decrease in Chorea Score				N	Pct	3pt Decrease in Chorea Score			
			No		Yes				No		Yes	
			N	Pct	N	Pct			N	Pct	N	Pct
wk7dose*												
0	0	.	.	.	.	.	1	1.9	1	100.0	0	0.0
25	0	.	.	.	.	.	2	3.7	0	0.0	2	100.0
37.5	0	.	.	.	.	.	5	9.3	3	60.0	2	40.0
50	0	.	.	.	.	.	10	18.5	1	10.0	9	90.0
62.5	0	.	.	.	.	.	3	5.6	1	33.3	2	66.7
75	0	.	.	.	.	.	3	5.6	1	33.3	2	66.7
87.5	2	6.7	1	50.0	1	50.0	8	14.8	2	25.0	6	75.0
100	28	93.3	22	78.6	6	21.4	22	40.7	8	36.4	14	63.6

* Actual dose is 0 for placebo but wk7dose/12.5 gives the number of placebo tablets taken

Withdrawal of Study Drug

At the end of week 12, study drug was discontinued per protocol and participants were followed up one week later. Participants on higher doses at the end of week 12, 5-8 tablets per day (62.5 to 100 mg), first had their dose reduced to 4 tablets at the start of week 13 and then discontinued entirely after 2 days on 4 tablets/day.

As seen in Table 5 below, week 13 mean Total Chorea Scores had returned to baseline levels in both treatment groups. The Tetrabenazine group average chorea score worsened by 5.67 points, a nominally significant increase, between week 12 and week 13. At week 13 the Tetrabenazine group average was 0.4 points worse than baseline while the placebo group average was 0.3 points better than baseline, but this difference is not statistically significant.

Table 5 TBZ 103,004: Mean Total Chorea Scores at Baseline, Week 12 and Week 13 (1 week after withdrawal)

	BASELINE		WEEK 12 (PRIMARY TIMEPOINT)		WEEK 13(1 WEEK AFTER WITHDRAWAL)	
Treatment	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Tetrabenazine	54	14.69 ± 3.84	54	9.41 ± 4.45	49	15.08 ± 4.21
Placebo	30	15.20 ± 4.41	30	14.07 ± 4.72	29	14.90 ± 4.47

3.1.1.7 Reviewer's Results

3.1.1.7.1 Primary Analysis

Centers 123 and 151 had less than 3 patients so they were pooled for the analysis as directed in the analysis plan. The maximal chorea score, UHDRS scale items 12a-g, ranges from 0 (best) to 28 (worst). The average baseline maximal chorea score was 15. As reported by the sponsor and verified by this reviewer, the primary endpoint, the difference between the average of the week 9 and week 12 scores and the baseline score, was estimated to be 3.5 (+/- 0.8 S.E.) points lower for the Tetrabenazine group. This is statistically significant, $p = 0.0001$. The change from baseline to week 12 (i.e., ignoring the week 9 score unless there was no week 12 score) was even larger (4.4 (+/- 0.9 S.E.) points, $p<0.0001$) since the Tetrabenazine group mean decreased by a point between week 9 and 12, while the placebo group mean increased by a point during the same time.

3.1.1.7.2 Assessment of the Impact of Missing Data

In order to investigate the effects of missing data and adherence to the protocol specified visit times on the primary analysis result this reviewer defined several subgroups of the ITT population. This reviewer determined that 23 placebo and 40 Tetrabenazine patients had chorea scores for all scheduled visits and for which the last two visits fell within 1 ½ weeks of the protocol specified visit times. This subgroup is denoted OC_1. In this reviewer-defined observed cases subgroup the treatment group difference was slightly smaller than in the primary analysis but Tetrabenazine was still statistically significantly better than placebo (p=0.0013). Another similar subgroup, denoted OC_2, dropped the requirement for having all visits prior to visit 6 but still required that visit 6 was within 1 ½ weeks of week 12. The result in this subgroup was also significant and close to the ITT-LOCF result. A pre-specified sensitivity analysis imputed one plus the worst week 9 or week 12 chorea score (which happens to be 27+1=28) for the three

participants with no week 9 or 12 scores (2 in the tetrabenazine group and 1 in the placebo group). After this imputation the corresponding p-value was 0.0015. This reviewer found that if one was to impute the best possible score for the placebo patient and the worst possible score for the 2 TBZ patients with no week 9 or 12 scores then the results would still be significant although the p-value would increase by several orders of magnitude to 0.0155. This is still significant and suggests that the three missing scores would likely have little impact on the results. Since all of these sensitivity analyses still result in a significant result in favor of the tetrabenazine group the primary analysis result appears to be robust to dropouts and missing data as well as deviations from the protocol specified visit times.

Table 6 TBZ 103,004: Sensitivity Analyses of Primary Endpoint

	Placebo		TBZ			
Population*	N	Change in UHDRS 12 LSMean	N	Change in UHDRS 12 LSMean	LSMean Difference	P-value
OC_1	23	-1.21	40	-4.54	3.33 +/- 0.98	0.0013
OC_2	27	-1.32	46	-4.92	3.60 +/- 0.95	0.0003
Sponsor's Worst Imputation	30	-0.83	54	-4.25	3.42 +/- 1.04	0.0015
Reviewer's Worst Case Scenario Imputation	30	-1.63	54	-4.17	2.54 +/- 1.02	0.0155
All-ITT-LOCF	30	-1.52	54	-5.04	3.52 +/- 0.82	0.0001

* OC_1 had all scheduled visits and visits 5 and 6 were within 1.5 weeks of weeks 9 and 12 respectively
OC_2 had visit 6 within 1.5 weeks of week 12.
Sponsor's worst case imputation imputed 1 plus the worst observed week 9 or 12 score (27) for the 3 patients (2 TBZ and 1 placebo) that did not have a week 9 or 12 score.
Reviewer's worst case scenario imputation imputed 1 plus the worst observed week 9 or 12 score (27) for the 2 TBZ patients that did not have a week 9 or 12 score and the best possible score for the 1 placebo patient that did not have a week 9 or 12 score.

A few patients had visit 6, which was scheduled for week 12, considerably later. In particular, seven patients had visit 6 at week 14 or later including one at week 17. However, excluding the chorea scores from these late visits did not affect the significance of the primary analysis result.

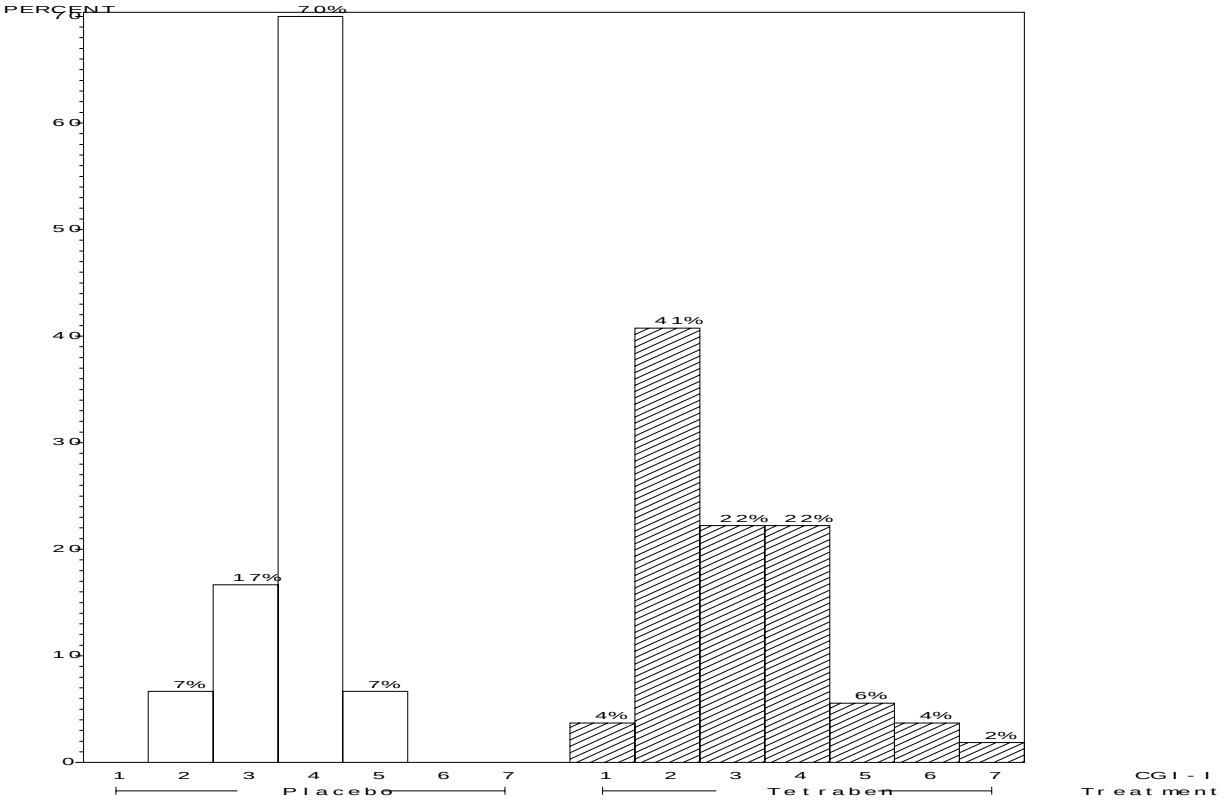
3.1.1.7.3 Secondary Analyses

The data analysis plan specified four secondary endpoints and proposed testing them conditionally in order (each at 0.05, given significance of previous endpoints at 0.05) to control the type I error rate. The specified order for testing was CGI Part 2 (Global Improvement),

UHDRS Total Motor Score, Functional checklist (sum of UHDRS questions 43-67), and, lastly, Gait score (UHDRS question 13).

The Tetrabenazine group was significantly better in terms of the clinical global improvement score as determined by the ANOVA analysis of the week 12 CGI score pre-specified by the sponsor (p=0.005). The estimated difference was 0.75 +/- 0.26 (1 S.E.) points on the 7 point scale. The adjusted means were 3.75 for Placebo and 3.00 for Tetrabenazine. The CGI (part 2) score can only assume the integer values between 1 and 7 and, therefore, the appropriateness of using an analysis like ANOVA that depends on a normality assumption is questionable. Nevertheless, this reviewer found that the ANOVA result was corroborated by the nonparametric, center adjusted, Cochran-Mantel-Haenszel ANOVA test (p=0.006). Seven patients did not have the last visit on treatment, which was supposed to be at week 12, until week 14 or later. If we exclude CGI scores from these late visits and use the next to last post-baseline score instead for these patients, we obtain a slightly larger, but still significant, p-value of 0.019.

Figure 2 TBZ 103,004: Distributions of CGI Global Improvement score at Week 12



Part I of the UH scale is the motor assessment. The scores can range from 0 (best) to 124 (worst). Chorea items 12a-12g, the sum of which constitutes the primary endpoint, are part of the motor assessment. The average baseline score was 46. The mean difference between the average of the week 9 and 12 scores (the "maintenance score") and the baseline score was estimated to be -3.51 for placebo and -6.84 for tetrabenazine. The estimated group difference is 3.3 (+/- 1.9 S.E.) points which is not nominally significant (p=0.075). Since this result is not significant at 0.05 the lower priority secondary endpoints, functional checklist and gait score, can not be tested without inflating the type I error. Note that the mean change from baseline to week 12 (not averaging over weeks 9 and 12) in the UH motor score (UH part I) was estimated to be -2.1 for placebo and -7.4 for Tetrabenazine, i.e., 5.3 (+/- 2.0 S.E.) points lower for the Tetrabenazine group. This is nominally significant, p=0.012. However, the analysis specified in the data analysis plan was the one described above that averaged over the week 9 and week 12 scores and did not produce a nominally significant result (p=0.075). Furthermore, although the sum of the non-chorea items of the motor assessment was not a secondary endpoint this reviewer investigated the possibility of group differences in the sum of the non-chorea motor assessment items. This sum can range from 0 to 96. The average baseline score was 30 for placebo and 32 for tetrabenazine. The group difference in the change from baseline to week 12 in the sum of the non-chorea items of the motor assessment was 1.5 +/- 1.5 (S.E.) points, numerically favoring tetrabenazine, but it did not reach the level of nominal significance (p=0.32). This suggests that the even if the observed difference on the change from baseline to week 12 in the motor assessment was significant it was primarily due to the difference on the chorea items.

Part IV of the UH scale is the functional assessment checklist. The scores can range from 0 (worst) to 25 (best). The average baseline score was 19. The average change from baseline to week 12 in the UH functional score (UH part IV) was 0.37 (slight improvement) for placebo and -0.81 for tetrabenazine (slight worsening). The difference was estimated to be 1.18 (+/- 0.49 S.E.) points lower (worse) for the Tetrabenazine group. This is nominally significant in favor of placebo, p=0.018. The difference between the average of the week 9 and 12 scores (the "maintenance score") and the baseline score was almost identical for the functional assessment and was also significant in favor of placebo. A similar difference was also apparent at week 7 and week 9 but the clinically relevance of the group difference on the functional assessment is not clear since it is not large and analysis of individual items in the checklist did not reveal any significant differences. The exploratory p-value for item 52, which related to the ability to do laundry without help (TBZ: 70.4% able vs. Pla: 90.0% able, p=0.051), was the closest to reaching nominal significance. A table of the week 12 results for each individual item of the functional assessment checklist can be found in the appendix which starts on page 37.

It is important to note that at week 12 there was a difference in Item 68 of the UHDRS which identifies whether the patient or the patient and caregiver filled out the functional assessment checklist. More placebo patients filled out the checklist by themselves (47% vs 26% p=0.04). This may raise the question of whether the group difference may be attributable to the differences in who was filling out the checklist rather than the treatment. This is not a randomized subgroup so we can't be sure but the difference was still nominally significant in the larger subgroup of patients that filled out the checklist with their caregiver. The difference on item 68 was smaller and not significant at earlier weeks.

The gait score (UHDRS question 13) was the lowest priority of the four key secondary endpoints specified in the data analysis plan. Scores can range from 0 (normal) to 4 (cannot attempt). The baseline score was 1.0 for the placebo group and 1.2 for the tetrabenazine group. The average change from baseline to week 12 was 0.11 +/-0.06 (slight worsening) for placebo as compared to -0.03 +/- 0.06 (very slight improvement) for Tetrabenazine. This group difference was not significant (p=0.241) according to the analysis specified by the sponsor (ANCOVA). Since the gait score can only assume the integer values between 0 and 4 the appropriateness of using an analysis like ANOVA that depends on a normality assumption is quite questionable. A proportional odds logistic regression model (which simultaneously models for j=0 to 3 the odds of a response <= j as compared to a response > j) adjusting for site, baseline gait score, and treatment group yielded a p-value of 0.62. So, there was no apparent difference between the treatment groups in gait at week 12 (or early termination) as measured by the UHDRS item 13 score.

For a subgroup of 23 patients videos of the patients were made at weeks 12 and 13 and then rated by an independent specialist. The specialist was blinded to the patient's treatment and adverse events, as well as, the order in which the patient's videos were made. This procedure was only implemented after the study was already partially completed. The date of randomization of the first patient who had a video made was Oct 3, 2003. This reviewer found that only 44% of the patients randomized on or after that date had videos made at weeks 12 and 13. Two patients in site 55 and one patient in site 45 did not have videos made despite the fact that previous patients in their sites had had them made. This suggests that if there were different implementation times for the video protocol at different sites it still couldn't completely explain why some patients did not have videos. Since videos were not obtained from all patients after the protocol amendment requiring them, there may be imbalances between the treatment groups within the subgroup with videos. Thus, the apparent treatment group difference within the video subgroup could potentially have been influenced by imbalances in patient characteristics other than treatment. For example, the difference in average age between the groups is 11.5 +/- 6 (S.E.) years. In addition, the treatment group difference in the primary endpoint is estimated to be about 2.2 +/- 1.9 (S.E.) points larger in the subgroup with videos than in the subgroup without videos. The treatment group difference in unadjusted mean changes was 4.8 in the subgroup with videos as compared to 2.8 in the subgroup without videos. This suggests the possibility that the subgroup of patients with videos is not representative of the entire randomized population. For these reasons, although the video ratings appear to support the primary analysis the evidence is not without question.

Analyses of Other endpoints

The placebo group was nominally significantly better than the tetrabenazine group on the change from baseline to week 12 in the sum of the cognitive items (UHDRS part II). The placebo group improved by 5.1 +/- 4.5 points from an average baseline score of 172 +/- 55 whereas the tetrabenazine group worsened by 7.7 +/- 3.3 points from an average baseline score of 156 +/- 56. The estimated group difference was 12.8 +/- 5.6. Looking at the cognitive items individually, i.e., UHDRS items 19-23 in Table 8 below, one finds that the group difference on the Stroop Interference Test –Word Reading surpassed the nominal level of significance ($p=0.012 < 0.05$) and the Stroop Interference Test-Interference nearly did ($p=0.053$). Placebo was also numerically better than tetrabenazine on the three other cognitive items. There was no significant group difference in mean change from baseline through the maintenance period in the behavioral assessments (UHDRS part III), the independence scale (UHDRS part V), or the functional capacity scale (UHDRS part VI) but all three numerically favored the placebo group. Note that more positive scores are better on the cognitive items, the independence scale, and the functional capacity, whereas more negative scores are better on the behavioral items. These tests were exploratory and not adjusted for other comparisons but the fact that the placebo group was numerically better in so many cases and nominally significantly better in some is striking. Recall from above that the placebo group was nominally significantly better than the tetrabenazine group on the secondary endpoint functional assessment checklist (UHDRS Part IV) as well.

Part III of the UH scale is the behavioral assessment. Part III consists of 11 items each with two subitems a) frequency and b) severity. The subitems are scored from 0 (best) to 4 (worst). If we investigate the individual items that comprise part III we find that both anxiety items 27a (frequency $p=0.028$) and 27b (severity $p=0.040$) are nominally significant in favor of placebo (i.e, Tetrabenazine appears worse). At the end of week 12, 90% of placebo had no evidence of anxiety as compared to 70 percent of Tetrabenazine. At baseline there was no difference in these items ($p=0.56$ and $p=0.55$, respectively). Of course, these two comparisons were not adjusted for multiple comparisons, but these results might lead us to hypothesize that the drug is associated with the occurrence of anxiety. This hypothesis would need external validation. Note that anxiety was listed as an adverse event for 4/54 (7%) TBZ patients and 1/30 (3%) placebo patients. Anxiety aggravated was listed as an adverse event for 4/54 (7%) TBZ patients and 0/30 placebo patients. No other behavioral items had group differences that reached nominal significance.

Patients with HAMD scores > 15, a benchmark for depression in this study, were excluded from the study. The average baseline HAMD score was 5.1 for placebo and 4.5 for Tetrabenazine. Eight of 54 (15%) tetrabenazine patients reported depression as an adverse event as compared to 0 placebo patients (two-sided exact test $p=0.046$). Sadly, one of the eight tetrabenazine patients actually completed suicide. This reviewer could not locate the sponsor's HAMD analysis results, but the sponsor reported that there was no group difference between the baseline HAMD score and the average of the week 9 and week 12 HAMD scores. However, this reviewer found the group mean as estimated by ANCOVA to be 1.6 (+/- 0.5 S.E.) points smaller for placebo than Tetrabenazine. The group difference is nominally significant based on ANCOVA ($p=0.003$) or a Wilcoxon rank sum test (0.009) or a center adjusted Cochran Mantel Haenszel nonparametric ANOVA test ($p=0.029$). The last two tests are nonparametric tests which may be more reliable here since the scores are near the low end of the HAMD and thus the distribution may not be normal. Nevertheless, the various tests are in agreement. Despite the apparent group difference,

the average score was still only about 2.5 for placebo and 3.9 for Tetrabenazine so neither group was depressed on average. However, this may be because many patients (60%) were using antidepressants concomitantly. Thus, although the average week 12 HAMD scores did not suggest depression the nominally significant group difference this reviewer found in the change in HAMD scores corroborates the observed increase in depression related adverse events in the tetrabenazine group.

Note that no significant difference was observed on UHDRS item 25a - depressed mood frequency (a five point scale), UHDRS item 25b - depressed mood severity (a five point scale), or item 38-"does the examiner believe the participant is depressed?". However, this doesn't seem to alleviate the increased incidence of depression adverse events in the tetrabenazine group or the significant group difference in the HAMD scores.

3.1.1.7.4 Summary of Secondary Endpoints Results

The sponsor designated four secondary endpoints as key secondaries in the data analysis plan. They planned to test them conditionally in the following order: CGI-I, UHDRS Motor, UHDRS Functional Assessment Checklist, and UHDRS Gait (item 13).
The only secondary endpoint that statistically significantly favored the tetrabenazine group was the first, the CGI-Improvement. The group difference on the 7 point scale was about 0.8 points (p=0.005). The group difference between the baseline score and the average of the week 9 and week 12 UHDRS motor total scores numerically favored tetrabenazine but was not significant (p=0.075), therefore, technically, testing should stop with this endpoint. It is important to note though that results on the third key secondary, the functional assessment checklist, were nominally significant in favor of placebo at week 12. A similar difference was also apparent at week 7 and week 9 but the clinically relevance of the group difference on the functional assessment is not clear since it is not large and analysis of individual items in the checklist did not reveal any significant differences. The exploratory p-value for item 52, which related to the ability to do laundry without help (TBZ: 70.4% able vs. Pla: 90.0% able, p=0.051), was the closest to reaching nominal significance. A table of the week 12 results for each individual item of the functional assessment checklist can be found in the appendix which starts on page 37. Differences on the other functional scales, the functional capacity (UHDRS part VI) and the functional impact scale, were not significant.

Part II of the UHDRS contains five items which measure cognitive abilities: Verbal fluency, Symbol digit modalities, Stroop Interference test -color naming, Stroop interference test - word reading, and Stroop interference test - interference. The result on the change in the sum of all five of the cognitive item responses was also nominally significant in favor of placebo as seen in Table 7 below. This may have been primarily due to the Stroop interference test items since there was a nominally significant difference in the change in the sum of the three Stroop items but not in the two non-Stroop items. However, all five items favored placebo numerically. In terms of individual items the word reading part of the Stroop interference test was nominally significant in favor of placebo (0.012) and the interference part of the Stroop interference test was nearly so (p=0.053). It should be mentioned that the p-values for the comparisons involving the cognitive

items were not adjusted for multiple comparisons. They were still felt to be important though since the placebo group was nominally significantly better than tetrabenazine in some cases.

Table 7 TBZ 103,004: Adjusted Mean Change from Baseline in UHDRS Part II - Cognitive Assessment Items

		PLACEBO (N=30)		TBZ (N=54)			
SCALE OR ITEM	SCORING INFORMATION	BASELINE MEAN (SD)	CHANGE LS MEAN (SE)	BASELINE MEAN (SD)	CHANGE LS MEAN (SE)	DIFFERENCE LS MEAN (SE)	P-VALUE*
Sum of Cognitive Items (Part II-items 19-23)	Higher scores are better Observed Range: 20-311	171.9 (55.2)	5.1 (4.5)	155.8 (56.2)	-7.7 (3.3)	12.8 (5.6)	0.025 (-)
Verbal Fluency (UHDRS 19)	Higher scores are better Observed Range: 2-51	19.0 (10.8)	-1.3 (1.1)	18.9 (9.1)	-2.6 (0.8)	1.3 (1.3)	0.305
Symbol Digit Modalities Test (UHDRS 20)	Higher scores are better Observed Range: 0-53	24.4 (11.5)	3.0 (1.0)	18.1 (11.5)	2.1 (0.8)	0.9 (1.3)	0.509
Stroop Interference Test (Color Naming;UHDRS 21)	Higher scores are better Observed Range: 8-82	47.2 (16.4)	1.3 (1.8)	42.4 (14.3)	-1.6 (1.3)	2.9 (2.2)	0.197
Stroop Interference Test(WordReading ; UHDRS 22)	Higher scores are better; Observed Range: 0-110	56.5 (20.5)	1.8 (2.1)	53.8 (20.9)	-4.8 (1.5)	6.6 (2.6)	0.012 (-)
Stroop Interference Test (Interference; UHDRS 23)	Higher scores are better; Observed range: 0-56	24.7 (8.8)	1.5 (1.2)	22.6 (10.1)	-1.5 (0.9)	3.0 (1.5)	0.053

Table 8 shows the results for primary, key secondary and other endpoints. It includes information on the scoring of the endpoints and the baseline mean values and ranges in an effort to aid in the interpretation of the differences.

Table 8 TBZ 103,004: Adjusted Mean Change (Average Week 9 and Week 12) from Baseline in Endpoints

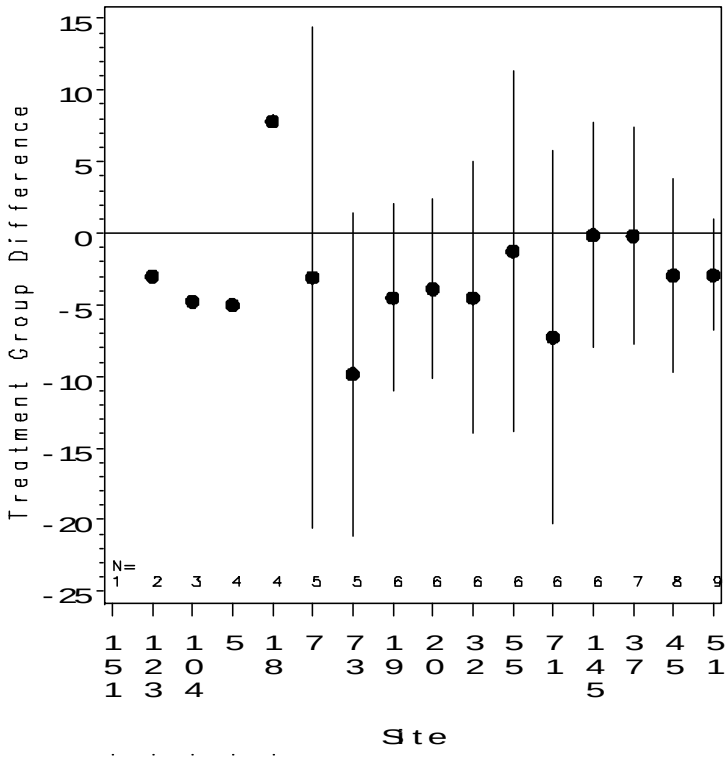
		PLACEBO (N=30)		TBZ (N=54)			
SCALE OR ITEM	**SCORING INFORMATION:**	**BASELINE MEAN (SD)**	**CHANGE LS MEAN (SE)**	**BASELINE MEAN (SD)**	**CHANGE LS MEAN (SE)**	**DIFFERENCE LS MEAN (SE)**	**P-VALUE***
Max Chorea (Item 12a-g) -Primary Endpoint	Higher Scores are Worse Possible Range: 0-28	15.2 (4.4)	-1.5 (0.7)	14.7 (3.8)	-5.0 (0.5)	3.5 (0.8)	<0.001 (+)
CGI-Improvement (Part 2) -Key Secondary #1	Possible Range: 1 (Very Much Improved) to 7 (Very Much Worse)	N/A	3.8 (0.2)	N/A	3.0 (0.2)	0.8 (0.3)	0.005 (+)
Motor (Part I) -Key Secondary #2	Higher scores are worse; Observed Range: 6-94	44.8 (15.4)	-3.5 (1.5)	47.0 (16.7)	-6.8 (1.1)	3.3 (1.8)	0.075
Functional Assessment Checklist(Part IV) -Key Secondary #3	Higher scores are better; Possible Range: 0-25	19.6 (3.8)	0.4 (0.4)	18.8 (4.4)	-0.8 (0.3)	1.2 (0.5)	0.018 (-)
Gait (Item 13) -Key Secondary #4	Scores can range from 0(normal) to 4 (can't attempt)	1.0 (0.5)	0.1 (0.1)	1.2 (0.6)	0.0 (0.1)	0.1 (0.1)	0.241
Sum of UHDRS Cognitive Items (items 19-23)	Higher scores are better Observed Range: 20-311	171.9 (55.2)	5.1 (4.5)	155.8 (56.2)	-7.7 (3.3)	12.8 (5.6)	0.025 (-)
Behavioral Assessments (Part III-items 25-35)	Higher scores are worse; Observed Range: 0-35	6.6 (6.2)	-2.2 (1.1)	7.4 (7.3)	-1.0 (0.8)	-1.2 (1.4)	0.363
Independence (Part V Item 69)	Scores can range from 0 (max disabled) to 100 (not)	80.2 (9.4)	0.6 (1.3)	76.9 (11.6)	-2.0 (1)	2.5 (1.7)	0.135
Functional Capacity (Part VI Items 70-74)	Scores can range from 0 (max dysfunction) to 13 (none)	8.6 (2.3)	-0.1 (0.3)	8.3 (2.4)	-0.4 (0.2)	0.4 (0.3)	0.291
Functional Impact Scale Total	Scores can range from 0 (independent) to 15 (complete assistance)	0.41 (0.68)	0.13 (0.23)	1.30 (2.20)	0.11 (0.17)	0.01 (0.28)	0.970

* based on ANCOVA model adjusting for baseline score, site, and treatment group

3.1.1.7.5 Group Differences on Change in Maximal Chorea within Individual Sites

Since there is only one acute study in this application we need to look for internal replication. One potential source of internal replication is significant treatment differences within individual centers. In this study there were 16 centers. As can be seen in Figure 3 below, almost all (14/15) of the treatment group differences on the change in chorea scores (difference between the baseline and the average of weeks 9 and 12) within individual centers favored Tetrabenazine, but none of the differences were nominally significant at the 0.05 level (based on an ANCOVA model including treatment and baseline as a covariate). In the figure the farther to the right a site is the more patients it had. The vertical lines passing through the black circles representing the means indicate the 95% confidence intervals. The vertical lines are not available for those sites on the extreme left because they had less than 2 patients in a treatment group. The failure of any intra-center treatment group differences to reach nominal statistical significance may be a case of a lack of power since the largest center had just 9 patients. Site 18, the only site with a treatment difference numerically favoring placebo, had just 1 placebo patient and 3 tetrabenazine patients.

Figure 3 TBZ 103,004: Treatment Group Difference in Change in Maximal Chorea Score by Center



3.1.2 Study TBZ 103,005

This study was initiated on November 11, 2003 and completed on December 10, 2004.

The primary objective of the study was to confirm the efficacy of tetrabenazine in Huntington's chorea by demonstrating in patients treated with tetrabenazine that when the drug is withdrawn chorea returns. A secondary objective was to evaluate whether chorea was more severe 5 days following treatment discontinuation than three days following treatment discontinuation.

3.1.2.1 Study Design

This was a single center, randomized, double-blind, placebo-controlled, staggered withdrawal study of tetrabenazine in three parallel unbalanced groups of participants suffering from manifest HD and being treated with tetrabenazine (administered at "best" dose). Duration of double-blind staggered withdrawal was to be no longer than 5 days. However, if during the double-blind portion of the study, participants experienced intolerable choreas (as judged by the Investigator), they could have been discontinued from the study. A total of at least 45 participants were to be enrolled in the study, 18(40%) were to initiate withdrawal on Study Day 1, 18 (40%) were to initiate withdrawal on Study Day 3, and 9 (20%) were to remain on tetrabenazine throughout the five-day study.

To be eligible, patients must have been receiving tetrabenazine for manifest HD as confirmed by clinical diagnosis and an expanded CAG repeat ($n \geq 37$). All patients were required to have been on a stable "best" dosage of tetrabenazine for two months prior to randomization and to have responded to this dose. Best dose is defined as the dose that provides moderate to marked improvement in the patient's condition while causing minimal side effects.
Participants were to be evaluated at screening, baseline/Randomization (Study Day 1), Study day 3, and Study Day 5. The duration of the study (five days) was justified on the basis of the plasma half-life of tetrabenazine (5.5 hours) and on published reports indicating that rapid return of chorea (within less than 24 hours), when tetrabenazine treatment is interrupted.

3.1.2.2 Efficacy Measures

The primary outcome measure is the change in Total Maximal Chorea Score (UHDRS questions 12a-g) from Baseline (Day 1) to Study Day 3.

Secondary efficacy parameters were to be the total score on the UHDRS Part I, II, III, IV, V, and VII. However, due to an administrative error (the protocol did not stipulate completion of these parts on day 3) these parts of the UHDRS were not collected at day 3, the timepoint for the primary analysis.

The functional capacity (part VI of the UHDRS) consists of three items scored between 0 (unable) and 3 (normal) and two items scored between 0 (unable) and 2 (normal). Thus the total score, sum of the 5 items, ranges from 0 to 13.

Reviewer's Comment: This assessment was listed under safety and tolerability assessments in the protocol rather than under efficacy assessments but in the study report the sponsor seems to regard it as a secondary efficacy endpoint.

3.1.2.3 Statistical Methods

Assuming a pooled standard deviation of the change score of the Total Maximum Chorea Score of 3.5, a sample size of 45 participants (18 in Group 1 starting withdrawal on Day 1; 18 in Group 2 starting withdrawal on Day 3; 9 in Group 3 with no withdrawal), would provide 80% power to detect a difference of 3.1 in change score between Group 1 and Group 2 + Group 3, using a two-sided level 0.05 test and allowing for a 10% drop-out rate.

The primary efficacy analysis was to compare Group 1 to Group 2 + Group 3 on change scores from baseline in Total Maximal Chorea Score on Study Day 3. Changed scores were to be analyzed by ANCOVA, adjusting for baseline scores.

Secondary efficacy analyses were to include:
ANCOVA analysis comparing group 1 to Group 2 + Group 3, on the change scores from baseline in total scores on the UHDRS Parts I, II, III, IV, V and VII on day 3.

Paired t-tests for Group 1 comparing changed scores in Total Maximal Chorea Score from Baseline to Day 3, and changed scores from Baseline to Day 5.

Exploratory analyses were to include ANCOVA analysis comparing the three treatment groups on the changed scores in all efficacy parameters from Baseline to Day 5.

3.1.2.4 Patient Disposition

There were major difficulties in enrolling patients into the study because patients already on tetrabenazine were reluctant to be withdrawn from tetrabenazine. A power calculation determined that the planned enrollment could be decreased from 45 to 30 participants without significantly compromising the ability of the study to detect treatment effects. Therefore, thirty patients were randomized (12 to Placebo/Placebo 12 to TBZ/Placebo, and 6 to TBZ/TBZ). All of them completed the study.

3.1.2.5 Patient Demographics

Since this is a withdrawal study patients were required to have been on stable doses of tetrabenazine for at least two months at baseline. The 30 randomized patients had been on tetrabenazine for an average of 2.5 years (the range was 0.21 to 7.07 years and the median time was 1.9 years). Summary statistics for the daily tetrabenazine dosage at study entry are displayed in Table 9.

Table 9 TBZ 103,005 Distribution of Stable Dose of Tetrabenazine prior to and at start of study

GROUP	MEAN DAILY DOSAGE (MG/DAY)	MEDIAN DAILY DOSAGE (MG/DAY)	MINIMUM (MG/DAY)	MAXIMUM (MG/DAY)
Group 1 (N=12)	59.38 ± 35.0	50.0	12.5	150
Group 2 (N=12)	45.83 ± 19.46	37.5	25.0	75.0
Group 3 (N=6)	54.17 ± 24.58	62.5	25.0	75.0
All	52.92 ± 27.4	50.0	12.5	150

Table 10 shows baseline demographic and disease characteristics of each group. Group 3, the group that stayed on tetrabenazine until day 5, was somewhat more affected at baseline than the other groups in terms of the CGI-Severity and the maximal Chorea score although the differences did not reach statistical significance. The randomized groups were reasonably comparable with respect to other characteristics.

Table 10 TBZ 103,005: Baseline Demographic and Disease Characteristics

Variable	Levels	Pla/Pla	TBZ/Pla	TBZ/TBZ	All	Any Group Differences P-value
Age	Mean (SD)	56.1 (9.7)	55.9 (8.5)	59.8 (14.2)	56.8 (10.0)	0.526
Age Group	< 60	6 (50.0)	8 (66.7)	3 (50.0)	17 (56.7)	0.665
Age Group	≥ 60	6 (50.0)	4 (33.3)	3 (50.0)	13 (43.3)	0.665
Cgi-Sev	3	0 (0.0)	2 (16.7)	0 (0.0)	2 (6.7)	0.170
Cgi-Sev	4	7 (58.3)	7 (58.3)	2 (33.3)	16 (53.3)	0.170
Cgi-Sev	5	4 (33.3)	1 (8.3)	1 (16.7)	6 (20.0)	0.170
Cgi-Sev	6	1 (8.3)	2 (16.7)	3 (50.0)	6 (20.0)	0.170
Cgi-Sev	Mean (SD)	4.5 (0.7)	4.3 (1.0)	5.2 (1.0)	4.5 (0.9)	0.262
Disease Duration	Mean (SD)	10.2 (4.5)	9.2 (6.1)	11.4 (4.8)	10.0 (5.1)	0.780
Father HD	0 No	5 (41.7)	5 (41.7)	3 (50.0)	13 (43.3)	0.944
Father HD	1 Yes	6 (50.0)	7 (58.3)	3 (50.0)	16 (53.3)	0.944
Father HD	Unknown	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.3)	0.944
Mother HD	0 No	6 (50.0)	7 (58.3)	3 (50.0)	16 (53.3)	0.944
Mother HD	1 Yes	5 (41.7)	5 (41.7)	3 (50.0)	13 (43.3)	0.944
Mother HD	Unknown	1 (8.3)	0 (0.0)	0 (0.0)	1 (3.3)	0.944
Prior suic attempt	0 No	12 (100.0)	10 (83.3)	6 (100.0)	28 (93.3)	0.200
Prior suic attempt	1 Yes	0 (0.0)	2 (16.7)	0 (0.0)	2 (6.7)	0.200
Prior suic ideation	0 No	11 (91.7)	11 (91.7)	6 (100.0)	28 (93.3)	0.765
Prior suic ideation	1 Yes	1 (8.3)	1 (8.3)	0 (0.0)	2 (6.7)	0.765
Race	Black	0 (0.0)	2 (16.7)	0 (0.0)	2 (6.7)	0.200
Race	White	12 (100.0)	10 (83.3)	6 (100.0)	28 (93.3)	0.200
Gender	Female	7 (58.3)	8 (66.7)	3 (50.0)	18 (60.0)	0.784
Gender	Male	5 (41.7)	4 (33.3)	3 (50.0)	12 (40.0)	0.784
Max Chorea (UHDRS 12)	Mean (SD)	9.4 (4.9)	9.1 (6.2)	11.2 (4.4)	9.6 (5.3)	0.594

3.1.2.6 Sponsor's Results

In Group 1 (Placebo/Placebo), mean Total Maximal Chorea Scores increased by 5.33 points between the Baseline visit and Day 3, and did not increase any further between Day 3 and Day 5, suggesting that wash-out was complete by Day 3. In Group 2(TBZ/Placebo), mean Total Chorea Scores increased by 3.6 points between the Baseline Visit and Day 3 and further increased by 1.9

points at Day 5. In Group 3 (TBZ/TBZ), mean Total Chorea Scores increased by 1.6 points between the Baseline Visit and Day 3 (this group remained on tetrabenazine between the Baseline visit and Day 3). In Group 3, mean Total Maximal Chorea Scores increased another 2.3 points between Day 3 and Day 5 following a 12-hour to 18-hour washout period.

As specified in the Data Analysis Plan, the primary outcome measure to be analyzed was the change in Total Maximal Chorea Score from the Baseline Visit to Day 3 where Group 1 (the group withdrawn from tetrabenazine at the Baseline Visit) was the experimental group and the combined Groups 2 and 3 (who should have received tetrabenazine prior to the Day 3 evaluations) was the control group. The mean change scores (± SD) from this analysis are summarized in Table 11. The Total Maximal Chorea scores for participants in Group 1 increased by a mean of 5.33 ± 3.47 units, while participants in the combined Groups 2 and 3 increased by a mean of 2.94± 3.52 units. The treatment effect was in the hypothesized direction with an estimated treatment effect of 2.39 units (p=0.0779).

The sponsor asserts that the withdrawal of tetrabenazine for group 2 on day 3 was to occur after the morning dose of the same study drug given on the previous day. However, because it was unclear in the protocol, the investigator made the switch before the morning dose on day 3 so that group 2 had been off tetrabenazine for 12-18 hours when the UHDRS maximal chorea ratings were made. Because this would tend to make group 2 more similar to group 1 the sponsor investigated several post-hoc analyses. The first investigated a difference between group 3 (TBZ/TBZ) and groups 1 (Pla/Pla) and 2 (TBZ/Pla) combined at day 3. However this difference was not nominally significant (Groups 1+ 2: 4.45 ± 3.20 vs. Group 3: 1.66 ± 4.71, p=0.1375). A pairwise comparison between groups 1 and 3 also failed to reach nominal statistical significance (Group 1: 5.33 ± 3.47 vs. Group 3: 1.66 ± 4.71, p=0.1111). The sponsor also performed a linear trend analysis, which they believe is reasonable because group 2 was withdrawn after group 1 but prior to group 3. This yielded a nominally significant result (p=0.0486) but this is also an exploratory post-hoc analysis. None of the planned primary or secondary efficacy analyses specified in the data analysis plan demonstrated nominally statistically significant treatment group differences.

Table 11 TBZ 103, 005: Analysis of Change from Baseline in Max Chorea scores at Day 3

GROUP 1 (N=12) PLACEBO/PLACEBO MEAN ± S.D.	**GROUP 2+3 (N=18) TBZ/PLACEBO AND TBZ/TBZ MEAN ± S.D.**	**ANCOVA P-VALUE FOR GROUP 1 VS. GROUP 2+3**
5.33 ± 3.47	2.94 ± 3.52	0.0779

3.1.2.7 Reviewer's Results

This study was conducted at a single site, Baylor College of Medicine. Because assessments for the primary analysis were taken shortly after withdrawal in this study there may have been a rebound effect, i.e., some patients may have had a transient dramatic worsening right after withdrawal that is not characteristic of the long term off-treatment efficacy score or the pre-treatment baseline score. However, since off-treatment baseline scores were not provided it is difficult to assess whether there was a rebound effect in this study. At day 3 a rebound effect could have affected the scores of group 1 (Placebo/Placebo), withdrawn on day 1, as well as group 2 (Placebo/TBZ), withdrawn on the morning of day 3.

This reviewer verified the sponsor's analyses and found that the p-value for the primary analysis was not significant (p=0.078). All patients completed the study so there are no missing data issues.

In addition to the primary comparison between the Placebo/Placebo group and the combined TBZ/Placebo and TBZ/TBZ groups at day 3, Table 12 shows p-values for other post-hoc comparisons. The post-hoc comparisons should be considered exploratory since they were not planned and are not adjusted for other tests.

Table 12 TBZ103,005: Day 1 Mean Total Chorea Scores and Changes from Day 1 at Days 3 and 5

	Day 1		Day 3			Day 5		
		Max Chorea Total		Change from Day 1			Change from Day 1	
TREAT	N	MEAN (SD)	N	MEAN (SD)	P-value for comparison with Placebo/Placebo	N	MEAN (SD)	P-value for comparison with Placebo/Placebo
Placebo/Placebo	12	9.4 (4.9)	12	5.3 (3.5)	N/A	12	5.3 (3.8)	N/A
TBZ/Placebo	12	9.1 (6.2)	12	3.6 (2.8)	0.201	12	5.5 (3.4)	0.918
TBZ/TBZ	6	11.2 (4.4)	6	1.7 (4.7)	0.062*	6	4.0 (3.0)	0.490
TBZ/Placebo & TBZ/TBZ	18	9.8 (5.6)	18	2.9 (3.5)	0.078			N/A

*based on an ANCOVA model including all 3 groups; ANCOVA model based on only Placebo/Placebo and TBZ/TBZ gives a p value of 0.111

If the study had been designed to be considered a win if either the protocol specified ANCOVA **or** the trend analysis was significant then the significance level would have to have been 0.025 (or less if more analyses were considered) to avoid inflating the type I error. The post-hoc p-value for the linear trend analysis is larger than 0.025 and thus would not be significant after the multiplicity adjustment. Furthermore, the trend analysis was not specified as even a secondary or exploratory analysis and if we adjusted for other secondary analyses the significance level for the trend analysis would have to be even smaller than 0.025. If group 2 had not been accidentally withdrawn from the drug before the day 3 morning assessments, then a linear trend analysis would not have been proposed. A trend analysis of the day 3 data among groups 1, 2, and 3 would not have made sense if the study had been conducted as the sponsor intended because group 2 and group 3 would have had identical treatment up to day 3, in which case $\mu_2 = \mu_3$.

Therefore, there would be no reason to expect the means to be ordered $\mu_1 > \mu_2 > \mu_3$, as required by a monotone trend, or as required for a linear trend (e.g., $\mu_1 > \mu_2 = \mu_1 - \beta > \mu_3 = \mu_1 - 2\beta$). Although there was limited power for detecting a difference between groups 2 and 3 the pairwise comparison between them is not nominally significant which would suggest that pooling these groups for the analysis as planned in the protocol is not necessarily inappropriate. A test for any differences (heterogeneity) among the 3 separate group mean changes at day 3 yielded a p-value of 0.15. None of the planned primary or secondary efficacy analyses specified in the data analysis plan demonstrated nominally statistically significant treatment effects. Due to an administrative error, patients were not rated on the non-chorea items of the UHDRS at day 3 so it is not possible to examine whether or not there were any treatment group differences on the following secondary variables: UHDRS parts I (Motor), II (Cognitive), III (Behavioral), IV (Functional), V (Independence), and VII (Clinical Summary). The Clinical Global Impression of Improvement was not administered after day 1 either. Thus, there were no secondary ratings to lend support to the insignificant primary analysis result.

Four patients (1 Pla/Pla, 2 TBZ/Plac, and 1 TBZ/TBZ) took prohibited neuroleptic medications (2 fluphenazine, 1 haloperidol, and 1 quetiapine) throughout the study. Excluding these four patients from the primary analysis yields a p-value of 0.118 and excluding them from the post-hoc analysis for trend also yields a p-value that exceeds 0.05 (p=0.0814).

Other Endpoints

The functional capacity assessment (UHDRS part VI) was listed under safety and tolerability assessments in the protocol rather than under efficacy assessments but in the study report the sponsor seems to regard it as a secondary efficacy endpoint. Notably, none of the Placebo/Placebo patients had a change in their score between day 1 and day 3 whereas the average change was -0.38 points (a slight worsening) in the combined other groups. Thus, the comparison between Group 1 (Placebo/Placebo) and Groups 2 (TBZ/Placebo) and 3 (TBZ/TBZ) combined at day 3 favored the Placebo/Placebo group numerically but did not reach the 0.05 level of significance (ANCOVA p=0.35).

3.2 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review(s) for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

This section contains this reviewer's summary statistics for gender, race, and age subgroups. The studies were not adequately powered to estimate treatment effects precisely in subgroups or to detect differences between subgroups. Since these subgroups were not part of the decision rule and no adjustments were made for multiple testing the following p-values should be regarded as exploratory.

Gender

About 38% of patients in the acute treatment study TBZ 103,004 were male. While the treatment group difference in mean change in chorea scores was numerically larger in males than females treatment group differences were nominally significant for both males and females. In contrast to the results on the chorea scores the treatment group difference on the Clinical Global Impression of Change (CGI) was numerically larger for females than males. Thus, overall there was no compelling or consistent evidence that the treatment group difference varied significantly with gender in the 12 week acute study (04).

Table 13 TBZ 103,004: Change in Chorea Score by Gender

	Female			Male			All	
TREAT	N	MEAN (SD)	P-value	N	MEAN (SD)	P-value	N	MEAN (SD)
Placebo	19	-2.0 (4.2)	.	11	-0.9 (1.7)	.	30	-1.6 (3.7)
TBZ	33	-4.6 (4.0)	0.005	21	-5.4 (4.6)	0.012	54	-4.9 (4.4)

Table 14 TBZ 103,004: Mean CGI by Gender

	Female			Male			All	
TREAT	N	MEAN (SD)	P-value*	N	MEAN (SD)	P-value*	N	MEAN (SD)
Placebo	19	3.7 (0.8)	.	10	3.8 (0.4)	.	29	3.7 (0.7)
TBZ	32	2.8 (1.1)	0.003	20	3.5 (1.5)	0.777	52	3.1 (1.3)

*P values based on ANOVA

Forty percent of the 30 patients in the staggered withdrawal study (TBZ 103,005) were male. Since there were 12 or fewer patients per group in Study 05 it was too small to permit meaningful estimates of gender specific treatment differences regarding the effects of withdrawal or differences between genders. Although the gender specific means are not shown because of the small numbers of patients in each group none of the treatment group differences reached the nominal significance level of 0.05.

Age

In the acute study (TBZ 103,004) ages ranged between 25 and 77 and the mean age was 49. The following table shows that there was only a slight difference between the treatment effects on the change in maximal chorea score in the AGE < 50 and Age >= 50 subgroups. In fact, there was no compelling evidence that the treatment group difference varied significantly with age. Note that only 7 (9%) patients (5 TBZ and 2 placebo) were 65 or older, so a meaningful analysis of patients over the age of 65 is not possible.

Table 15 TBZ 103,004: Change in Chorea scores by Age Group

	Age < 50			Age ≥ 50			All	
TREAT	N	MEAN (SD)	P-value	N	MEAN (SD)	P-value	N	MEAN
Placebo	15	-0.7 (2.6)	.	15	-2.5 (4.2)	.	30	-1.6 (3.7)
Tetrabenazine	27	-4.3 (4.2)	0.004	27	-5.5 (4.2)	0.009	54	-4.9 (4.3)

Table 16 shows the mean CGI improvement scores at Week 12 for each group. There was no significant difference in the treatment effects within the two age groups.

Table 16 TBZ 103, 004 Mean CGI scores at Week 12 by Age Group

	Age < 50			Age ≥ 50			All	
TREAT	N	MEAN (SD)	P-value	N	MEAN (SD)	P-value	N	MEAN
Placebo	14	3.8 (0.4)	.	15	3.7 (0.9)	.	29	3.7 (0.7)
Tetrabenazine	26	3.2 (1.4)	0.16	26	2.9 (1.2)	0.049	52	3.1 (1.3)

The mean age in the staggered withdrawal study was 57. Since there were 12 or fewer patients per group in Study 05 it was too small to permit meaningful estimates of any age group specific treatment differences regarding the effects of withdrawal or differences between age groups. Although the age-group specific means are not shown because of the small numbers of patients in each group, none of the treatment group differences for the Age ≥ 60 and Age < 60 groups reached the nominal significance level of 0.05.

Race

Since only 5 (6%) patients in study 103,004 were not white no meaningful analysis of race subgroups is possible. Likewise, no meaningful analysis of race is possible for the withdrawal study 103,005, since only 2 patients were not white.

4.2 Other Special/Subgroup Populations

No other special populations or subgroups were investigated.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Because the pre-specified primary analysis of the second study, the staggered withdrawal study, was not significant at the 0.05 level (p=0.078) it is important to check for internal replication in the positive, acute study. Within all individual sites except one group differences in the primary endpoint favored tetrabenazine. None were nominally significant but there was limited power since all sites had 9 patients or less.

The sponsor specified four secondary endpoints for the acute study (TBZ 103,004) and proposed a prioritized order for testing each of them at 0.05 as long as all prior tests were significant at 0.05. The statistically significant treatment difference on the CGI part 2 (p=0.005), the secondary endpoint that the sponsor considered the highest priority, provides some internal replication of the primary analysis result. The sponsor's pre-specified analysis of the change from baseline to maintenance in the UHDRS motor subscale, which contains the chorea items of the primary endpoint, did not reveal a statistically significant group difference. The difference was in the right direction but the p-value was greater than 0.05 (p=0.08). Because of this insignificant result and the sponsor's conditional sequential testing procedure any differences on the secondary endpoints of lower priority can only be considered exploratory. However, on the UHDRS functional assessment scale a small but nominally statistically significant difference favoring placebo was seen. The fourth and final secondary endpoint in the prioritized list was the UHDRS gait score. No difference was observed in the UHDRS gait score. Thus, the secondary endpoints provide limited internal replication.

Some of the other endpoints that were of lower priority than the four mentioned above had results that were somewhat unexpected. In particular, the placebo group was nominally significantly better than the tetrabenazine group on the change from baseline to week 12 in the sum of the cognitive items (UHDRS part II). Looking at the cognitive items individually, one finds that the group difference on the Stroop Interference Test –Words surpassed the nominal level of significance (p=0.012 < 0.05), the Stroop Interference Test-Interference nearly did (p=0.053), and Placebo was numerically but not significantly better than tetrabenazine on the three other cognitive items. There was no significant group difference in mean change from baseline through the maintenance period in the behavioral assessments (UHDRS part III), the independence scale (UHDRS part V), or the functional capacity scale (UHDRS part VI) but all three numerically favored the placebo group. Thus, the secondary endpoints provide limited internal replication and raise questions about the drug's effect on non-chorea aspects of Huntington's disease.

Patients with HAMD scores > 15, a benchmark for depression, were excluded from the study. The average baseline HAMD score was 5.1 for placebo and 4.5 for Tetrabenazine. Eight of 54

(15%) tetrabenazine patients reported depression as an adverse event as compared to 0 of 30 placebo patients (two-sided exact test p=0.046). Sadly, one of the eight tetrabenazine patients actually completed suicide. This reviewer could not locate the sponsor's HAMD analysis results, but the sponsor reported that there was no group difference between the baseline HAMD score and the average of the week 9 and week 12 HAMD scores. However, this reviewer estimated the group mean change by ANCOVA to be 1.6 (+/- 0.5 S.E.) points smaller for placebo than Tetrabenazine (p=0.003). A nonparametric test yielded the same conclusion. Despite the apparent group difference, the average week 12 score was still only about 2.5 for placebo and 3.9 for Tetrabenazine, so neither group was depressed on average. However, this may be because many patients (60%) were using antidepressants concomitantly. Thus, although the average week 12 HAMD scores did not suggest depression the nominally significant group difference this reviewer found in the change in HAMD scores corroborates the observed increase in depression related adverse events in the tetrabenazine group.

After the 103,004 study was underway a protocol was introduced for videotaping patients at the end of treatment (week 12) and one week after the cessation of treatment (week 13). An expert in Huntington's disease was to determine chorea scores for the videotapes without knowing the treatment group of the patient or to which visit the tape corresponded. While the data from the videotapes seems to support the primary analysis result only 23 (27%) patients had videotapes made. Some patients who should have been videotaped were not, therefore, within the videotaped subgroup the treatment groups may not be balanced with respect to important baseline characteristics. For this reason it is not clear that the observed group difference within the subgroup with videos is due to the treatment alone. Therefore, the video rating results do not seem to have added much to the primary analysis result.

Although the group differences in chorea scores in the randomized staggered withdrawal study (TBZ 103,005) favored the combined group of those withdrawn on day 3 or day 5 over the group withdrawn at day 1 the primary analysis did not reach statistical significance (p=0.078). Fewer patients were enrolled than originally planned (30 vs. 45) after it was determined that a smaller sample size would be adequate because, apparently, patients were reluctant to agree to be taken off the drug. An ambiguity in the protocol resulted in patients that were supposed to be withdrawn on day 3 after the morning efficacy assessment, receiving placebo instead of tetrabenazine just prior to the day 3 morning assessment. The sponsor reasoned that since this made the 3 groups ordered at day 3 with respect to time of withdrawal a trend analysis would be more appropriate than the pre-specified comparison. A post-hoc trend analysis yielded an unadjusted p-value of 0.048 but this would not be significant after adjusting for the other tests that were conducted. In fact, a trend analysis was not specified in the protocol and would not have made sense for the day 3 data if the study had been conducted as planned because groups 2 and 3 would have been treated identically up to day 3. Thus, the trend analysis is an attempt to save the study from not only an insignificant primary result but also the error in study conduct and in this sense is a more of a stretch than a typical post hoc analysis. Note that four patients took protocol prohibited neuroleptics throughout the study and if these patients are excluded from the analyses neither the pre-specified primary comparison or the post-hoc trend analysis is nominally significant.

5.2 Conclusions and Recommendations

The primary endpoint data from the 12 week study of tetrabenazine for the treatment of acute chorea in patients with Huntington's disease support the proposed indication ($p<0.0001$). The result on the clinical global improvement endpoint was also statistically significant in favor of tetrabenazine. However, results on two other secondary endpoints related to other aspects of Huntington's disease were nominally statistically significant in favor of placebo and this is the only acute study in the application. In this study there was also one suicide in the drug group but none in the placebo group. It should be noted that there is a high prevalence of suicide in Huntington's disease and twice as many patients were randomized to the drug. On the other hand, there were 8 (15%) depression adverse events in the drug group and 0 in the placebo group, which is a nominally significant difference. The other study was a very small 5 day randomized staggered withdrawal study. Although the group that had Tetrabenazine withdrawn first had a numerically higher mean chorea score than the other groups the p-value was not significant ($p=0.078$).

Appendix – Individual Items of the Functional Assessment Checklist

Since there was a significant difference favoring placebo in the change from baseline to week 12 in the sum of the functional assessment checklist item responses (UHDRS items 43-67) this reviewer investigated the results on the individual items that comprise the functional checklist. Each item is answered either yes or no. Table 17 shows the results. The items are presented in the table sorted by the size of the group difference in percentages that answered yes at week 12. The p-values should be considered exploratory since the tests were not pre-planned or adjusted for other analyses.

It is important to note that at week 12 there was a difference in Item 68 of the UHDRS which identifies whether the patient or the patient and caregiver filled out the functional assessment checklist. More placebo patients filled out the checklist by themselves (47% vs 26% p=0.04). This may raise the question of whether the group difference may be attributable to the differences in who was filling out the checklist rather than the treatment. This is not a randomized subgroup so we can't be sure but the difference on the change from baseline to week 12 in the sum of all items was still nominally significant in the larger subgroup of patients that filled out the checklist with their caregiver. The difference on item 68 was smaller and not significant at earlier weeks.

There were six items that had group differences greater than 15% in the percentage of patients that were able to do the item. Note that there were group imbalances at baseline on some of these items although none were significant at the nominal level. Most of the differences on individual items at week 12 were less significant after adjusting for the baseline responses. Item 52, related to doing laundry, has a p value of 0.051 after adjusting for the baseline responses. This was the smallest baseline adjusted p-value among the individual functional checklist items.

Table 17 Week 12 (or LOCF) Responses on Individual Items of UHDRS Part IV Functional Assessment Checklist

		BASELINE			WEEK 12 OR LAST OBSERVATION				
UHDRS FUNCTIONAL CHECKLIST ITEM	LEVELS	TBZ (N=54)	PLACEBO (N=30)	CHISQ P-VALUE	TBZ (N=54)	PLACEBO (N=30)	PERCENT DIFFERENCE	UNADJUSTED CHISQ P-VALUE	BASELINE ADJUSTED P-VALUE
68 Obtained from Participant Only	N(%) YES	18 (33.3)	10 (33.3)	1.000	14 (25.9)	14 (46.7)	-20.8 %	0.053	0.043
47 Shop for Groceries	N(%) YES	36 (66.7)	24 (80.0)	0.195	28 (51.9)	22 (73.3)	-21.4 %	0.055	0.159
49 Supervise children	N(%) YES	28 (51.9)	20 (66.7)	0.189	25 (46.3)	20 (66.7)	-20.4 %	0.073	0.227
52 Do Laundry	N(%) YES	44 (81.5)	26 (86.7)	0.541	38 (70.4)	27 (90.0)	-19.6 %	0.039	0.051
51 Do Housework	N(%) YES	35 (64.8)	22 (73.3)	0.423	31 (57.4)	23 (76.7)	-19.3 %	0.078	0.089
59 Public transport	N(%) YES	37 (68.5)	23 (76.7)	0.428	35 (64.8)	25 (83.3)	-18.5 %	0.072	0.096
55 Take meds w/o help	N(%) YES	44 (81.5)	28 (93.3)	0.137	42 (77.8)	28 (93.3)	-15.5 %	0.067	0.265
46 Manage Finances	N(%) YES	16 (29.6)	11 (36.7)	0.508	12 (22.2)	11 (36.7)	-14.5 %	0.155	0.170
50 Operate Auto	N(%) YES	20 (37.0)	14 (46.7)	0.389	19 (35.2)	14 (46.7)	-11.5 %	0.302	0.570
60 Walk in	N(%)	48	27	0.875	43	27	-10.4 %	0.222	0.205

		BASELINE			WEEK 12 OR LAST OBSERVATION				
UHDRS FUNCTIONAL CHECKLIST ITEM	**LEVELS**	**TBZ (N=54)**	**PLACEBO (N=30)**	**CHISQ P-VALUE**	**TBZ (N=54)**	**PLACEBO (N=30)**	**PERCENT DIFFERENCE**	**UNADJUSTED CHISQ P-VALUE**	**BASELINE ADJUSTED P-VALUE**
neighborhood	YES	(88.9)	(90.0)		(79.6)	(90.0)			
58 Bathe self	N(%) YES	49 (90.7)	29 (96.7)	0.312	49 (90.7)	30 (100.0)	-9.3 %	0.086	0.941
44 Engage in any gainful employment	N(%) YES	11 (20.4)	7 (23.3)	0.751	10 (18.5)	8 (26.7)	-8.2 %	0.383	0.326
57 Dress self	N(%) YES	46 (85.2)	29 (96.7)	0.103	48 (88.9)	29 (96.7)	-7.8 %	0.217	0.935
45 Engage in volunteer or non gainful work	N(%) YES	30 (55.6)	17 (56.7)	0.922	31 (57.4)	19 (63.3)	-5.9 %	0.596	0.502
48 Handle purchase	N(%) YES	49 (90.7)	26 (86.7)	0.563	46 (85.2)	27 (90.0)	-4.8 %	0.531	0.273
54 Use telephone	N(%) YES	52 (96.3)	28 (93.3)	0.541	48 (88.9)	28 (93.3)	-4.4 %	0.506	0.380
56 Feed self	N(%) YES	51 (94.4)	30 (100.0)	0.189	50 (92.6)	29 (96.7)	-4.1 %	0.450	0.892
63 Comb hair w/o help	N(%) YES	54 (100.0)	30 (100.0)	.	52 (96.3)	30 (100.0)	-3.7 %	0.286	0.953
53 Prepare meals	N(%) YES	39 (72.2)	20 (66.7)	0.594	38 (70.4)	22 (73.3)	-2.9 %	0.773	0.378
43 Engage in accustomed gainful employment	N(%) YES	6 (11.1)	4 (13.3)	0.763	4 (7.4)	3 (10.0)	-2.6 %	0.680	0.782
61 Walk w/o falling	N(%) YES	51 (94.4)	27 (90.0)	0.449	49 (90.7)	28 (93.3)	-2.6 %	0.680	0.433
67 Care provided at home	N(%) YES	54 (100.0)	30 (100.0)	.	53 (98.1)	30 (100.0)	-1.9 %	0.453	0.950
64 Transfer between chairs	N(%) YES	54 (100.0)	30 (100.0)	.	54 (100.0)	30 (100.0)	0 %	1.000	0.953
65 Get in/out of bed	N(%) YES	54 (100.0)	29 (96.7)	0.177	54 (100.0)	30 (100.0)	0 %	1.000	0.953
66 Use toilet	N(%) YES	54 (100.0)	29 (96.7)	0.177	54 (100.0)	30 (100.0)	0 %	1.000	0.953
62 Walk w/o help	N(%) YES	53 (98.1)	29 (96.7)	0.670	54 (100.0)	29 (96.7)	3.3 %	0.177	0.809

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

/s/

Tristan Massie
3/23/2006 09:42:49 AM
BIOMETRICS

Kun Jin
3/23/2006 09:51:17 AM
BIOMETRICS

Kooros Mahjoob
3/23/2006 10:15:53 AM
BIOMETRICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Senior Director, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your new drug application (NDA) dated September 23, 2005, received September 26, 2005, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine (tetrabenazine) Tablets 12.5mg and 25mg.

We acknowledge receipt of your submissions dated:

18-Oct-2005	09-Dec-2005	14-Dec-2005	15-Dec-2005
19-Dec-2005	23-Dec-2005	23-Dec-2005	23-Dec-2005
18-Jan-2006	27-Jan-2006	06-Feb-2006	21-Feb-2006
21-Feb-2006	01-Mar-2006	06-Mar-2006	

We also acknowledge receipt of your submissions dated:

1-Mar-2006	6-Mar-2006	10-Mar-2006	14-Mar-2006
15-Mar-2006	16-Mar-2006		

These latter submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following issues:

CLINICAL
We believe that you have provided substantial evidence of effectiveness for Xenazine as a treatment for chorea in patients with Huntington's Disease (HD).

Specifically, the results of Study 004 are clearly and robustly consistent with this conclusion. Not only is the p-value for the primary contrast extremely small ($p < 0.0001$), but the results clearly favor drug over placebo in 14 of the 15 study sites. In addition, other analyses of the data in this study also document the robustness of this finding. Specifically, we note that upon drug withdrawal at Week 12, patients' chorea scores returned to baseline levels by Week 13, confirming the drug effect seen over the previous 12 weeks. In addition, exploratory analyses document that the responses of patients during the first 11 weeks of Study 007, the open-label extension to Study 004, during which all patients were re-titrated, were essentially identical to the responses seen in the drug treated patients during the titration period in Study 004. This effect in Study 007 was seen in both patients who had previously received active treatment in Study 004 as well as in those who had previously

received placebo. A similar effect was seen for patients enrolled in Study 006, the open-label extension to Study 005. That is, although patients (after their participation in Study 005) were placed back on their best dose in Study 006 (as opposed to being re-titrated, as the patients in Study 007 were), their responses over the first 12 weeks in Study 006 were also essentially identical to those of the drug treated patients in Study 004. Further, although patients were not randomized to fixed dose in Study 004, PK/PD analyses strongly suggest a dose response relationship in that study.

The drug effect seems to be present regardless of the baseline degree of severity of the chorea.

We recognize that the results of the analyses of Study 005 do not meet the usual test for being considered "positive" (p=0.078). However, we note your observation that patients in Group 2 were not treated in compliance with the protocol (that is, placebo was inadvertently substituted for active drug on the morning of Day 3), and we agree that the protocol-specified prospective analysis is therefore inappropriate. We believe that the comparison of Group 1 to Group 3 on Day 3 is an appropriate post hoc analysis under these circumstances, because it is consistent with the rationale for your prospective analysis (that is, it compares patients off drug [Group 1] with patients continuing on treatment [Group 3]). Although the results of this analysis do not achieve nominal statistical significance (p=0.11), the estimate of the treatment effect is essentially identical to that seen in Study 004 (mean between treatment difference of about 3.5 points). In this case, we believe that the absence of statistical significance for this comparison is related to the extremely small sample size (12 patients in Group 1 and only 6 patients in Group 3).

We believe, given the results described above, that the findings establish the effectiveness of Xenazine as a treatment for the chorea of HD, under FDAMA's provision that substantial evidence can consist of the results of a single adequate and well-controlled investigation plus confirmatory evidence. We believe that the statistically strong result of Study 004, its marked internal consistency, as well as the results of Study 005, provide the necessary confirmatory evidence required by this provision of the Act.

Despite the documented effect on chorea, there remain troubling questions about the utility and ultimate approvability, of this application.

In particular, we note that there was a consistent tendency for the results of the analyses of multiple secondary outcomes to favor placebo in Study 004. Specifically, the between-treatment comparisons on the Cognitive Assessment (UHDRS Part 2), the Behavioral Assessment (UHDRS Part 3), the Functional Assessment (UHDRS Part 4), the Independence Scale (UHDRS Part 5), the Functional Capacity (UHDRS Part 6) all numerically favored placebo, and the comparisons on the Cognitive Assessment (UHDRS Part 2) and the Functional Assessment (UHDRS Part 4) actually achieved nominal statistical significance in favor of placebo (p=0.025 and p=0.018, respectively). We also note that there were no patient – rated measures of overall benefit in Study 004. These results, taken together, raise serious questions, not only about the overall utility of Xenazine's effect on chorea, but also, of course, about Xenazine's capacity to cause harm in these patients. We acknowledge that the (negative) effects seen on these secondary measures appear to be numerically small, but we do not have a good understanding of the effects on patient functioning of these sorts of changes. We also do not have data on the consequences of long-term treatment with Xenazine. If overall patient functioning continues to worsen (in the face of reasonable control of the chorea) as a result of chronic treatment, we are not confident that such deterioration could easily be detected clinically (because detailed neuropsychiatric testing may be necessary to detect it). In such a case, clinical deterioration may continue unnoticed; when it does become manifest, the patient's clinical condition would very probably be attributed to progression of the underlying HD.

Beyond the question of these specific ways in which treatment with Xenazine may harm patients, we are concerned with Xenazine's capacity to cause other, serious, adverse events.

In particular, among the numerous adverse events seen in association with the use of tetrabenazine, we note parkinsonism, akathisia, depression, and dysphagia (with associated aspiration pneumonia). Although we acknowledge that the incidence of some of these events in Study 004 is not significantly different from placebo

(e.g., parkinsonism, dysphagia) the incidence of others is substantially greater in the drug-treated patients than in the placebo patients (e.g., depression: 15% vs 0; akathisia: 9% vs 0). Further, it is not clear that other events coded differently from akathisia do not, in fact, represent the same phenomenon (e.g., agitation, anxiety, irritability). All of these events are consistent with the pharmacologic effects of the drug, and the incidence of these events increases with increasing duration of use. We acknowledge, of course, that the long-term safety data were collected in an open-label, uncontrolled setting, and also that these can themselves be manifestations of progressive HD. For these reasons a definitive conclusion about causality clearly can not be made at this time. Nonetheless, we are concerned that these events may be drug-related.

We are particularly concerned about the ability of practitioners to readily identify these events and consider the possibility that they may be drug -related. We would agree that, should these events occur relatively acutely after treatment initiation (or dose increase), the prescriber might consider them drug related (and take the appropriate action). However, to the extent that they might be drug-related, but occur slowly over time, it is less likely that they will be considered potentially drug-related and more likely to be considered related to disease progression. In such a scenario, the possibility that the specific symptom might reach a severe stage (with the possibility that it may become irreversible), or result in a serious outcome even if reversible (e.g., depression leading to suicide), is raised. (In the case of parkinsonism, an article in the literature (Satou T et al. Exp Toxic Pathol 53:303-308, 2001) suggests that there is irreversible damage to the substantia nigra pars compacta in Wistar rats following 7 daily i.p. doses of tetrabenazine.)

Also, in regard to dysphagia specifically, we note the disturbing finding that Dr. Jankovic did not systematically record episodes of dysphagia in many of his patients because he considered it to be a symptom of progression of the underlying HD. Because his experience represents a large portion of the clinical experience submitted in this application, we are concerned that the incidence of dysphagia (which can have devastating clinical consequences) may be significantly underestimated.

For all of these reasons, then, we are not sure Xenazine can be used safely, even with labeling that describes, as accurately as possible, the known risks of its use. Because we are unable to reach a definitive conclusion about the ultimate approvability of the application at this time, we plan to discuss your NDA at a public meeting of the Peripheral and Central Nervous Systems Advisory Committee (PCNSAC). We will attempt to arrange this meeting as soon as possible.

CMC

1.

2.

3. Approval from a CMC standpoint will be contingent on the overall recommendation on establishment from the Office of Compliance.

NON-CLINICAL

Prior to approval, you will need to address the following nonclinical issues:

1. There is a lack of adequate in vivo metabolism data in the animal species used in the definitive nonclinical studies. There is a similar lack of metabolism data in humans. You need to provide additional data identifying and quantitating the major circulating metabolites in animals and humans. These data are needed in order to determine the relevance (and adequacy) of the nonclinical studies to an assessment of human risk. In particular, there is concern that the potential toxicity of the major circulating drug-related material in humans (peak 16) may not have been adequately assessed in animals.

2. The 26-week oral toxicity study is the only definitive toxicity study conducted in rats. Therefore, it is particularly important that you provide the data from this study in a complete and accurate manner. The following deficiencies were identified in the report of the study:

    a. The reporting of clinical signs is incomplete. For example, several instances of convulsions observed in two high-dose animals were not listed in the summary table. Similarly, instances of "lethargy" were noted in the summary table, but not in any individual animal line listing. You need to address the apparent discrepancies between the summary of clinical signs and the individual animal line listings.

    b. The study report did not include a signed Pathologist's Report. In order to document the gross pathology and histopathology findings in the chronic study, you need to provide a copy of this report.

3. You conducted a 14-day oral study of tetrabenazine to assess toxicokinetics and effects on serum prolactin in rats (Covance Study # 7425-114). The toxicokinetics data have been provided, but the serum prolactin data have not. You need to submit a final report of the serum prolactin data. These data are important for the interpretation of the results of the chronic toxicity study in rats.

4. The published findings of Satou et al. (Satou T et al. *Exp Toxicol Pathol* 53(4):303-308, 2001) raise a concern that tetrabenazine may have neurotoxic effects. Therefore, it is particularly important to understand how extensively the brain was examined in the 26-week and 9-month oral toxicity studies in rats and dogs, respectively. The reports of these studies do not provide sufficient detail regarding the methodology used in the microscopic examination of brain. You need to document that the microscopic examination of brain in the chronic studies was conducted using techniques sensitive enough to have detected, if present, neuropathological findings similar to those reported by Satou et al (2001).

5. The equivocal finding in females in the in vivo micronucleus assay in rat needs to be further investigated, particularly considering the lack of carcinogenicity data on tetrabenazine. The in vivo micronucleus assay needs to be repeated exploring a range of doses. Although the equivocal finding was only in females, it is difficult to understand why females would be more sensitive than males based on the available plasma exposure data; therefore, we ask that you include both males and females in the repeat assay.

6. You need to commit to initiating carcinogenicity studies. Your protocol for a 26-week p53 transgenic mouse assay has been reviewed by the Division and the Executive CAC; minutes of the Executive CAC meeting were sent to you on October 27, 2005. You have recently submitted a protocol for a 2-year carcinogenicity study in rats that is currently under review. You need to commit to a timeline for conduct of the studies and submission of final reports of these studies. Final study reports would not be required prior to approval.

CLINIAL PHARMACOLOGY & BIOPHARMACEUTICS

Before approval, we ask you to address the following:

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: ≥ (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).

   1. 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.
   2. 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 reactions.
   3. 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.
   4. 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.
   5. 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.

6. The results of adequate *in vitro* drug metabolism studies will guide the need for further *in vivo* drug interaction studies.
7. Since CYP2D6 appears to be involved in the metabolism of TBZ and HTBZ, we recommend genotyping for CYP2D6 in future TBZ clinical trials.
8. 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.

Phase 4 Commitments
NON-CLINICAL

We ask that you address the following issues as Phase 4 commitments:

1. Submission of final study reports for the 26-week p53 transgenic mouse assay and the 2-year carcinogenicity study in rats.

2. Conduct of a fertility and early embryonic development (to implantation) study. You should commit to a timeline for conduct of the study and submission of the final study report.

3. The following apparent discrepancies in the report of the pre- and post-natal development study need to be addressed:

   a. the lack of corpora lutea and preimplantation loss data in F1 females. These data need to be submitted if collected.

   b. the number of stillbirths versus early postnatal deaths. You need to specify which pups were determined to be stillborn due only to the lack of milk in the stomach versus those determined to be stillborn by the lack of lung floatation (with or without lack of milk in the stomach); the lack of milk in the stomach alone does not necessarily indicate a stillborn pup. In addition, you need to explain why the summary table (page 39) indicates a dose-related increase in stillbirths, whereas the individual line listings (page 204-207) fail to indicate a stillbirth in any litter.

   c. apparent discrepancies in the data for individual dams, low-dose female B73509, mid-dose female B73526, and high-dose female B73557. You need to provide all data (including pregnancy, litter, and final disposition) for these dams.

Although not needed prior to approval, we ask that you address these issues in a timely manner.

CLINICAL PHARMACOLOGY

We ask that you address the following issues 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.

In addition, it will be necessary for you to submit draft labeling revised as attached.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Robert Temple

3/24/2006 05:58:02 PM

Review and Evaluation of Clinical Data

NDA (Serial Number):	**NDA 21-894**
Sponsor:	**Prestwick Pharmaceuticals**
Drug:	**Xenazine® (tetrabenazine)**
Proposed Indication:	**Chorea of Huntington Disease**
Material Submitted:	**Clinical Response to Approvable Letter**
Submission Date:	**April 05, 2007**
Reviewer:	**Carole L. Davis, DO, MPH Medical Reviewer, DNP, ODE 1**

1. Introduction

The submission, by Prestwick Pharmaceuticals, is a Clinical Response to the Approvable Letter for tetrabenazine (TBZ) issued March 34, 2006 (NDA 21-894, tetrabenazine for the treatment of the chorea of Huntington's disease). The Approvable Letter expressed Agency concern about several of the outcomes in the pivotal study (TBZ103,004; Study 004). Of primary concern was the consistent tendency of multiple secondary outcomes of the study to favor placebo. Also, some adverse events (AEs) observed in the clinical trial could possibly be attributed to the underlying disease rather than recognized as drug-related events, and might progress to a severe stage, or result in a serious outcome.

The only endpoint on which the application was able to show convincing statistical results was on chorea scores (the primary endpoint). The initial assumption that improvement of chorea control would result in improvements in gait safety and functional activities (activities of daily living) was not substantiated in the clinical trials. An additional concern was that lack of ratings by the subjects on whether the study drug affected their functioning or quality of life.

An End-of-Review meeting was held May 25, 2006 and the sponsor proposed to reexamine endpoints of Study 004 to determine if alternative explanations such as between-group differences at baseline, chance findings, or treatment emergent AEs could explain the observed treatment group differences in function, cognition and behavior.

2. Review Conclusions

This efficacy review is only a part of the complete review for NDA 21-894. The issues raised in this review will be included in the scheduled Advisory Committee consideration of the NDA application.

3. Brief Background

Tetrabenazine (TBZ) is as an oral medication currently marketed overseas with the trade name of Xenazine or Nitoman. It is a centrally-acting catecholamine depleting drug with two modes of action: depletion of pre-synaptic stores of monoamines, and a postsynaptic blocking action. The result is a selective depletion of brain amines, especially dopamine. Tetrabenazine was submitted by Prestwick Pharmaceuticals, Inc. for the indication of chorea associated with Huntington's disease (HD). It was approved in the United Kingdom in 1971 for the treatment of chorea, and is currently available there in addition to Australia, Canada, Denmark, Ireland, Israel, New Zealand, and Portugal.

Tetrabenazine was introduced by Hoffmann-LaRoche. In the 1950s, it was shown to have use in the treatment of schizophrenia. It was approved for that indication in Europe, but later withdrawn for the indication because of the entry of more efficacious psychiatric drugs.

Prestwick Pharmaceuticals, Inc. submitted the NDA application (NDA 21-894, tetrabenazine for the treatment of the chorea of Huntington's disease) to the Agency for review on September 23, 2006. They presented a clinical development program including:

Phase I Studies – six in healthy volunteers, and one in liver-impaired subjects

Phase II/III Studies – the pivotal efficacy and safety studies consisted of:

(a) two randomized, double-blinded, placebo-controlled clinical studies of efficacy involving HD subjects for the indication of chorea: the Prestwick Tetra HD Study and the Prestwick Tetra Withdrawal Study,

(b) interim reports of two open-label safety studies which are extension studies of the two controlled trials.

(c) additional submissions included in the application as safety studies were the Baylor Chorea Database, and the Baylor Non-Chorea Database. These were not conducted by the Sponsor, but based on the assessment of patients previously treated by Dr. J. Jankovic, under IND 16,161 for tetrabenazine at Baylor College of Medicine, Houston, Texas.

Also submitted was a review of previously published literature citing studies done on the use of tetrabenazine for chorea and non-chorea movement disorders.

A total of 114 HD subjects were enrolled in the two pivotal efficacy trials. Upon the completion of those trials, subjects that qualified could be enrolled in the matching open-label extension studies. The Sponsor also submitted information on 145 chorea patients (including 98 with HD) in the Baylor Database study for safety review.

The two primary efficacy studies were done for the chorea indication. These were randomized, double-blinded, placebo-controlled trials, consisting of:
(a) Prestwick Tetra HD Study (TBZ 103,004)/Study 004).
Objective: Evaluate the change in chorea of HD subjects newly started on TBZ or placebo. Primary endpoint: change in Total Maximal Chorea Score (TCS) for the TBZ group compared to the placebo group
Important secondary endpoints: change in scores from baseline on the Total Motor Score(TMS), the Functional Assessment (FA) Checklist, and Gait on the UHDRS, and change in the Clinical Global Impression, Part II.

(b) Prestwick Tetra Withdrawal Study (TBZ 103,005)/Study 005.
Objective: Evaluate the return/increase of chorea in HD subjects following TBZ discontinuation
The primary endpoint: change in Total Maximal Chorea Score (TCS) of the first group withdrawn from TBZ compared to the other 2 groups still receiving the drug
Important secondary endpoints: change in the Total Functional Capacity (TFC) score of the UHDRS from Day I to Day 3 comparing Group1 to the combined average scores of Group 2 and Group 3.

Both of the efficacy studies used the Unified Huntington's Disease Rating Scale (UHDRS), copyright 1999, Huntington's Study Group. The scale has Parts I – VII rating motor (including chorea and gait), cognitive, behavioral, and functional areas. Both studies used changes in the Total Maximal Chorea Score (TCS), Item 12 a-g (a sub-part of Part I - Motor Assessment) as the primary objective measurement. The secondary or exploratory objectives used were the Parts I, II, III, IV, V, and VII of the UHDRS, along with the physician-rated Clinical Global Impression Scale (CGI). The same rating scales were used to evaluate either secondary or exploratory analysis of efficacy in each of the follow-on studies (Protocol TBZ 103,007 and Protocol TBZ 103,006).

The primary study upon which demonstration of the efficacy of tetrabenazine for the treatment of chorea relied was the Prestwick Tetra HD Protocol TBZ 103,004. It enrolled HD patients that had not previously used tetrabenazine, randomized at a ~2:1 ratio of drug:placebo. The study was conducted with 84 subjects at 16 sites in the US over a 12 week treatment period, followed by a follow-up assessment after a 1-week drug withdrawal at the end of the study.

Primary Endpoint:
The primary endpoint in Protocol TBZ 103,004 was the change in the Total Maximal Chorea Score (TCS) from baseline to the maintenance phase (average of the Week 9 and Week 12 scores) The mean TCS for the tetrabenazine group was 14.69 ($\pm$3.84) UHDRS points at baseline, and 9.41 ($\pm$4.45) points at the End of Week 12. This gave them a change in score of -5.04 ($\pm$0.49) points. This was compared to the placebo group's mean TCS decrease of 1.52 UHDRS points (15.20 $\pm$4.41at baseline, and 14.07 $\pm$4.72 at End of Week 12). The resulting mean decrease in the TCS attributable to the drug treatment for the TBZ Group was 3.52 UHDRS points (ANCOVA p-value = <0.0001) favoring the TBZ group. Since the Steering Committee for the study had established a decrease of 3

chorea points on the TCS scale as clinically significant, the treatment result met their criteria for clinical significance as well as statistical significance.

The criterion for efficacy was met; there was a significant reduction in the observed chorea of the subjects receiving tetrabenazine compared to the placebo group. The results were consistent across population subgroups based on gender, age, length of illness, severity of disease, and use of concomitant medications, and were consistent at the various study sites. The small number of non-white subjects limited generalization by race or ethnic group.

The reduction in the chorea scores followed the anticipated curve showing a steady increase over the first 5 weeks while doses were being titrated upward, and a fairly steady level throughout the maintenance phase. The study also found that there was a larger effect of TBZ treatment on the scores of the subjects that had higher baseline chorea scores. This observation had been suggested in previous studies.

At the Week 13 evaluation, which was to be done one week after withdrawal from the drug, the mean TCS for the TBZ Group was 15.08 ($\pm$4.21) UHDRS points, only slightly higher than their baseline score of 14.69 ($\pm$3.84) points. The placebo group had a baseline TCS of 15.20 (+4.41), and a Week 13 TCS of 14.90 (+4.47).

Secondary Endpoints:
Evidence of efficacy was supported in only the first of the four secondary endpoints.

- The Clinical Global Impression (CGI) Part 2 is an investigator assessment of whether total improvement is due entirely to drug treatment. A rating of 1 = very much improved, 4 = no change, and 7 = very much worse. A significant number of the TBZ subjects were rated by the investigators as "much" or "very much" improved by Week 12, compared to the placebo group. The difference at Week 12 between groups was 0.75 ($\pm$0.26) point on the 7-point scale. Although not a full point difference, it was statistically significant favoring TBZ treatment (p-value = 0.0074).

The next three secondary outcome measures failed to show a statistically significant treatment effect. These evaluated changes in the Total Motor Score, the Functional Assessment Checklist, and the Gait score:

- The second endpoint, Total Motor Score (TMS), (UHDRS Part I questions 1 – 17), included the Chorea Score (UHDRS question 12 – the primary endpoint of the study), and the Gait score (UHDRS question 13). Scores could range from 0 (best) to 124 (worst), and the average baseline score was 46 points. The mean change from baseline to maintenance (Week 9 + 12 averaged) was -6.84 points for the TBZ group and -3.5 points for the placebo group, giving a group difference of 3.3 ($\pm$1.9) points. The TBZ scores were better than placebo, but did not reach statistical significance (p-value = 0.075). Evaluating the TMS for the non-chorea items (all the items except # 12), the difference between the groups

was lower at 1.5 (±1.5) points (p-value = 0.32) suggesting that the significance of the TMS was due mainly to the change in the chorea score which had already been evaluated separately. Since this endpoint did not reach the pre-specified p-value of 0.05 for significance, the lower priority endpoints could not be accepted for support of the application without inflating the type I error rate, but they have been included in this review.

- The Functional Assessment Checklist (UHDRS Part IV) scores were rated by the subjects and/or caregivers, and ranged from 0 (worst) to 25 (best). The average baseline score was 19 points. The difference between groups from baseline to maintenance phase was 1.18 (±0.49) points which was statistically significant (p-value = 0.018), but favored the placebo group. The Sponsor attributed the lack of treatment benefit to the "ceiling effect" since most of the subjects had high functioning (and gait) scores at baseline.

- The Gait score (UHDRS sub-section TMS, question 13) used a 5-part rating of 0 (normal) to 4 (cannot attempt). The change from baseline to Week 12 for the TBZ group was -0.03 (±0.06) point indicating trace improvement, and 0.11 (±0.06) point for the placebo group suggesting slight worsening. The ANCOVA p-value of 0.2410 does not show a statistically significant difference. The difference in the baseline-to-endpoint change of only a fraction of a point for either group shows virtually no change occurred and makes clinical comparisons meaningless.

Exploratory Endpoints:
Due to the prioritization of endpoints for significance, none of the results of the exploratory endpoints were submitted for support of the application. The study included 10 exploratory endpoints, and the Functional Impact Scale.

- Only in the investigator-rated CGI Part 3 (the Efficacy Index), matching therapeutic effect to side effects, did TBZ treatment show statistical significance (p-value = 0.001). The score was an assigned number, not a change from baseline. By the end of the study, 51% of the subjects on TBZ were judged to be a "treatment success", compared to 7% of the subjects on placebo.
  The rating for the placebo treated subjects was 11.41 (+2.88) at Week 12 (11=slight improvement with side effects significantly interfering with functioning), compared to the TBZ score of 8.22 (+4.00) at Week 12 (8=moderate improvement but side effects outweighs therapeutic effect, and 9=slight improvement not altering status of care, with no significant side effects)

The other exploratory endpoints included CGI Part 1, behavioral and cognitive assessments and three additional functional assessments.

- In the CGI Part 1 (Severity of Illness), investigators rated each subject from 1 (normal) to 7 (among most severely ill). Both groups showed virtually no change between baseline and maintenance phase (p-value = 0.9186).

- The Behavioral Assessment (BA, UHDRS Part III) included 11 items scored from 0 (best) to 4 (worst) on both the frequency and severity of various behaviors such as depressed mood, suicidal ideation, compulsive behavior, delusions, apathy, etc..). The information was given by the subject or subject and caregiver, with 5 additional assessments done by the investigator. Both groups had a nominal decrease in scores suggesting slight improvement. The mean difference between the groups was -1.2 points (p-value = 0.363) favoring the placebo group. The only behavioral item that had group differences reaching significance was on the anxiety rating. At Week 12, 70% of the TBZ group had no evidence of anxiety, compared to 90% of the placebo group. Both anxiety items statistically favored the placebo group (frequency p-value = 0.028, and severity p-value = 0.040).

- Each question of the Cognitive Assessment (UHDRS Part II) was analyzed individually as an exploratory endpoint assessing change from baseline to Week 12. These included Verbal Fluency, Symbol Digit Modalities, and the 3 Stroop Interference Tests (Color Naming, Word Reading and Interference). All of the items at least nominally favored placebo, the Stoop Interference –Words reached statistical significance (p-value = 0.0123), and Stoop Interference – Interference nearly did (p-value = 0.0532). The sum of the Total Cognitive Assessment Score showed TBZ group worsened by 7.7 ($\pm$3.3) points from its mean baseline of 156 ($\pm$56) points, while the placebo group improved by 5.1 ($\pm$4.5) points from a baseline of 172 ($\pm$55) points. The estimated difference of 12.8 ($\pm$5.6) points was statistically significant, at ANCOVA p-value = 0.025, favoring placebo.

- The 3 additional functional assessments looked at mean change scores from baseline and Week 12. These are additionally notable for being rated by the subject and/or caregiver. The Independence scale (INS, UHDRS Part V) is a one-score rating between 100 (no special care needed) and 010 (tube fed, total bed care). The Total Functional Capacity (TFC) scale (UHDRS Part VI) rates the areas of occupation, finances, chore, ADLs on a 0 (unable) to 3 (normal) scale, and care level at 0 (full time skilled nursing) to 2 (home). Both scales nominally favored placebo (p=0.135, and p=0.291 respectively). The Functional Impact Scale was a new test piloted on this study. It addressed 4 basic ADL items (bathing, dressing, feeding and toileting) and a social isolation item all on a scale of 0 (best) to 3 (worst). Baseline scores for both groups were 1.3 points and showed no noticeable change by Week 12 (P-value = 0.970).

The tetrabenazine application had been granted a priority status review on the expectation that gains in chorea control might improve the walking safety, daily functional activities, or quality of life of HD patients. The secondary and exploratory endpoints failed to establish any connection with these measures for the drug. The 10 exploratory endpoints included additional assessments of functional status (change in the Independence Scale and in Total Functional Capacity), and in these, placebo showed superiority over the TBZ group, but did not reach statistical significance.

After the 12 week study was underway, there was a change in protocol to accommodate the FDA recommendation of videotaping of the subjects for rating of the chorea score (TCS) by an outside expert blinded as to drug treatment and study week. The outside ratings showed some variation from the site investigator scores. There was a difference in chorea scoring between the site investigator and the outside reviewer of $\geq$ 5 points on the TCS for 20.5% (9 of 44 Week 12 and Week 13 videotapes reviewed). Overall, the outside ratings support the primary endpoint of chorea reduction with TBZ treatment (p-values = <.0001 at Week 12, and .0004 at Week 13). However, due to a lack of consistency in implementation, they are limited in their ability to support the application. Only 21 of the subjects on the study (27.4%) had both the Week 12 (on TBZ) and Week 13 (off TBZ) videotapes evaluated. Two of the 23 videotaped subjects lacked either a Week 12 or Week 13 rating by the outside reviewer. The first videotape of a subject was done on October 3, 2003, but only 44% of the subjects enrolled after that date had videotapes made. At some sites, subjects did not have videotapes done despite being enrolled later than other subjects that were taped.

4. Organization of Review

The second pivotal trial, the withdrawal study (study 005), showed a trend suggestive of effectiveness, but was not statistically significant. It experienced major implementation flaws, and other problems that limited its usefulness in support of the application. The concern that the Agency has with the clinical data regards measurements (of function, cognitive and behavioral changes and AEs) that were used primarily in the longer trial (Study 004). The CR re-analyses by Prestwick addressing these issues uses the data from Study 004 and the open-label extension, Study 007, so the Study 005 is not included in this review.

In their Response to Approvable Letter, Prestwick has re-examined the data from Study 004 to consider possible alternative explanations for the findings of the secondary and exploratory endpoints. The company acknowledges that due to the retrospective nature of the analyses, their interpretations are exploratory. The re-analyses by the company focused on whether the between group differences in endpoints might be attributable to:

- Between-group differences in baseline demographics (such as disease severity, length of diagnosed disease, functional level, cognitive level, and behavioral status).
- Possible chance findings in a relatively small single study
- Known/predictable pharmacologic effects of TBZ
- The natural history and progression of Huntington's disease

This review focuses on the sponsor's Response to Approvable Letter for the sections of effectiveness of tetrabenazine in relation to chorea, functional activities, cognitive aspects, and quality of life issues. Full review of the clinical trials applicable to the NDA application is contained in the Clinical Review of March 23, 2006. The following sections address the sponsor's re-examination of the Study 004 data and exploratory analyses submitted for the CR regarding the cognitive and functional assessments:

The usefulness of chorea management is addressed in section 5.

The incidence of functional changes associated with TBZ vs placebo is addressed in Section 6.
The incidence of cognitive changes associated with TBZ vs placebo is addressed in Section 7.
The discussion of the sponsor's comparison of the databases of Study 004 to the CARE-HD Study is addressed in Section 8.

Table 1. UHDRS Components, Clinical Global Impression and Functional Impact Scale from Study 004: Adjusted Mean Change (± s.e.m.) from Baseline to Aver. of Week 9 + Week 12

	Endpoint	TBZ (N= 54)	Placebo (N=30)	p-value ANCOVA	Difference Numerically Favors
UHDRS Components					
I. Total Motor Score (Part 1; items 1-15)	2°	-6.84 ± 1.11	-3.51 ± 1.49	0.0752	TBZ
Total Chorea Score (Part 1, item 12a-g)	1°	-5.04 ± 0.49	-1.52 ± 0.67	< 0.0001	TBZ
Gait Score (Part 1, item 13)	2°	0.001±0.05	0.11± 0.07	0.2410	TBZ
II. Cognition (Part 2; items 19-23)					
Verbal Fluency	Exp.	-2.61 ± 0.77	-1.27 ± 1.05	0.3045	Placebo
Symbol Digit Modalities Test	Exp.	2.15 ± 0.76	3.02 ± 1.05	0.5087	Placebo
Stroop Color Naming	Exp.	-1.69 ± 1.22	1.25 ± 1.74	0.1767	Placebo
Stroop Word Reading	Exp.	-4.84 ± 1.53	1.80 ± 2.09	0.0123	Placebo
Stroop Interference Test	Exp.	-1.52 ± 0.90	1.47 ± 1.23	0.0532	Placebo
III. Behavioral Assessment (BA) (Part 3; items 25-35)	Exp.	-0.96 ± 0.81	-2.22 ± 1.09	0.3549	Placebo
IV. Functional Assessment Checklist (Part 4; items 43-67)	2°	-0.81 ± 0.29	0.37 ± 0.40	0.0183	Placebo
V. Independence Scale (IND) (Part 5; item 69)	Exp.	-1.98 ± 1.00	0.55 ± 1.35	0.1347	Placebo
VI. Total Functional Capacity (TFC) (Part 6; items 70-74)	Exp.	-0.43 ± 0.21	-0.06 ± 0.28	0.2906	Placebo
Functional Impact Scale (FIS)	Exp.	0.12 ± 0.17	0.13 ± 0.23	0.9712	TBZ
Clinical Global Impression – Part 1 (CGI-1)	Exp.	-0.06±0.48	-0.02±0.40	0.9186	TBZ
Clinical Global Impression – Part 2 (CGI-2)	2°	2.99+0.17	3.73+0.22	0.0074	TBZ
Clinical Global Impression – Part 3 (CGI-3)	Exp.	8.63±3.56	11.28±0.67	0.0010	TBZ

Source: CSR TBZ 103,004, Tables 14.2.1, 14.2.16,14.2.19, 14.2.21, 14.2.22, 14.3.5.2, and 14.3.5.5
Missing scores were replaced by last available assessment.
ANCOVA = analysis of covariance; TBZ = tetrabenazine; UHDRS = Unified Huntington's Disease Rating Scale; Exp.=exploratory endpoint
Note: Higher scores on Functional Assessment, TFC, IND, and lower scores on Chorea and Total Motor Score are associated with better function. Higher scores on cognitive tests and lower scores on BA are associated with improvement.

Table 1shows the results of the re-analysis of LOCF mean change from baseline to maintenance (average of Weeks 9 and 12) and the observed case mean change at Week 12 for many of the functional, cognitive and behavioral measures listed in Table 21. There were no meaningful differences in treatment effects between the LOCF re-analysis

compared to the original LOCF analysis presented in the NDA. Findings from observed case analyses are used for the CR re-analysis. It's not always appropriate to exclude a week 12 measurement as they did if the patient had stopped taking drug. It seems to violate the ITT principle, but it's adequate for a sensitivity analysis, and it doesn't show much of a statistical difference here. The change made no significant difference in the CR review, since in the review of the initial NDA submission, the Agency did an analysis of the Week 12 (rather than Week 9 and 12 scores averaged) observations assuming that AEs and dosage adjustment were most likely to have been resolved by the end-of-study, and the Week 12 measurements the mostly to be accurate for the treatment effect.

5. Utility of Reducing Chorea

There is some evidence in the literature that chorea is not perceived as problematic by the HD patients. There is also concern that patients would be started on a drug for the chorea, and be left on it, although chorea is characteristic of the middle course of Huntington's Disease and usually diminishes or disappears in the later stage. The Agency queried the usefulness of chorea management. Prestwick was asked to analyze the rationale for chorea management and address the benefit/risk ratio.

Supporting Analyses submitted by sponsor:

- Clinical Global Impression-Part 2 (CGI—2) at end of treatment
- Responder analysis (i.e., reduction of chorea $\geq$ 3 points)
- Patient rated measure of benefit
- Patients with substantial clinical benefit (narratives)

Evidence of efficacy was supported in only one of the four secondary objectives. Using the Clinical Global Impression Part 2 (CGI-2) endpoint, a significant number of the TBZ subjects were rated "much" or "very much" improved compared to the placebo group. The CGI-2 is a subjective assessment, by the physician/investigator of the subject's symptoms. There is no actual baseline assessment with which to compare it, so the number listed is an assigned score, not a difference in points that occurred. Sixty-nine percent (69%, 31/51) of the TBZ-treated patients compared to 24% (7/29) of the placebo patients were assessed as improved by the investigator at the end of treatment (p=0.0063). The score of 2.99 on the scale for the TBZ-treated group is closest to the score of 3 = "minimally improved". The placebo group had a mean score of 3.73 which is only slightly improved from 4 = "no change". At Week 12, the difference in scores between the groups was statistically significant, but not large (less than one point). There are several weaknesses in this measurement. Although the intent was an assessment of "overall status" the responses were nearly identical to the change in chorea score, so it is possible, given the focus of the study, only chorea change was assessed by the question. This possibility is suggested in the next analysis (Responder Analysis).

Responder Analysis was defined as the pre-specified reduction in the total maximal chorea score (UHDRS question 12,) by $\geq$ 3 points. The total score is 0 to 28; 0(absent) to 4 (marked/prolonged) for each extremity, face & bucco-oral. The reduction of chorea by $\geq$ 3 points was pre-determined by the Study 004 Steering Committee as the "clinically significant level of change. Analysis of this primary endpoint showed that 69% of the

TBZ-treated subjects compared to 23% of the placebo-treated subjects had reduction in chorea that was statistically significant ($p<0.0001$). Analysis of the subject data shows the same subjects rated "decreased chorea" and improved in CGI-2. Interpretation could be that they were improved on always improved on both measures, or that it was only one measure that was assessed (chorea change).

Patient-rated measure of benefit: Response to question 79 of the UHDRS at Week 13 (washout). "Since your last assessment, does the participant feel improved, worsened, or about the same?" A higher percentage of the tetrabenazine-treated subjects reported feeling worse at Week 13 (p-value = 0.005). (See Table 2). Meaningful responses are difficult to interpret since there is no possible comparison to baseline. As with many of the questions, it is not even clear, or consistent, whether the responses were provided by the subject or the caregiver. Unfortunately, this was the closest the study came to providing a subject-rated "benefit to the subject" assessment. The question was asked on Week 13, so on average, the subjects had discontinued the drug the previous week. Assumption is made that if subjects respond as "feeling worse" that it confirms the benefit of the drug treatment. However, possible rebound effect cannot be ruled out since the follow-up chorea scores were higher for TBZ-treated subjects than at baseline, although not reaching a statistically significant level.

Study 04: UH item 79 at Week 13

	Treatment Name											
	Placebo						**Tetrabenazine**					
	Since last assessment/participant feel						**Since last assessment/participant feel**					
	improved		**worsened**		**stayed about the same**		**improved**		**worsened**		**stayed about the same**	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**	**N**	**Percent**	**N**	**Percent**	**N**	**Percent**
Visit Number	1	3.4	9	31.0	19	65.5	2	4.1	34	69.4	13	26.5
7 (week 13)												

Patients with substantial clinical benefit: Investigators were asked to identify subjects with improvements in HD symptoms with clinical improvement unlikely to occur spontaneously. Narrative reports of improvement were obtained for 13 subjects (from

Study 004 and the follow-on open-label study). Two of the subjects that related improvement in functional levels while receiving tetrabenazine in the Study 004 were reported in the CR. No formal analysis of these reports was done by the sponsor. Again, the way the reports read, it is not clear if the subject, caregiver or investigator is supplying the information, so it does not provide the subject-rated assessments that the studies needed.

The sponsor feels that the analyses listed above, when taken together, confirm meaningful benefit associated with chorea reduction from TBZ. The review dilemma is that the "analyses" are based on a) subjective assessments of investigators that may have been rating the primary endpoint characteristic rather than a vague "overall" assessment, b) reference to the primary endpoint (chorea change) which in no way addresses the utility, c) a subjective patient assessment unlinked to a baseline, no reliability of whether the subject or caregiver was the responder, and with possible confounding effects such as drug withdrawal, or d) subjective narratives by a few subjects (or, probably their caregivers). None of these directly address the utility of chorea treatment or could be used for a benefit/risk analysis.

6. Functional changes associated with tetrabenazine vs placebo

Relationship between Chorea and Function

As previously noted, in the Study 004, nearly all the functional assessments favored the placebo-treated group. In the CR, the sponsor responds that since "HD is a multimodal disease, it is difficult to isolate the effect of reducing chorea on function using instruments that were not designed for this specific purpose". They feel that the functional scales employed in Study 004 lack specificity for assessing changes solely due to chorea reduction and do not ascertain whether impairment results from chorea or another deficit of HD which may not be affected by treatment with TBZ. Any changes in the chorea scale "may be confounded by impairments in other domains, which if unaddressed by treatment, may contribute to the lack of measurable functional improvement". Based on the Pearson correlation coefficients between baseline UHDRS measures, the sponsor feels that the correlation between Functional Assessment Checklist scores and the cognitive measures of the Stroop word Reading and Symbol /Digit is greater (r = 0.56 and 0.66 respectively) than the correlation between baseline Functional Assessment Checklist scores and chorea scores (r = -0.35) suggesting that the functional scores of the Functional Assessment Checklist are more closely associated with cognitive levels than with chorea.

Table 2. Pearson Correlation Coefficients (r) Between Baseline UHDRS Measures

	Functional Assessment Checklist	Independence Scale	Total Functional Capacity	Functional Impact Scale

CGI-1	-0.39‡	-0.43‡	-0.41‡	+0.47‡
Chorea	-0.35‡	-0.38‡	-0.19*	+0.21*
Behavioral Assessment	-0.02	-0.06	-0.18	+0.11
Stroop Word Reading	0.56‡	0.45‡	0.49‡	-0.43‡
Symbol Digit	0.66‡	0.57‡	0.56‡	-0.42‡

Source: CR Table 1.4 in Appendix 2

* $p < 0.10$ and > 0.05

‡ $p < 0.01$

The response doesn't adequately address why with the use of multiple functional scales, the secondary functional endpoints nearly all favored placebo. Four functional scales were used in Study 004 and re-analyses provided opportunities to delve into additional analyses of items or factors that the sponsor considered essential for extra scrutiny. However, not much emerged that was relevant for the efficacy review of the CR.

Agreeing with the sponsor's conclusions still does not resolve the question of whether a recommendation of approval should be made for a drug with known risk of adverse reactions since the scales in the clinical trials are considered lacking specificity, and the functional changes of the disease syndrome are more closely tied to factors other than chorea.

Effect of Baseline Differences

The sponsor posed the possibility that between-group differences in baseline demographics or disease severity that could explain the differential decline in functional measures between the tetrabenazine and placebo groups during the treatment period.

In the comparison of baseline demographics and disease characteristics between treatment groups, the sponsor notes that TBZ-treated subjects were more affected in functional, cognitive and behavioral domains at baseline than were placebo-treated subjects. These differences (see Table 3) were generally slight but consistent, and had statistical significance only for the FIS and the Symbol Digit Modalities test.

Table 3. Baseline Demographic and Clinical Characteristics of Patients in Study 004

Variable	Tetrabenazine (N=54)	Placebo (N=30)	p-value (t-test)
Disease duration, yr	8.68	7.47	0.25
CGI-1*	3.98	3.83	0.36 **
Total Maximal Chorea Score (TCS)	14.69	15.20	0.57
Total Functional Capacity (TC)	8.28	8.60	0.56
Functional Assessment Checklist	18.80	19.63	0.38
Independence Scale (IND)	76.94	80.17	0.20
Functional Impact Scale (FIS)*	1.28	0.40	< 0.01*
Stroop - Word Reading	53.83	56.27	0.61
Symbol Digit Modalities Test	18.07	24.37	0.02
Behavioral Assessment(BA)*	7.39	6.60	0.62 *

* Lower numbers indicate less severe disease or better function

** Favored placebo

The differences noted raise the question - Did the between-group differences in baseline demographics or disease severity account for the differential decline in FA between treatment groups?

The sponsor computed the mean and mean change in the Functional Assessment Checklist scores for the treatment groups by baseline severity (tertile) of the variable of interest (Functional Assessment Checklist, chorea, CGI-1, Stroop Word, Symbol Digit and Behavioral Assessment [BA] score). Similar analyses were also conducted for IND, TFC and FIS with baseline tertiles of the above variables of interest. The result was that re-analysis of these variables did not identify any clear confounding of the treatment effect by baseline levels. The between-group difference in the Functional Assessment Checklist was generally independent of the baseline severity of the Functional Assessment Checklist, chorea, CGI-1, Stroop Word, Symbol Digit and Behavioral Assessment scores. Likewise, no baseline measure was found to be associated with the results for IND, TFC and FIS (Table 4).

Sponsor Conclusions from the baseline data and analyses:

- Baseline data illustrate that HD is a multi-dimensional disease that affects numerous cognitive, behavioral and motor domains on the UHDRS.
- As HD is a multimodal disease, it is difficult to isolate the effect of reducing chorea on function using instruments that were not designed for this specific purpose. Indeed, all functional scales employed in Study 004 lack specificity for assessing changes solely due to chorea reduction.
- Any observed changes in the scales may be confounded by impairment in non-motor domains that, if unaddressed by treatment, may contribute to the lack of measurable functional improvement.

Table 4. Mean and Mean Change in Functional Assessment (FA)Checklist score by Baseline Functional Assessment Severity

Change in F at:	Mean (N) at Corresponding Week†		Mean Change from Baseline (N) at Corresponding Week†		Unadjusted Effect Size
	Tetrabenazine	Placebo	Tetrabenazine	Placebo	
Week 7					
Tertile 1 (≤ 17)	13.83 (18)	15.14 (7)	0.11 (18)	1.00 (7)	-0.89
Tertile 2 (18-21)	18.83 (18)	20.00 (11)	-1.06 (18)	0.27 (11)	-1.33
Tertile 3 (≥ 22)	23.33 (15)	23.18 (11)	-0.33 (15)	0.18 (11)	-0.51
Week 12					
Tertile 1 (≤ 17)	13.58 (19)	15.14 (7)	-0.26 (19)	1.00 (7)	-1.26
Tertile 2 (18-21)	19.40 (15)	20.00 (11)	-0.47 (15)	0.27 (11)	-0.74
Tertile 3 (≥ 22)	22.92 (13)	23.00 (11)	-0.54 (13)	0.00 (11)	-0.54

Source: CR Table 2.6 in Appendix 2

† At either Week 7 or Week 12 as labeled in the left-most column

Note: Higher scores on Functional Assessment Checklist are associated with better function.

It can be concluded that there was no clear evidence of confounding of the treatment effect by baseline levels. For example, for the Functional Assessment Checklist score, Table 4 shows that the mean change was better for placebo in each of the tertiles of the baseline score. So the baseline imbalance where it exists doesn't necessarily explain the unexpected observed differences in cognitive and functional endpoints.

Possibility of a Chance Finding

The sponsor analyzed the possibility that the differences in functional scores between groups resulted from a chance finding. Table 5 shows the change in scores by functional test.

Table 5. Mean Change in Functional Parameters from Baseline to Week 12 (Observed Cases)

Functional Scale (Range of Scores)	Δ Score with Improvement	Change (N)		p-value t-test	Unadjusted Effect Size	Difference Numerically Favors
		Tetrabenazine	Placebo			
Functional Assess -ment Checklist (FA) (0*-25)	↑	-0.40 (47)	0.34 (29)	0.0485†	-0.74	Placebo
Independence Scale (IND) (10*-100)	↑	-1.17 (47)	0.34 (29)	0.3976	-1.51	Placebo
Total Functional Capacity (TFC) (0*-13)	↑	-0.25 (48)	-0.03 (29)	0.5074	-0.22	Placebo
Functional Impact Scale (FIS) (0-15*)	↓	-0.21 (47)	0.14 (29)	0.1757	-0.35	TBZ

Source: CR Tables 2.3, 2.4, 3.3, 3.4, 4.3, 4.4, 5.3 and 5.4 in Appendix 2
* Score associated with maximal impairment or deterioration
† Unequal variance t-test

How strong is the evidence that the observed differential decline in FA in Study 004 is due to tetrabenazine rather than a chance finding in an otherwise small clinical trial? The sponsor's re-analysis states that "Although a nominally significant differential decline in Functional Assessment Checklist scores was noted in the tetrabenazine group in, the treatment effect was numerically quite small. The degree to which this effect may be explained by the observed improvement in the placebo group (a finding inconsistent with the natural history of HD) is not known. In contrast, ADLs, as assessed by the FIS and TFC, trended in favor of tetrabenazine suggesting that significant daily tasks may be improved with tetrabenazine use. Thus, the balance of evidence does not suggest that tetrabenazine has a clinically relevant or consistent adverse effect on function."

The sponsor feels that the individual items (FA, TFC, and FIS) that deal most directly with ADLs show an advantage favoring the tetrabenazine-treated group. They have submitted the following conclusions:

- The treatment-associated difference in Functional Assessment (FA) Checklist scores between tetrabenazine and placebo is small and unlikely to be clinically relevant.
- None of the changes observed on the individual items of the Functional Assessment Checklist are large enough to be clinically significant.
- On several scales, changes from baseline in the items evaluating daily functioning, typically referred as ADLs, favor tetrabenazine.

The statement about Activities of Daily Living (ADLs) as assessed by the TFC on page 87 of the clinical response seems a little misleading: TFC trended in favor of placebo overall, and only one of the five items trended in favor of tetrabenazine. This was the ADL item but the other four, as well as overall, trended in favor of placebo.

The individual items dealing most directly with ADLs were evaluated separately by the FDA (see Statistical Review and Evaluation by Tristan Massie, Ph.D.), part of the September 23, 2006 NDA review for tetrabenazine. In it, he states his conclusions of the analysis of individual ADL questions of the UHDRS (see Table 6):

> "Since there was a significant difference favoring placebo in the change from baseline to week 12 in the sum of the functional assessment checklist item responses (UHDRS items 43-67) this reviewer investigated the results on the individual items that comprise the functional checklist. Each item is answered either yes or no. The items are presented in the table sorted by the size of the group difference in percentages that answered yes at week 12. The p-values should be considered exploratory since the tests were not pre-planned or adjusted for other analyses. It is important to note that at week 12 there was a difference in Item 68 of the UHDRS which identifies whether the patient or the patient and caregiver filled out the functional assessment checklist. More placebo patients filled out the checklist by themselves (47% vs 26% p=0.04). This may raise the question of whether the group difference may be attributable to the differences in who was filling out the checklist rather than the treatment. This is not a randomized subgroup so we can't be sure but the difference on the change from baseline to week 12 in the sum of all items was still nominally significant in the larger subgroup of patients that filled out the checklist with their caregiver. The difference on item 68 was smaller and not significant at earlier weeks.
>
> Six of the items had group differences greater than 15% in the percentage of patients that were able to do the item. Note that there were group imbalances at baseline on some of these items although none were significant at the nominal level. Most of the differences on individual items at week 12 were less significant after adjusting for the baseline responses. Item 52, related to doing laundry, has a p value of 0.051 after adjusting for the baseline responses. This was the smallest baseline adjusted p-value among the individual functional checklist items."

Table 6. Week 12 (or LOCF) Responses on Individual Items of UHDRS Part IV Functional Assessment Checklist

		BASELINE	WEEK 12 OR LAST OBSERVATION

UHDRS FUNCTIONAL CHECKLIST ITEM	LEVELS	TBZ (N=54)	PLACEBO (N=30)	CHISQ P-VALUE	TBZ (N=54)	PLACEBO (N=30)	PERCENT DIFFERENCE	UNADJUSTED CHISQ P-VALUE	BASELINE ADJUSTED P-VALUE
68 Obtained from Participant Only	N(%) YES	18 (33.3)	10 (33.3)	1.000	14 (25.9)	14 (46.7)	-20.8 %	0.053	0.043
47 Shop for Groceries	N(%) YES	36 (66.7)	24 (80.0)	0.195	28 (51.9)	22 (73.3)	-21.4 %	0.055	0.159 *
49 Supervise children	N(%) YES	28 (51.9)	20 (66.7)	0.189	25 (46.3)	20 (66.7)	-20.4 %	0.073	0.227 *
52 Do Laundry	N(%) YES	44 (81.5)	26 (86.7)	0.541	38 (70.4)	27 (90.0)	-19.6 %	0.039	0.051 *
51 Do Housework	N(%) YES	35 (64.8)	22 (73.3)	0.423	31 (57.4)	23 (76.7)	-19.3 %	0.078	0.089 *
59 Public transport	N(%) YES	37 (68.5)	23 (76.7)	0.428	35 (64.8)	25 (83.3)	-18.5 %	0.072	0.096 *
55 Take meds w/o help	N(%) YES	44 (81.5)	28 (93.3)	0.137	42 (77.8)	28 (93.3)	-15.5 %	0.067	0.265 *
46 Manage Finances	N(%) YES	16 (29.6)	11 (36.7)	0.508	12 (22.2)	11 (36.7)	-14.5 %	0.155	0.170 *
50 Operate Auto	N(%) YES	20 (37.0)	14 (46.7)	0.389	19 (35.2)	14 (46.7)	-11.5 %	0.302	0.570 *
60 Walk in neighborhood	N(%) YES	48 (88.9)	27 (90.0)	0.875	43 (79.6)	27 (90.0)	-10.4 %	0.222	0.205 *
58 Bathe self	N(%) YES	49 (90.7)	29 (96.7)	0.312	49 (90.7)	30 (100.0)	-9.3 %	0.086	0.941 *
44 Engage in any gainful employment	N(%) YES	11 (20.4)	7 (23.3)	0.751	10 (18.5)	8 (26.7)	-8.2 %	0.383	0.326 *
57 Dress self	N(%) YES	46 (85.2)	29 (96.7)	0.103	48 (88.9)	29 (96.7)	-7.8 %	0.217	0.935
45 Engage in volunteer or non gainful work	N(%) YES	30 (55.6)	17 (56.7)	0.922	31 (57.4)	19 (63.3)	-5.9 %	0.596	0.502 *
48 Handle purchase	N(%) YES	49 (90.7)	26 (86.7)	0.563	46 (85.2)	27 (90.0)	-4.8 %	0.531	0.273 *
54 Use telephone	N(%) YES	52 (96.3)	28 (93.3)	0.541	48 (88.9)	28 (93.3)	-4.4 %	0.506	0.380 *
56 Feed self	N(%) YES	51 (94.4)	30 (100.0)	0.189	50 (92.6)	29 (96.7)	-4.1 %	0.450	0.892
63 Comb hair w/o help	N(%) YES	54 (100.0)	30 (100.0)	.	52 (96.3)	30 (100.0)	-3.7 %	0.286	0.953 *
53 Prepare meals	N(%) YES	39 (72.2)	20 (66.7)	0.594	38 (70.4)	22 (73.3)	-2.9 %	0.773	0.378 *
43 Engage in accustomed gainful employment	N(%) YES	6 (11.1)	4 (13.3)	0.763	4 (7.4)	3 (10.0)	-2.6 %	0.680	0.782 *
61 Walk w/o falling	N(%) YES	51 (94.4)	27 (90.0)	0.449	49 (90.7)	28 (93.3)	-2.6 %	0.680	0.433 *
67 Care provided at home	N(%) YES	54 (100.0)	30 (100.0)	.	53 (98.1)	30 (100.0)	-1.9 %	0.453	0.950 *
64 Transfer between chairs	N(%) YES	54 (100.0)	30 (100.0)	.	54 (100.0)	30 (100.0)	0 %	1.000	0.953
65 Get in/out of bed	N(%) YES	54 (100.0)	29 (96.7)	0.177	54 (100.0)	30 (100.0)	0 %	1.000	0.953 *
66 Use toilet	N(%) YES	54 (100.0)	29 (96.7)	0.177	54 (100.0)	30 (100.0)	0 %	1.000	0.953 *
62 Walk w/o help	N(%) YES	53 (98.1)	29 (96.7)	0.670	54 (100.0)	29 (96.7)	3.3 %	0.177	0.809

* = favored placebo

The following items most directly deal with the ADLs (on the UHDRS Part IV FA Checklist) that determine whether a patient could remain unsupervised in the home for periods of the day (i.e., prevent or postpone nursing home placement). These are listed

along with the number of subjects improved (+), declined (-) or no change (0) between baseline and Week 12 (see also Tables 7 and Table 8):

	ADL	TBZ	placebo
#53	Prepare meals	-1	+2
#54	Use telephone	-4	0
#55	Take meds without help	-2	0
#56	Feed self	-1	-1
#57	Dress self	+2	0
#61	Walk without falling	-2	+1
#62	Walk without help	+1	0
#64	Transfer between chairs	0	0
#65	Get in/out of bed	0	+1
#66	Use toilet	0	+1

Immediately evident is that the actual number of subjects reporting change in each of these categories is very small (Table 8 provides the percentages these represent in each group). The placebo group did not show a robust improvement that would have significantly skewed the analysis of the treatment group. Again, it is difficult to account for the gains in the placebo group in view of the progressive nature of the illness. However, this group of essential ADLs does show that although changes were slight, they did not favor the tetrabenazine-treated group. The selection of these ADLs also addresses the concerns of the sponsor that too many of the functional tests were evaluating the more complex issues such as employment, driving, managing finances, etc... that would be unlikely to change during the duration of a 12-week study.

Table 7. Change from Baseline to Week 12 (or LOCF) in Functional Assessment Checklist ADL and Non ADL Items

	TETRABENAZINE		PLACEBO		DIFFERENCE LSMEAN (S.E.)	PVALUE
Functional Assessment Checklist	Baseline Mean (S.D.)	Change LSMEAN (S.E.)	Baseline Mean (S.D.)	Change LSMEAN (S.E.)		
ADL items*	9.22 (1.13)	-0.10 (0.12)	9.30 (1.09)	0.13 (0.17)	0.23 (0.21)	0.278
Non ADL items	9.57 (3.46)	-0.81 (0.25)	10.33 (2.90)	0.17 (0.34)	0.99 (0.42)	0.022

Items 53,54,55,56,57,61,62,64,65,66

Table 8. Change from Baseline to Week 12 (or LOCF) in Functional Assessment Checklist ADL Items

		TETRABENAZINE			**PLACEBO**	
#	DECLINED N (%)	UNCHANGED N (%)	IMPROVED N (%)	DECLINED N (%)	UNCHANGED N (%)	IMPROVED N (%)
53	4.0	47.0	3.0	1.0	26.0	3.0

	(7.4)	(87)	(5.6)	(3.3)	(86.7)	(10)
54	6.0 (11.1)	46.0 (85.2)	2.0 (3.7)	. (0.0)	30.0 (100)	. (0.0)
55	4.0 (7.4)	48.0 (88.9)	2.0 (3.7)	. (0.0)	30.0 (100)	. (0.0)
56	2.0 (3.7)	51.0 (94.4)	1.0 (1.9)	1.0 (3.3)	29.0 (96.7)	. (0.0)
57	2.0 (3.7)	48.0 (88.9)	4.0 (7.4)	. (0.0)	30.0 (100)	. (0.0)
61	3.0 (5.6)	48.0 (88.9)	3.0 (5.6)	. (0.0)	29.0 (96.7)	1.0 (3.3)
62	. (0.0)	53.0 (98.1)	1.0 (1.9)	. (0.0)	30.0 (100)	. (0.0)
64	. (0.0)	54.0 (100)	. (0.0)	. (0.0)	30.0 (100)	. (0.0)
65	. (0.0)	54.0 (100)	. (0.0)	. (0.0)	29.0 (96.7)	1.0 (3.3)
66	. (0.0)	54.0 (100)	. (0.0)	. (0.0)	29.0 (96.7)	1.0 (3.3)

The fact that tetrabenazine looked better on the FIS could be due to a floor effect. tetrabenazine was worse at baseline (significant) and placebo was close to the lower limit (better function) and had less room for improvement. Tetrabenazine had a very small improvement. In fact, the average week 12 score for placebo was still less than tetrabenazine (placebo: 0.55 vs TBZ: 1.15) even though the average changes from baseline numerically favored tetrabenazine (placebo +0.14 vs TBA -0.21). At baseline 58% of patients had the best possible score (=0) on the FIS. This would suggest that either the FIS is not capturing the functional impairment of these patients or they are not functionally impaired, which is unlikely. In addition, if the treatment effect varies with the baseline score in reality then comparison of the two groups that were different at baseline would not be fair. Also, the validity of the statistical tests based on ANCOVA that the sponsor presented for the FIS are questionable because the change in FIS fails a test for normality which is an underlying assumption. Therefore, the usefulness of the FIS seems questionable in this study. The FIS was one of the exploratory endpoints in the NDA submission since it had not been previously used. By contrast there is a long history of the use of the UHDRS, so the items regarding ADLs were singled out and analyzed separately on out initial review.

Known Adverse Events Attributable to Tetrabenazine as a Possible Explanation of Between-Group Differences in Endpoints

(see Safety Review by Dr. Lourdes Villalba)

The sponsor addressed the question "Are there alternative explanations for the differential decline in FA in Study 004, such as adverse effects from tetrabenazine?"
Sponsor's Supporting Analysis:

- Correlation between changes in functional parameters with changes in the scales used to assess safety in the trial: HAM-D, Barnes Akathisia Rating Scale (BARNES), BA and the Epworth Sleepiness Scale (ESS)
- Any correlations found were further evaluated by examining the change in function by the degree of change (i.e., tertile) in the safety scale.

The sponsor states that with increasing impairment on Behavioral Assessment (BA) there is greater decline in the Functional Assessment Checklist.

Complementary analyses of the change in the IND, TFC and FIS by change in BA, HAM-D and ESS were conducted but were unrevealing. In the analyses, only the Functional Assessment (FA) Checklist appeared to be associated with changes in BA, HAM-D and ESS; the reason that an association is found only with the FA scale is unknown but one possible explanation is that FA is more sensitive in detecting subtle functional changes due to changes in cognitive and behavioral domains.

Sponsor's Interpretation:

> "The association between the magnitude of FA decline in tetrabenazine-treated patients and the degree of change in BA, HAM-D and ESS raises the possibility of an association between the observed decline in FA and adverse effects of tetrabenazine. These observations are consistent with the side effect profile of tetrabenazine, which includes insomnia, sedation, fatigue and anxiety. However, while these analyses raise an alternative explanation for the small differential decline in FA between tetrabenazine and placebo in Study 004, they do not establish a cause and effect relationship."

The sponsor feels that the association between the magnitude of FA decline in tetrabenazine-treated patients and the degree of change in BA, HAM-D and ESS raises the possibility of an association between the observed decline in FA and adverse effects of tetrabenazine, does not establish a cause and effect relationship.

This section is reviewed in the Safety Review, by Dr. Lourdes Villalba. The possibility of a cause and effect relationship is evaluated with a re-review of all reported AEs. The Safety Review will be submitted separately.

The sponsor feels that if the acute effects of tetrabenazine are causing small declines on the FA scale, the adverse effects can be described in product labeling, appropriately monitored and detected by physicians, and show reversibility upon dose reduction or discontinuation from therapy.

The effect of this argument must be addressed in the efficacy review. It is evident from the safety review that the AEs of tetrabenazine can adversely affect functional, cognitive

and behavioral measurements. The sponsor's argument that these are known AEs and can be monitored poses a unique set of challenges with HD. One of the problems with that approach is the difficulty for the physician, or the caregiver, picking up on cognitive or behavioral changes that might be due to the drug treatment rather than to the progression of the disease. No new information has been presented in the CR that would make these changes easier to recognize or modify. Particularly problematic in the review is the inconsistency who was the responder on questions. For example, if a subject became more sedated, they might be easier for a caregiver to manage, thus rated improved rather than experiencing AEs.

7. Cognition changes associated with tetrabenazine vs placebo

Part II of the UHDRS contains five items which measure cognitive abilities (specifically evaluating attention and concentration). Each part of the Cognitive Assessment (UHDRS Part II) was analyzed individually by the sponsor as an exploratory endpoint assessing change from baseline to Week 12. These included Verbal Fluency, Symbol Digit Modalities, and the 3 Stroop Interference Tests (Color Naming, Word Reading, and Interference). The total score of the Cognitive Assessment showed the placebo group improved by 5.1 ($\pm$4.5) points from an average baseline score of 172 ($\pm$55), whereas the TBZ-treated group worsened by 7.7 ($\pm$3.3) points from its mean baseline of 156 ($\pm$56) points. The estimated difference of 12.8 ($\pm$5.6) points was statistically significant (at ANCOVA p-value = 0.025) favoring the placebo group. All of the items at least nominally favored placebo. The Stroop Interference – Word Reading reached statistical significance (p-value = 0.0123).

In the CR, Prestwick addressed the FDA's concern that treatment with tetrabenazine may be associated with a decline in cognitive measures. Specifically, they looked at the observed difference in Stroop Word Reading between the tetrabenazine and placebo groups in Study 004.

Sponsor's Supporting Analysis:

- Mean and mean change in cognitive parameters at Week 12
- Correlation between change in cognitive parameters and changes in BA, HAM-D, ESS and BARNES at Week 12
- Analysis of change in cognitive parameters by:
    - o Degree of change in BA, HAM-D, ESS
    - o Presence or absence of anxiety and depression
- Comparison of the change in cognitive parameters (vs. Stroop Word/Symbol Digit) between Study 004 and CARE-HD

Possible alternative explanations include:

- baseline imbalances in cognitive impairment within the tetrabenazine group;
- a degree of decline in the tetrabenazine group, but not the placebo group, that is consistent with the natural history of cognitive decline in HD over 12 weeks;
- the acute and predictable pharmacologic effects of tetrabenazine.

Effect of Baseline Differences
At baseline, the tetrabenazine group was measured as slightly more cognitively impaired on four of the five cognitive tests. However, there is no significant difference in the sum of all the Stroop item's scores at baseline. The between-group difference on individual items eached statistical significance only for the Symbol Digit test (p=0.0176). At Week 12, tetrabenazine-treated patients had small declines in all three components of the Stroop test while the placebo-treated group showed small increases. The between-group difference achieved statistical significance for the total Cognitive Assessment score (total of the five cognitive tests) and on one of the individual components, the Stroop Word Reading test. Analyses of the Symbol Digit showed small numerical improvements in the tetrabenazine group over the placebo group at Week 12. The Symbol Digit test was the only cognitive component which had been measured as statistically significant in the evaluation of baseline differences between the treatment and placebo groups. Again, as in the functional FIS analysis, the fact that the tetrabenazine-treated group looked better on the Symbol Digit test endpoint could be due to a floor effect, especially since this is an item for which there is no post-treatment difference.

The CR re-analysis showed that there was no clear evidence of confounding of the treatment effect by baseline levels on the cognitive scores. The baseline imbalance where it exists doesn't necessarily explain the unexpected observed differences in cognitive and functional endpoints

Possibility of a Chance Finding
The sponsor states that the lack of decline in the cognitive measures in the small placebo group in Study 004 was atypical for HD, and may have contributed to the observed differential decline in Stroop Word Reading between the tetrabenazine and placebo groups of Study 004. The comparison of the Study 004 endpoints to the CARE-HD Study is provided in the CR, and is contained in the following section (Section 8).

Known Adverse Events Attributable to Tetrabenazine
The sponsor's re-analysis deals primarily with the possibility that the known side-effects of tetrazenazine are responsible for the endpoint changes observed between groups in Study 004. The review of the possibility is addressed in the Safety Review by Dr. Lourdes Villalba.

The tetrabenazine treatment group was re-analyzed by the sponsor looking specifically at the subjects with reported AEs such as anxiety or depression at any time during the trial, or that required adjustment in medication dosage due to AEs. Patients who experienced an AE of depression during the trial, and to a lesser extent anxiety, had greater declines in Stroop Word Reading, and experienced a decline in Stroop test parameters that is consistent with the natural history of HD. Several of the subjects with the largest declines in Stroop Word Reading scores also had evidence of sleepiness or drowsiness. Among the tetrabenazine-treated subjects greater impairment on the BA, HAM-D and ESS was associated with greater decline in Stroop Word Reading.

During the study, 12 tetrabenazine-treated subjects and one placebo-treated subject had a decline in Stroop Word Reading scores of $\geq$ 14 words (range: -35 to -14 words). Of the

12 tetrabenazine-treated subjects 4 had increased ESS scores, 3 had reports of drowsiness or fatigue, 3 had changes in depression or anxiety at Week 12. The placebo-treated subject with a large decline on the Stroop Word Reading (-29 words) did not have a reported CNS-related AE.

The sponsor's conclusion of the cognitive endpoint differences is:

> "Taken together, these data raise the question of a possible association between the observed decline in Stroop Word Reading and acute pharmacologic effects of tetrabenazine, such as anxiety and depression. However, these analyses do not establish a cause and effect relationship but suggest an alternative possible explanation for the differential decline in Stroop Word Reading between treatment groups. Importantly, if acute AEs are causing small declines on Stroop Word Reading, it should be remembered that that these AEs can be described in product labeling, recognized and properly managed by treating physicians, and show reversibility with dose reduction or discontinuation of therapy."

The conclusions continue to pose the same dilemma for the efficacy review that was addressed in the initial NDA review. There were slight differences in cognitive measurements at baseline between the two groups and it is not possible to determine the exact significance of the role these might have had in the study outcome. There was statistical significant difference only for one of the five cognitive tests. The total cognitive score (the five assessments combined) showed a statistically significant difference between the tetrabenazine-treated and the placebo-treated groups and re-evaluation in the CR has not changed the finding. The relationship of changes in cognitive assessments and AEs of tetrabenazine (see Safety Review) provides some input on the causal effect of the AEs on the drug efficacy, and in subjects not experiencing AEs, the differences are minimized. However, without effective monitoring and dosage adjustments, efficacy is affected.

8. Comparison of the databases of the Study 004 to the CARE-HD Study

Natural History of Functional and Cognitive Decline in HD

The HSG clinical study, the CARE-HD Study (HSG, 2001) was analyzed as a "pseudo-cohort" to provide comparative information on the natural history and progression of HD. The CARE-HD Study was a 30-month trial of coenzyme Q10 (600 mg/d), remacemide (600 mg/d) and placebo in HD subjects. Although treatment interventions were used in the trial, the sponsor considers the trial population to be similar to a placebo comparison cohort since no short-term treatment effects on function or cognition were shown with any intervention. Three comparison populations were selected from the study:

- All patients regardless of treatment assignment (N=3447)
- Placebo-treated patients only (N=87)

- A sub-group of all patients similar to the "Tetra-HD" Study 004 patients with respect to chorea severity and Total Functional Capacity (TFC) at baseline. The group is termed the "THD" population (N=102). The THD population scored below the median CARE-HD TFC score (<10) and above the median chorea score (>9).

In Table 9, the data from the THD patients in the CARE-HD Study at Week 16 is compared to the Study 004 TBZ-treated subjects and placebo subjects at Week 12. The CR analyses were focused on comparison of the Study 004 subjects to the THD subgroup of subjects from the CARE-HD Study.

Table 9. Comparison of Functional and Cognitive Assessment in Study 004 and CARE-HD: Mean Change from Baseline in Observed Cases

	CARE-HD (at Week 16)	**Study 004 (at Week 12)**	
Scale	**THD Patients (N=99*)**	**Tetrabenazine (N=48†)**	**Placebo (N=29)**
Functional Assessment test	-0.82 ± 1.72	-0.40 ± 2.13	0.34 ± 1.11
Independence Scale Score	-2.47 ± 6.68	-1.17 ± 7.16	0.34 ± 8.12
Total Functional Capacity	-0.25 ± 1.10	-0.25 ± 1.44	-0.03 ± 1.27
Cognitive Assessment:			
Verbal Fluency	-4.59 ± 5.76	-2.69 ± 6.91	-1.07 ± 6.06
Symbol Digit	-0.57 ± 7.08	2.88 ± 6.27	2.52 ± 4.73
Stroop Interference Test:			
Color Naming	-1.88 ± 6.87	-1.17 ± 8.31	0.79 ± 12.46
Word Reading	-3.69 ± 9.57	-5.17 ± 12.81	0.97 ± 10.55
Interference	-0.62 ± 5.34	-1.92 ± 6.87	1.10 ± 6.04

Source: CR Tables 1.3.3, 1.3.4, 2.4, 3.4, 4.4, 6.1.4, 6.2.4 and 6.3 in Appendix 2
* N = 98 for Verbal Fluency and Color Naming and 97 for Word Reading and Symbol Digit
† N = 47 for FA and IND
Note: Higher scores on FA, TFC and IND are associated with better function. Higher scores on cognitive tests are associated with improvement.

The decline in the functional scales show somewhat similar changes when the Study 004 subjects are compared to the THD subjects (the sub-group of patients considered most similar at baseline to the Study 004 subjects) of the CARE-HD Study. The placebo-treated subjects of Study 004 showed an increase in FA (+0.34) and IND (+0.34), and a slight decrease in TFC (0.03) which was not consistent with the decline on functional measures in the CARE-HD Study THD subjects.

On two of the individual test of the cognitive assessment, the Study 004 subjects showed a greater decline than the CARE-HD THD patients, but in the other three tests, the Study 004 TBZ-treated subjects showed less cognitive decline.
Sponsor's Interpretation:

> "The tetrabenazine treatment group in Study 004 experienced a decline in functional parameters that is consistent with the natural history of HD. The lack of decline in these measures in the small placebo group in Study 004 was atypical for HD and may have contributed to the observed differential

decline in functional parameters between the tetrabenazine and placebo groups of Study 004"

Long-term Treatment with Tetrabenazine

The changes in functional and cognitive parameters over the course of Study 007 (the open-label follow-on of Study 004) are summarized in Table 10. These provide some information on the longer-term use of tetrabenazine for HD. Comparison data from the CARE-HD Study (the THD subgroup) are included in the table to offer a larger historical database,.

Table 10. Mean Baseline and Mean Change from Baseline in Functional and Cognitive Measures: Study 007 vs. THD Subset of CARE-HD

	Study 007		CARE-HD (THD Group)	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Functional Assessment				
Baseline	47†	17.79 (4.62)	102	20.46 (2.43)
Change From Baseline				
4-6 Months*	45	-0.47 (2.81)	99	-0.82 (1.72)
12 Months	38	-1.39 (2.25)	97	-2.67 (2.70)
20 Months	30	-3.40 (3.33)	90	-4.04 (3.31)
Total Functional Capacity				
Baseline	47†	7.62 (2.39)	102	8.73 (1.05)
Change From Baseline				
4-6 Months*	45	-0.49 (1.52)	99	-0.25 (1.10)
12 Months	38	-1.05 (1.39)	97	-1.30 (1.54)
20 Months	30	-2.03 (2.27)	90	-2.13 (1.70)
Independence Scale				
Baseline	47†	74.15 (12.26)	102	81.27 (8.43)
Change From Baseline				
4-6 Months*	45	-1.44 (6.54)	99	-2.47 (6.68)
12 Months	38	-3.55 (6.36)	97	-5.57 (7.21)
20 Months	30	-7.00 (9.15)	90	-10.50 (8.25)
Word Reading				
Baseline	47†	49.83 (20.57)	101	57.46 (17.88)
Change From Baseline				
4-6 Months*	44	-1.16 (9.35)	97	-3.69 (9.57)
12 Months	33	-5.58 (12.49)	95	-5.23 (10.00)
20 Months	28	-8.61 (17.62)	89	-10.44 (10.25)
Symbol Digit				
Baseline	44†	20.57 (10.29)	101	22.26 (8.53)
Change From Baseline				
4-6 Months*	41	-0.63 (5.30)	97	-0.57 (7.08)
12 Months	30	-1.47 (4.48)	93	-3.05 (4.42)
20 Months	21	-4.24 (10.98)	85	-3.34 (5.32)

Source: CR Tables 1.3.3, 1.3.4 and 9.1 in Appendix 2

* 4 months in CARE-HD and 6 months in Study 007

† Data provided for 47 (44 for Symbol Digit) of the 75 patients who had a delayed rollover from Study

004 into Study 007 and full UHDRS at baseline. Baseline for the 28 patients who rolled over directly from Study 004 into Study 007 came from the Week 13 UHDRS assessment, which was conducted after a one- week washout of tetrabenazine.

The CARE-HD TDR scores on the functional scales FA, TFC and IND and the cognitive scales are compared at 6, 12, and 20 months of therapy to the scores of the tetrabenazine-treated subjects on the extension Study 007 that followed-on from the Study 004. The sponsor presented the data for Stroop Word Reading and Symbol Digit. Their rationale is that these tests are deemed to be most sensitive to change among HD cognition experts.

Among tetrabenazine-treated patients, the decrease in FA at 12 and 20 months was -1.39 and -3.40, respectively, which is similar in magnitude to the decline observed in CARE-HD THD group. Mean decline in TFC at 12 and 20 months among tetrabenazine patients (-1.05 and -2.03, respectively) is similar to that observed in the CARE-HD THD population.

Decline on the two cognitive scores showed a similar trend for the Study 007 and the CARE-HD THD group. It should be noted, however, that the significantly higher score of the tetrabenazine-treated subjects in the Symbol Digit test has been discussed earlier in this review as possibly due to an outlier effect at the baseline scores and subject to a floor effect. By the 20-month comparison, the score on the test had significantly decreased (-4.24, compared to -3.34 for the CARE-HD THD group).

The comparison of either Study 004 or Study 007 subjects to the CARE-HD THD sub-group is difficult to assess. It can only be suggestive, but it is a reminder of why placebo groups are important to clinical trials since the stimulation of study inclusion cannot otherwise be assessed. Similarly, the measurements of long-term trials for efficacy and safety are difficult to adequately interpret without the inclusion of placebo groups within the clinical trials.

Prestwick's CR Conclusions from Additional Analysis of Function and Tetrabenazine

Prestwick conducted extensive descriptive analyses to investigate the difference in FA that emerged in Study 004. These analyses support the following conclusions.

- There was a small decline in the FA part of the UHDRS in patients assigned to tetrabenazine in Study 004 that achieved modest statistical significance.
- The overall FA effect size (change with tetrabenazine minus change with placebo) was small, measuring less than 1 unit on a 25-point scale. On analysis of individual items of the FA and TFC, those that assess complex tasks and, therefore, are susceptible to decreased attention, appear to decline more than ADLs. The FIS, which is a measure of ADLs, trended in favor of tetrabenazine.
- Baseline imbalances in disease severity were found between treatment

groups, however a clear relationship between these baseline differences and on-treatment differences in secondary endpoints could not be established.

- The between-group difference in the FA was larger in patients having larger increases in BA, HAM-D, and ESS. Subsequent review of the individual items of the BA and HAM-D revealed that these changes were related primarily to increased anxiety and anxiety-related effects.
- Individual review of patients with declines in FA in Study 004 further supports the link between FA decline and acute changes due to tetrabenazine.
- Prestwick cannot exclude the possibility that the observed differential decline in FA is associated with the established side effect profile of tetrabenazine, e.g., anxiety, sedation, and depressive symptoms.
- Many of these patients with FA decline in Study 004 were also treated with tetrabenazine in Study 007. In many cases, the FA returned toward the patient's baseline level or maintained the gradual decline expected in HD. These findings indicate that the small decline from baseline in FA after 12 weeks of tetrabenazine are acute, not chronic, effects.
- Individual review of patients in Study 004 who also were treated in the long-term Study 007 also confirmed the correlation between changes in FA and changes in BA, HAM-D and ESS. In many cases, the change in FA occurred without any change in TFC or FIS.
- The gradual decline in FA, IND and TFC observed among the tetrabenazine patients in Study 004 is consistent with the natural history of HD progression observed in CARE-HD. The lack of decline in these measures in the small placebo group was atypical for HD and may have contributed to the observed differential decline in functional parameters between the tetrabenazine and placebo groups in Study 004.

The review responses to the issues raised with Prestwick's conclusions have been included in the relevant sections. Prestwick undertook the re-analyses of the Agency's areas of concern and presented these in the CR. The material does not provide new insights. The arguments presented by the company are plausible as explanations of why the secondary and exploratory endpoints trended toward the placebo group. However, they still fail to provide reliable internal verification for the studies on which the NDA application depends. Particularly problematic is the lack of measures that could be used for looking at benefit, which makes any benefit:risk assessment purely speculative. These all provide interesting issues for the Advisory Committee to consider.

Office of Clinical Pharmacology

NDA	21894
Drug	Tetrabenazine
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D
Pharmacometrics Team Leader	Joga Gobburu, Ph.D
Clinical Pharmacology Reviewer	Sally Yasuda, PharmD
Clinical Pharmacology Team Leader	Ramana S Uppoor, Ph.D

Table of Contents

List of Figures

List of Tables

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, un-controlled 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.

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?

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:

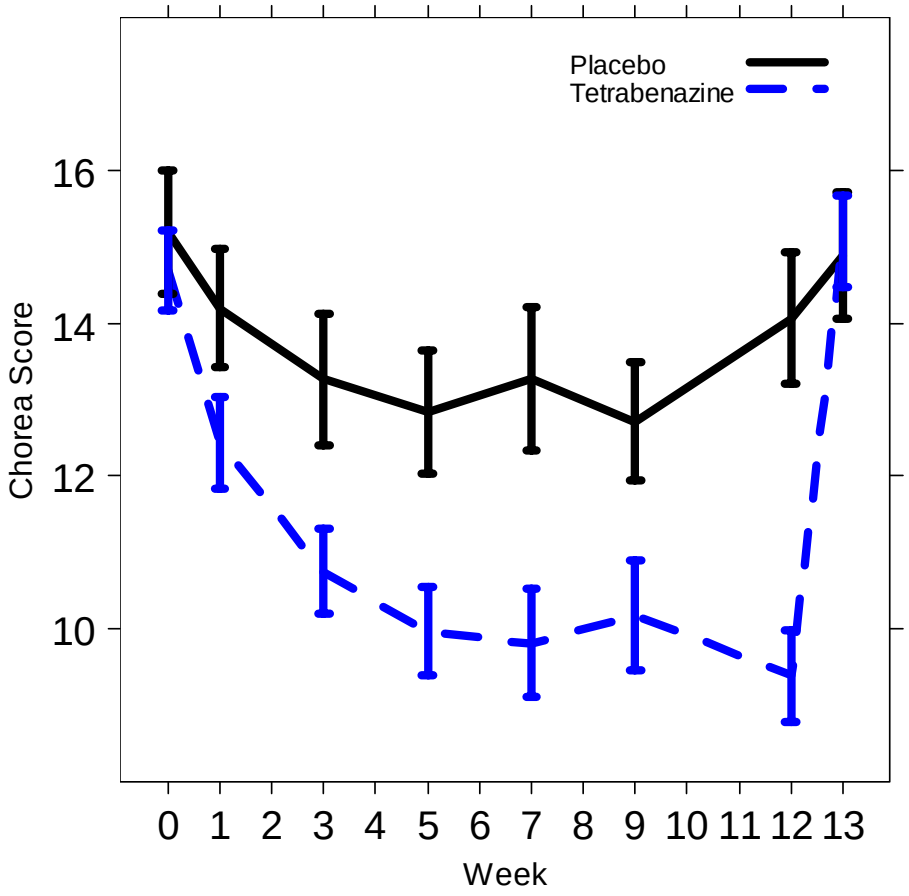
1. TBZ 103,004 demonstrates that Tetrabenazine treatment over 5 weeks of maintenance offers superior lowering of chorea scores, relative to placebo.
2. TBZ, 103, 004 also clearly shows a dose-response. Further, the drug effect at week 12 is completely washed-out by week 13 upon withdrawal.
3. TBZ 103,007 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 primarily 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 1, 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 1. 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 2,

Figure 3, Figure 4, Figure 5 and Figure 6 suggests that chorea scores remain reasonably unchanged over time in most patients.

Figure 2. 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.

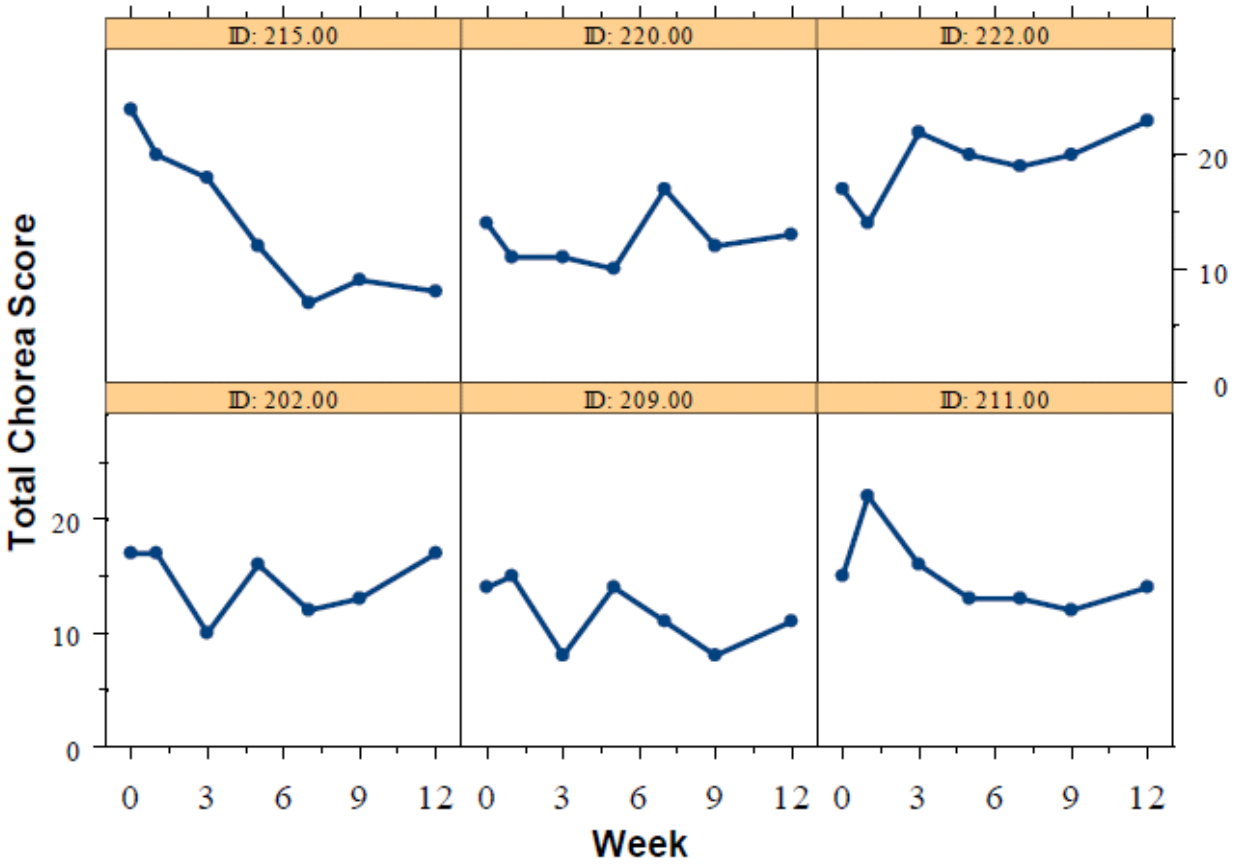


Figure 3. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by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

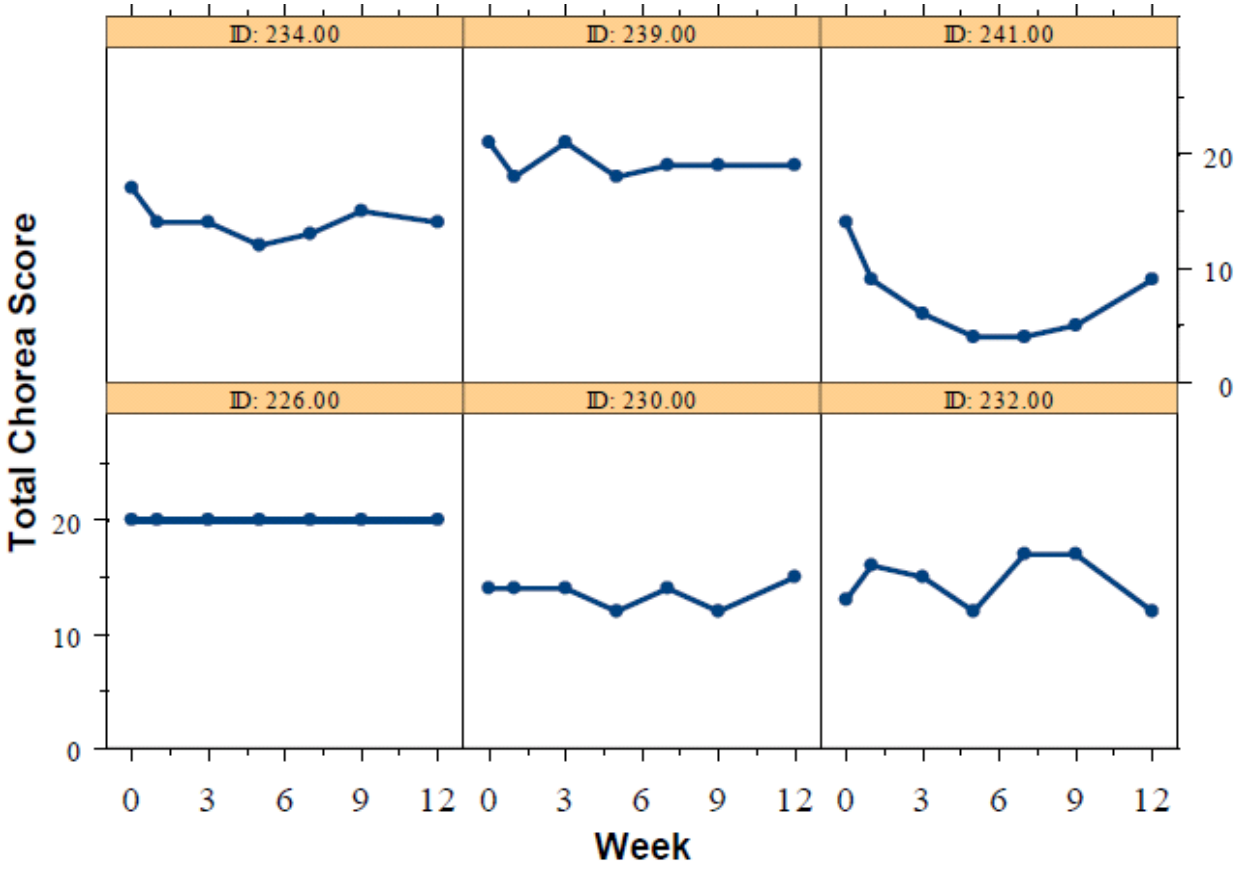


Figure 4. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by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

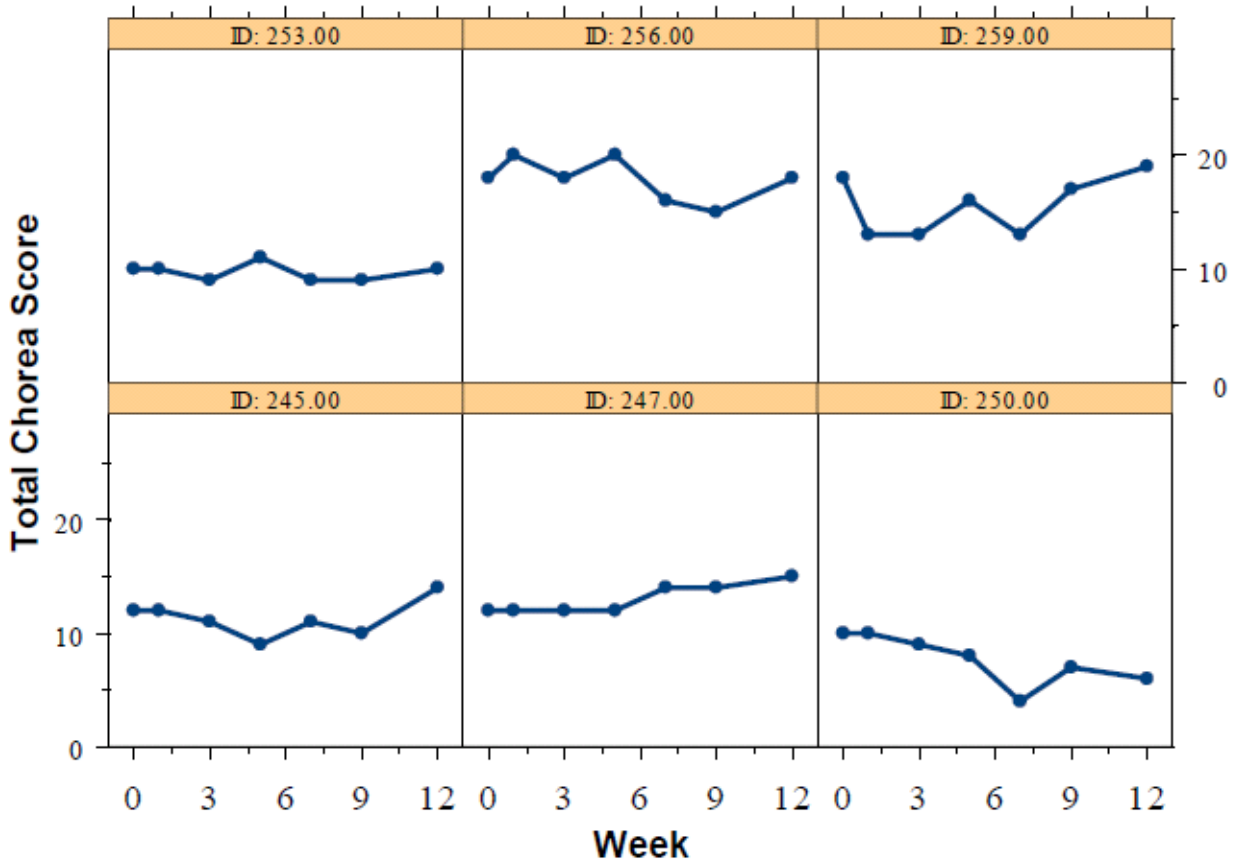


Figure 5. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by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

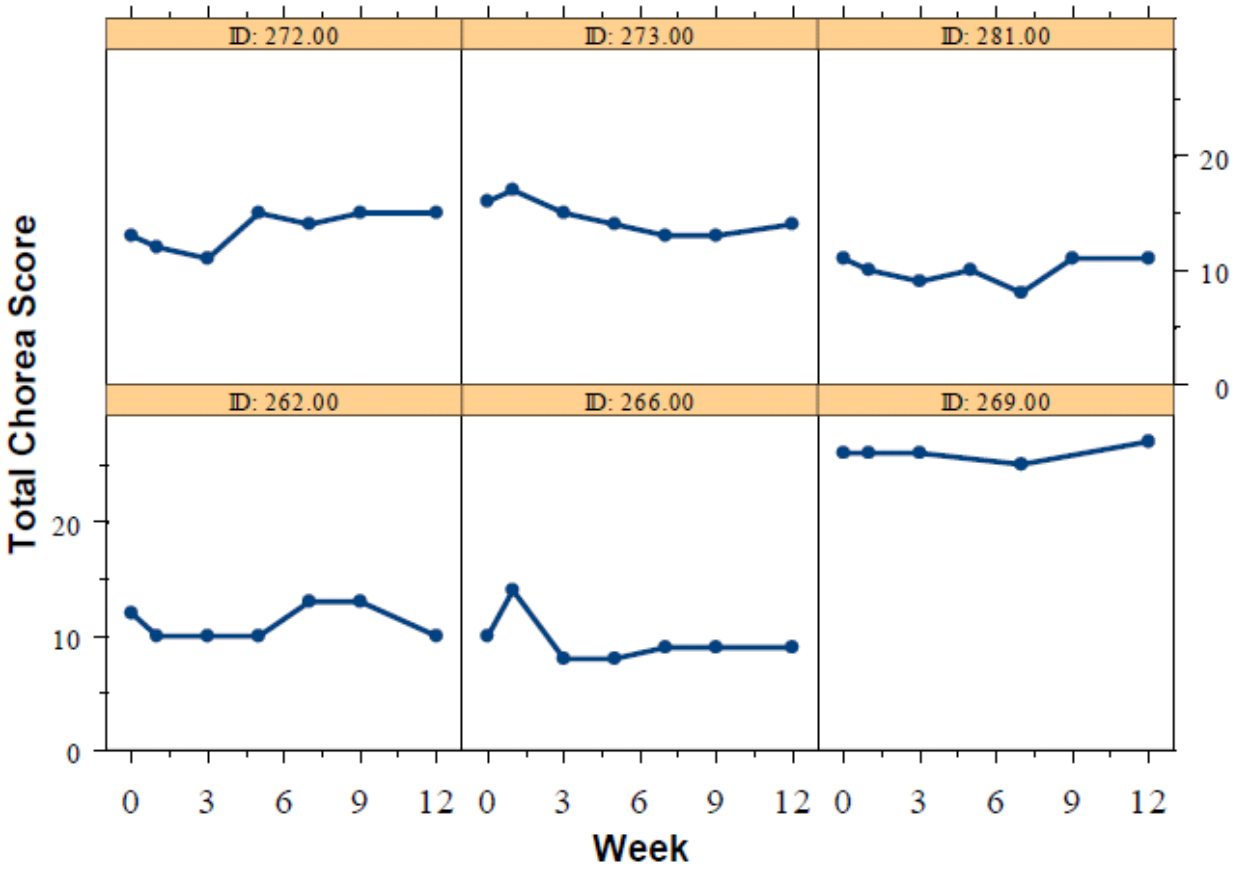
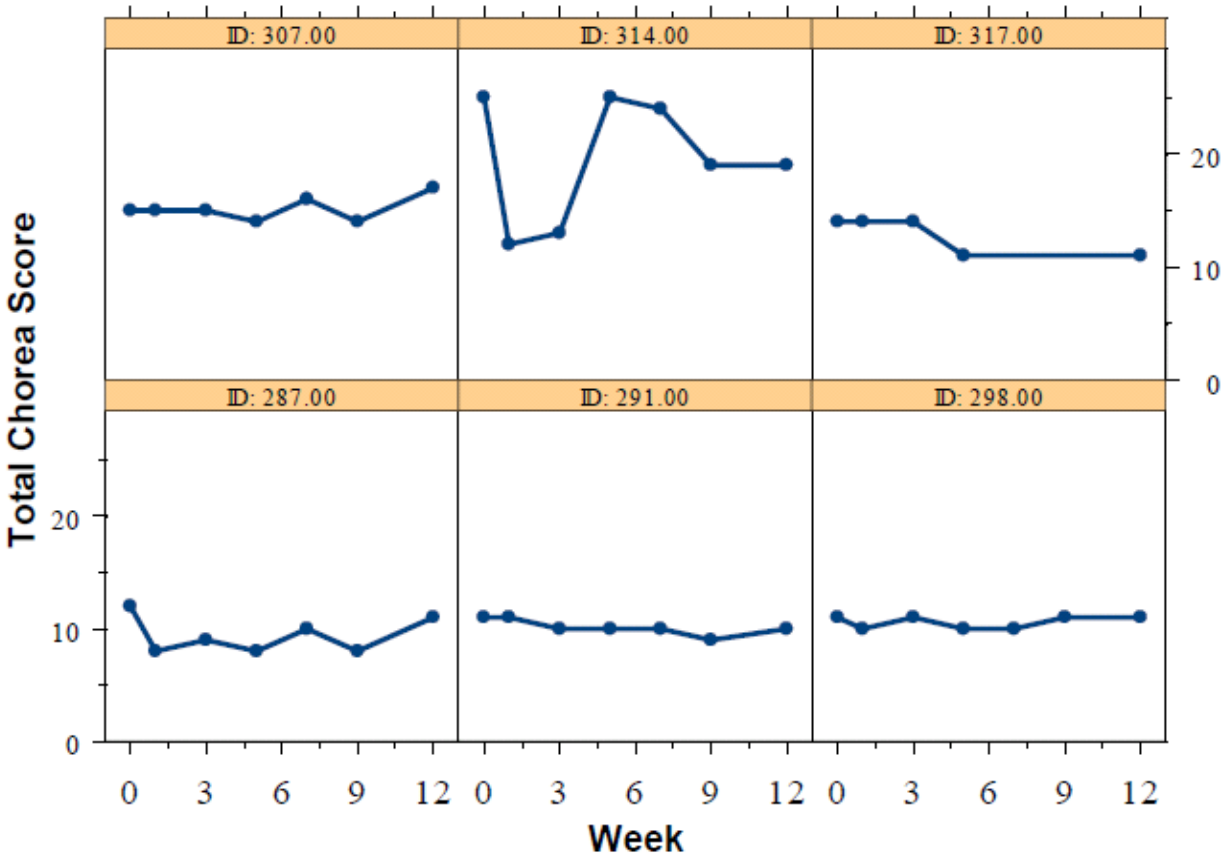


Figure 6. Total chorea score over 12 weeks in 30 HD patients randomized to placebo - Protocol TBZ 103,004. The graphs are presented as 5 sets with 6 plots per set. The patient ID is shown at the top of each plot. The ID number was truncated to the last 3 digits, but the original ID can be restored by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



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 1. The diagnostic plots for assessing the adequacy of the model fit are shown in Figure 7.

Figure 7. 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.

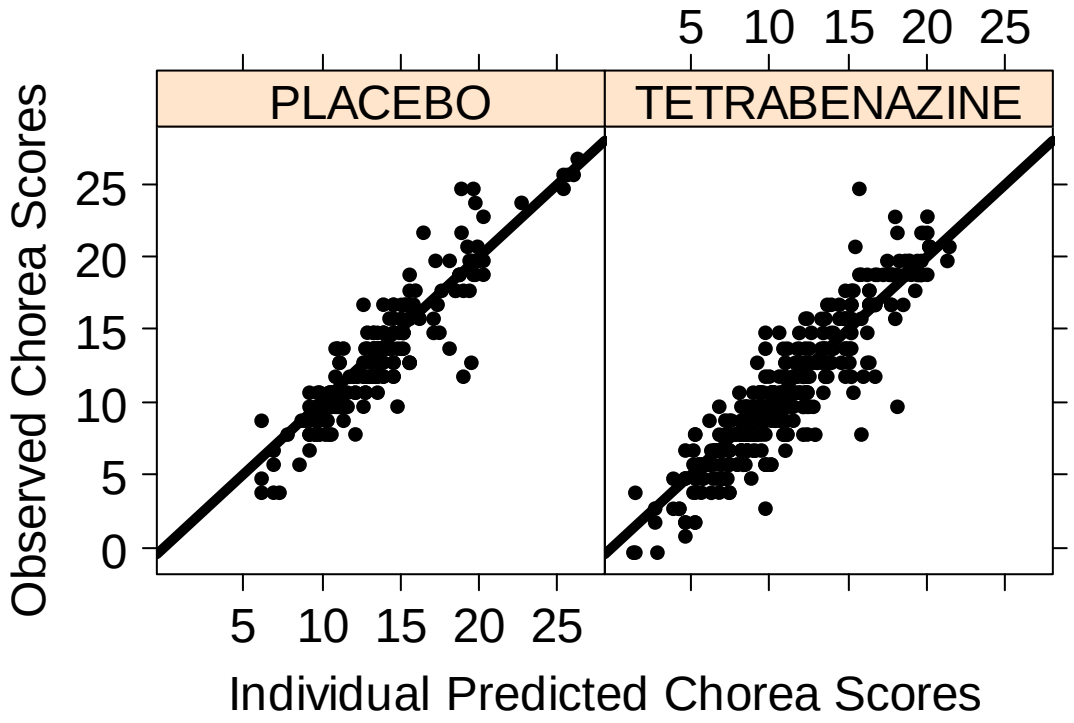
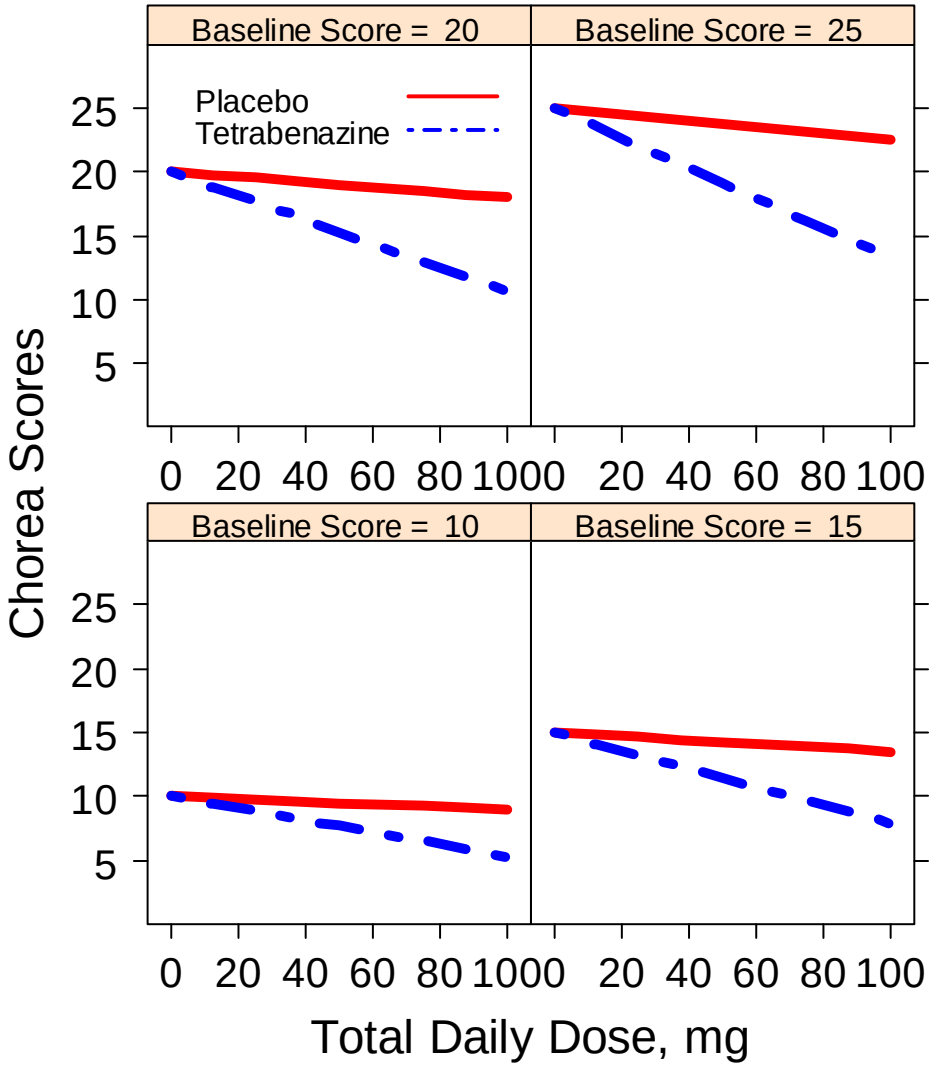


Table 1. Dose-response model parameter (mean and between-subject variability (BSV)) estimates and the 95% confidence intervals- Protocol TBZ 103,004. The slope of the dose-response is expressed as % change relative to baseline per mg of Tetrabenazine dose.

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 8 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 8. Typical dose-response curve based on parameters as shown in Table 1 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 2 shows the mean total chorea scores in the all the 3 groups and Table 3 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 2. Mean (± 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 ± 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

Table 3. Mean (± 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 ± 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

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 9. 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 10.

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 9. 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.

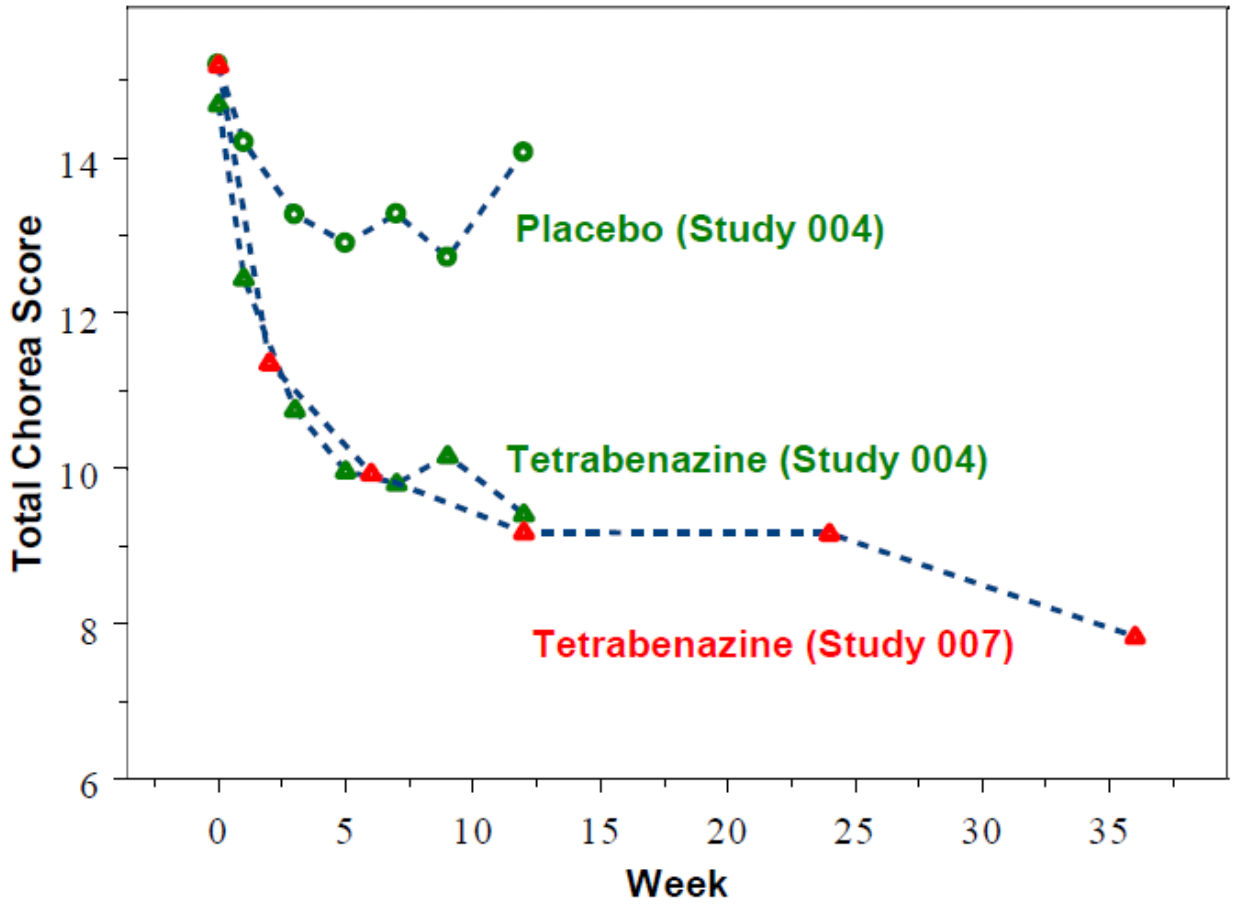


Figure 10. Mean total chorea scores of patients who received placebo in study TBZ 103,004 and then received Tetrabenazine in study TBZ 103,007. The total chorea scores are lower in patients when they received Tetrabenazine (TBZ).

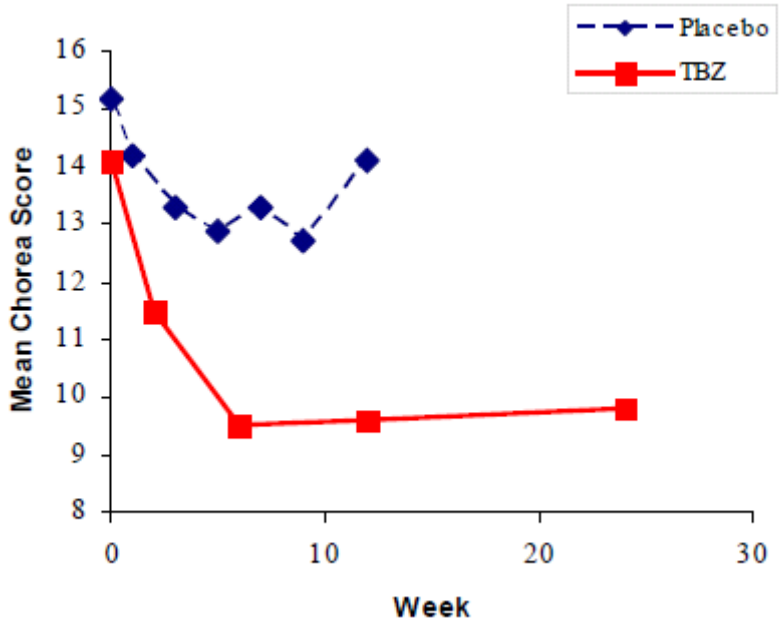


Table 4. Dose-response model parameter (mean and between-subject variability (BSV)) estimates and the 95% confidence intervals- TBZ 103,007. The slope of the dose-response is expressed as %change relative to baseline per mg of Tetrabenazine dose. These estimates are consistent with those reported in Table 1 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. **Chorea scores significantly increase, in fact reach baseline, within a week upon cessation of Tetrabenazine. This result also supports the effectiveness of**

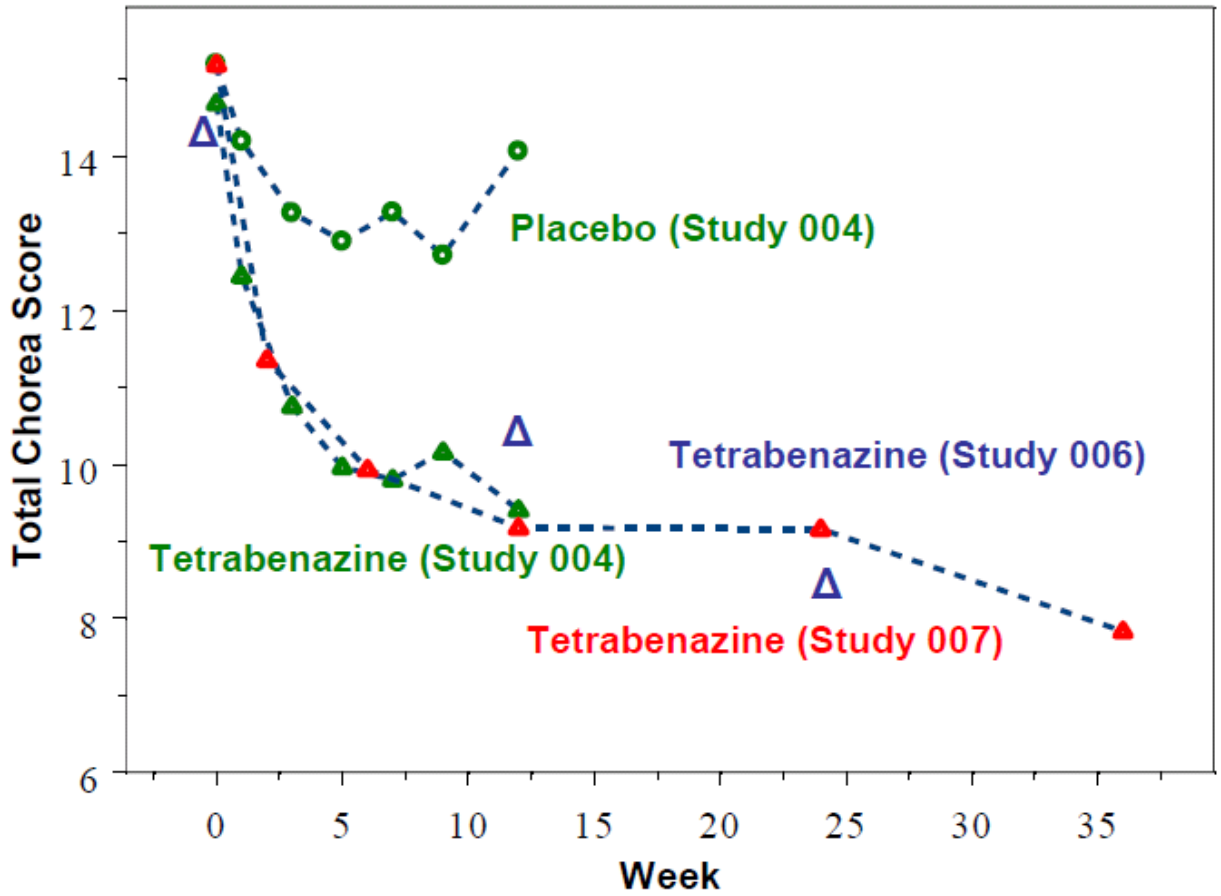
Tetrabenazine.

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 11.

Figure 11. 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 11, 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.**

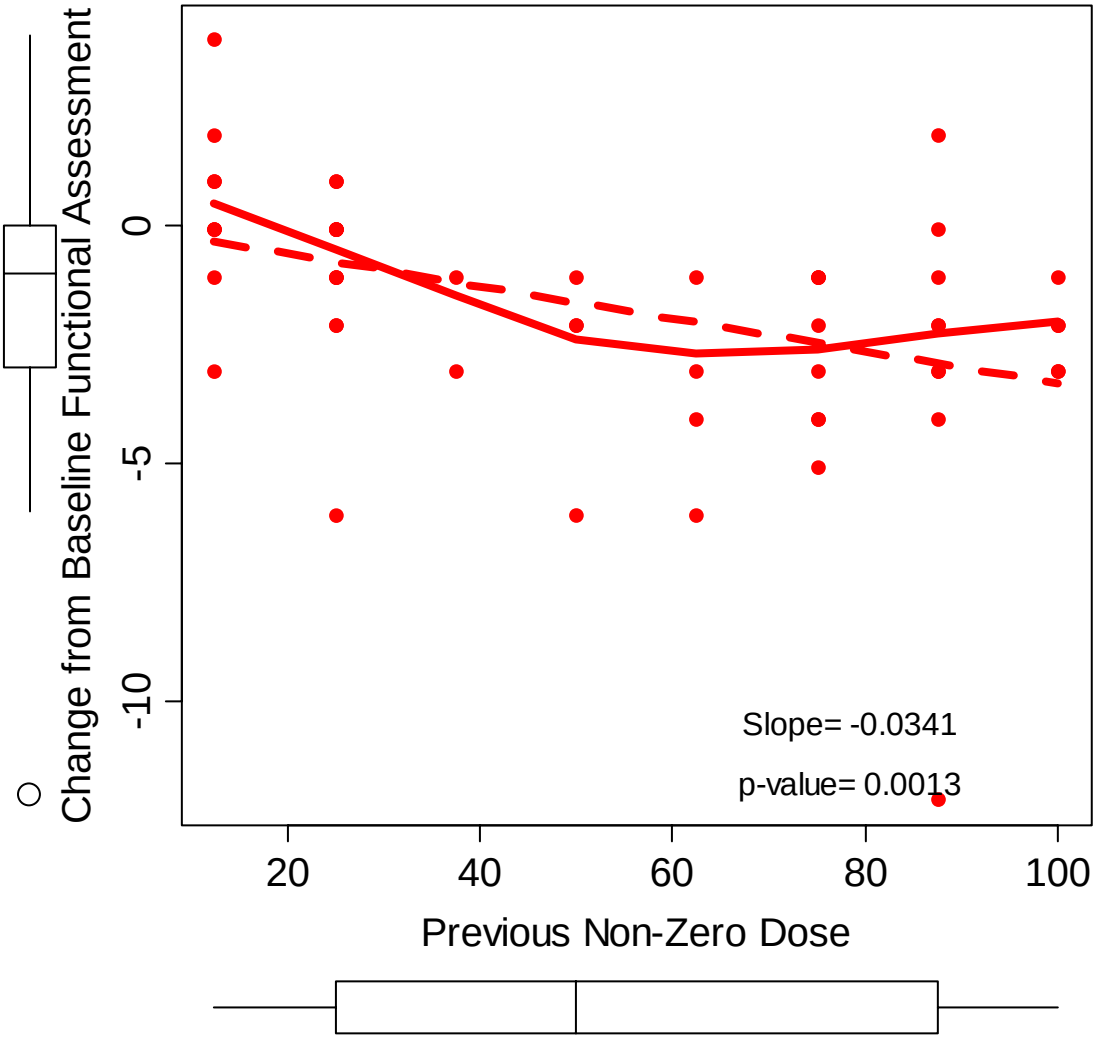
2. Is the worsening of Functional Scores, Cognitive Scores, Sedative Scores related to dose?

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 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18 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 12. 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.



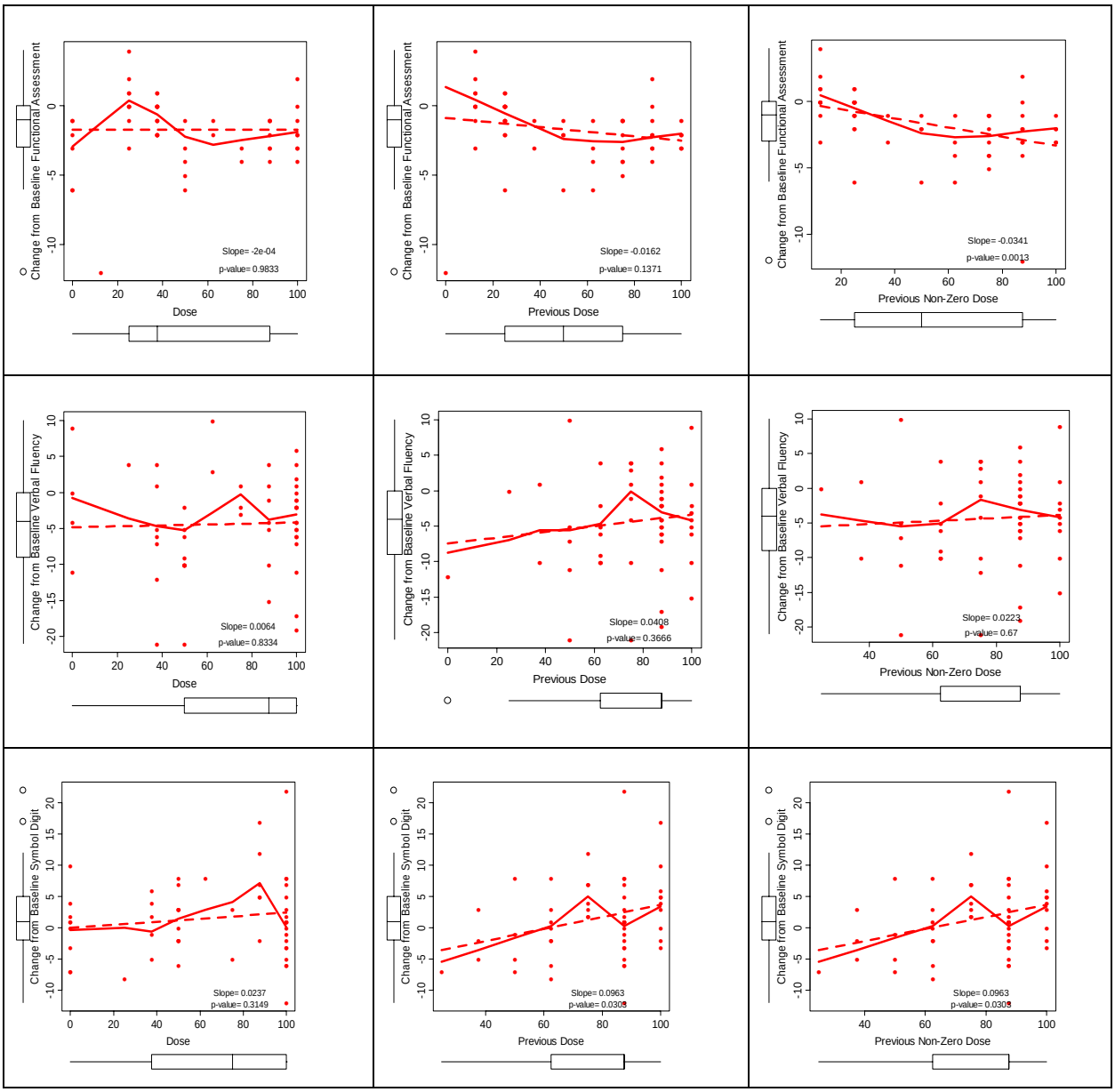


Figure 13. Relationship between change from baseline scores (worst score) for functional status, verbal fluency, symbol digit and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,004.

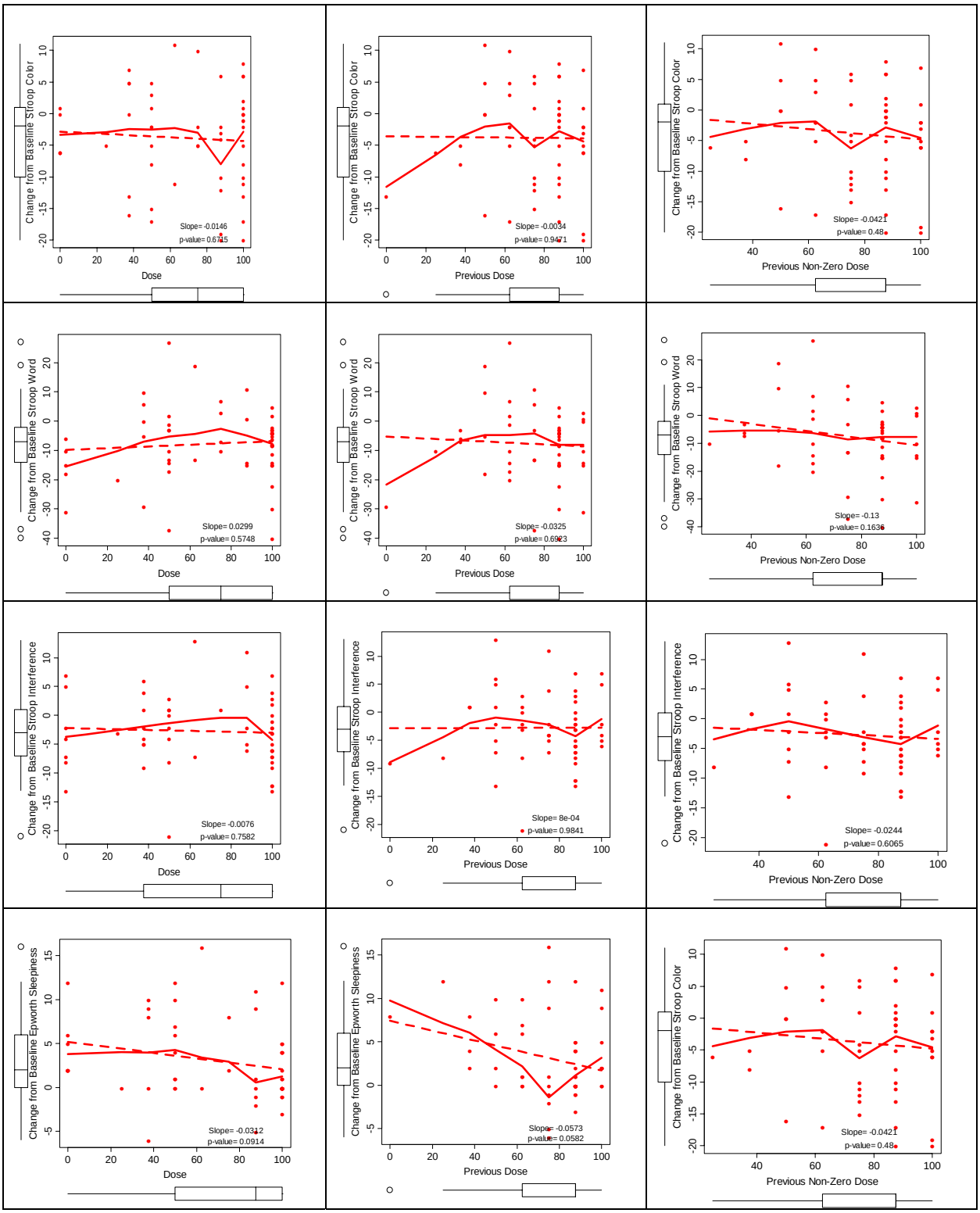


Figure 14. Relationship between change from baseline scores (worst score) for stroop color, stroop word, stroop interference, epworth sleepiness and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,004.

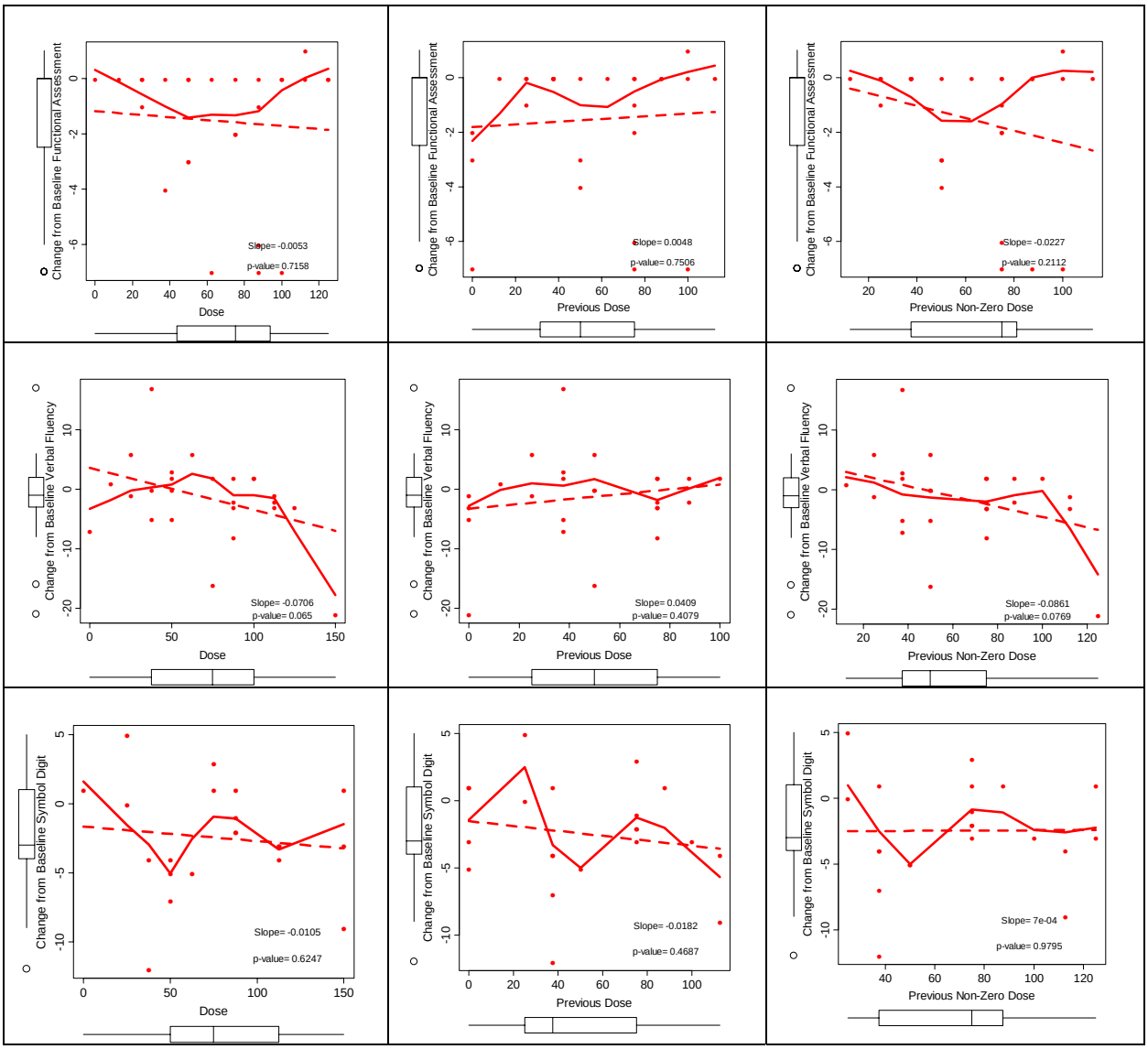


Figure 15. Relationship between change from baseline scores (worst score) for functional status, verbal fluency, symbol digit and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,006.

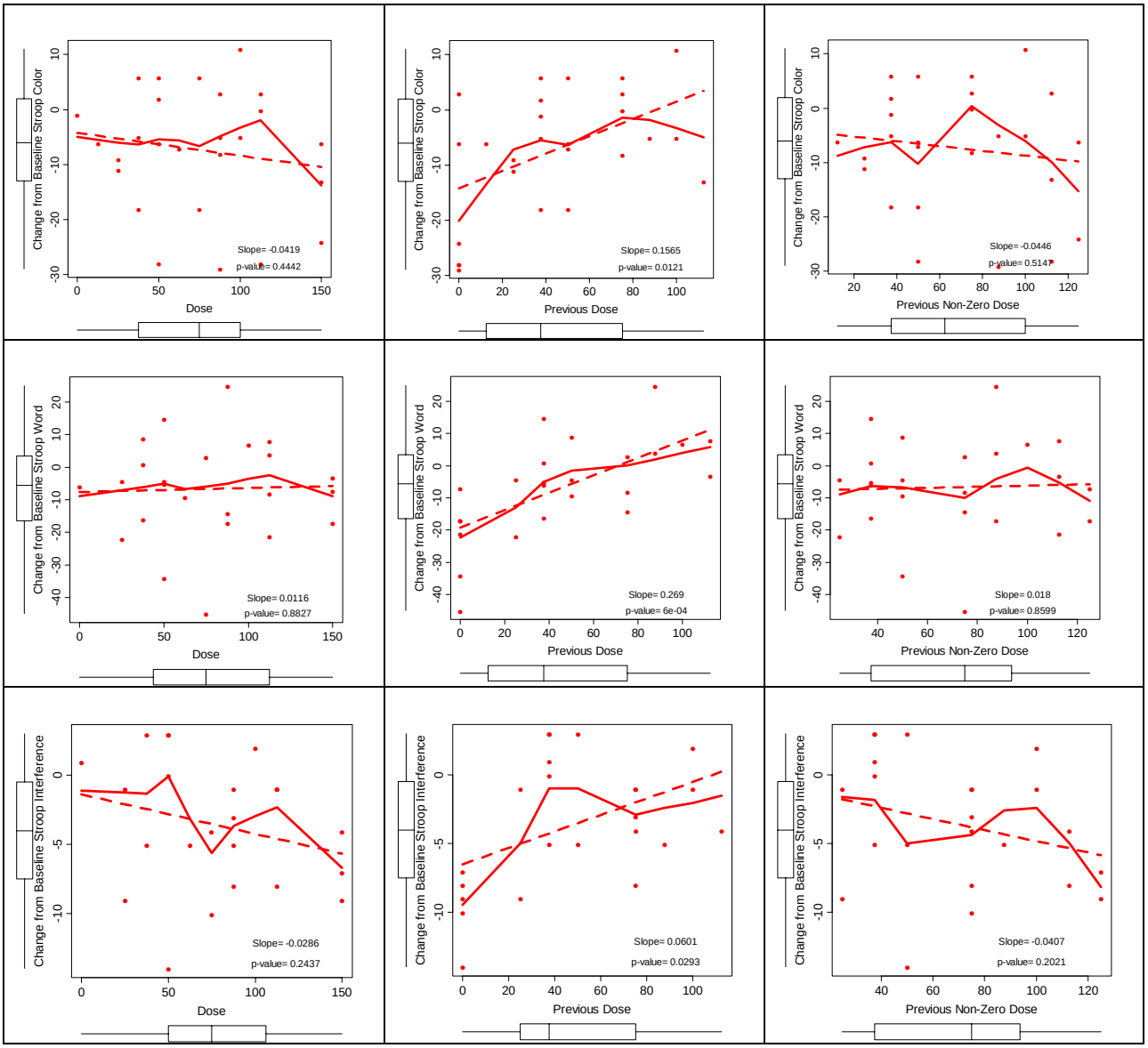


Figure 16. Relationship between change from baseline scores (worst score) for stroop color, stroop word, stroop interference, epworth sleepiness and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,006.

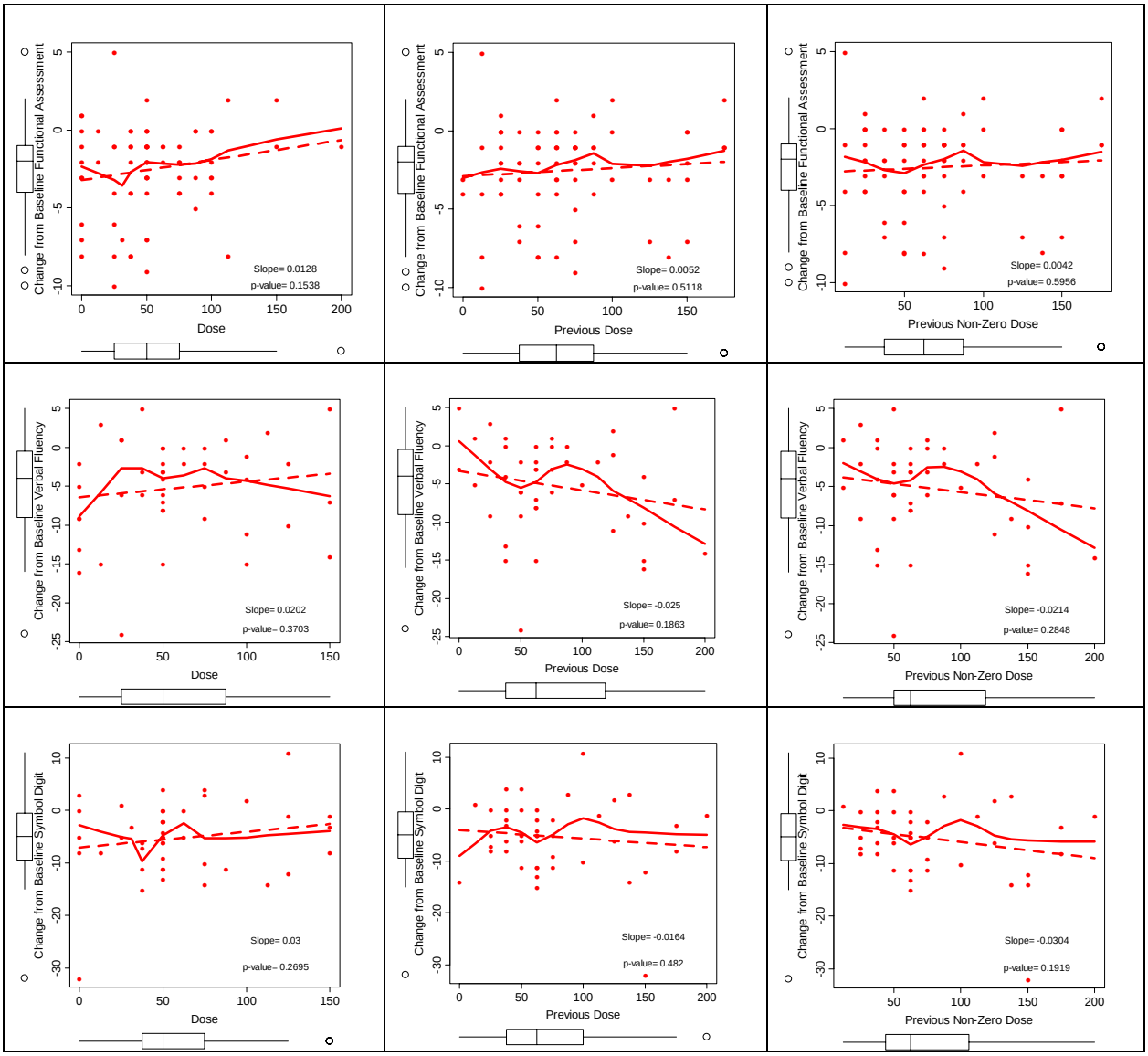


Figure 17. Relationship between change from baseline scores (worst score) for functional status, verbal fluency, symbol digit and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,007.

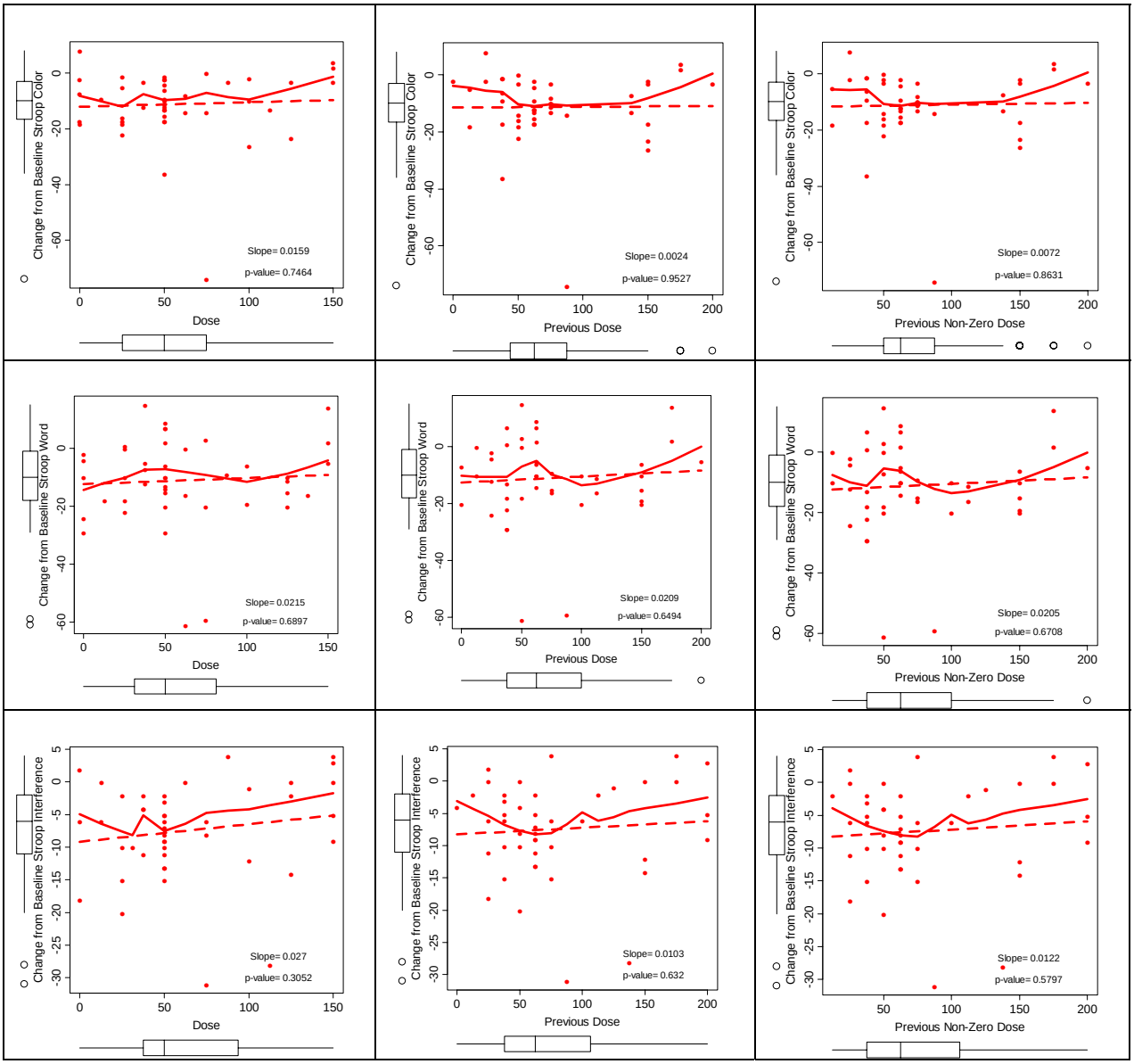


Figure 18. Relationship between change from baseline scores (worst score) for stroop color, stroop word, stroop interference, epworth sleepiness and dose at the visit week, previous dose at the visit week or previous non-zero dose if the dose was not administered for adverse event in Study TBZ 103,007.

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.

Figure 19 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.

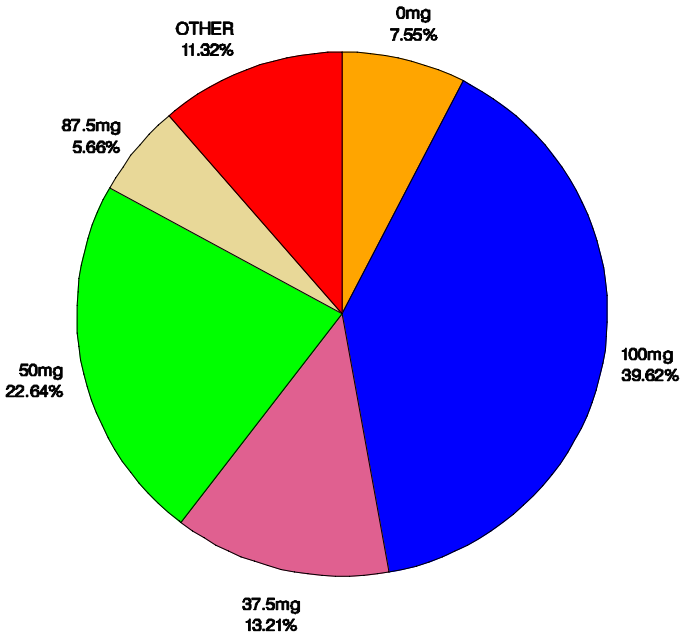


Figure 19. Distribution of tetrabenazine dose levels received by patients at week 12 in Study TBZ 103,004 (Double-Blind).

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.

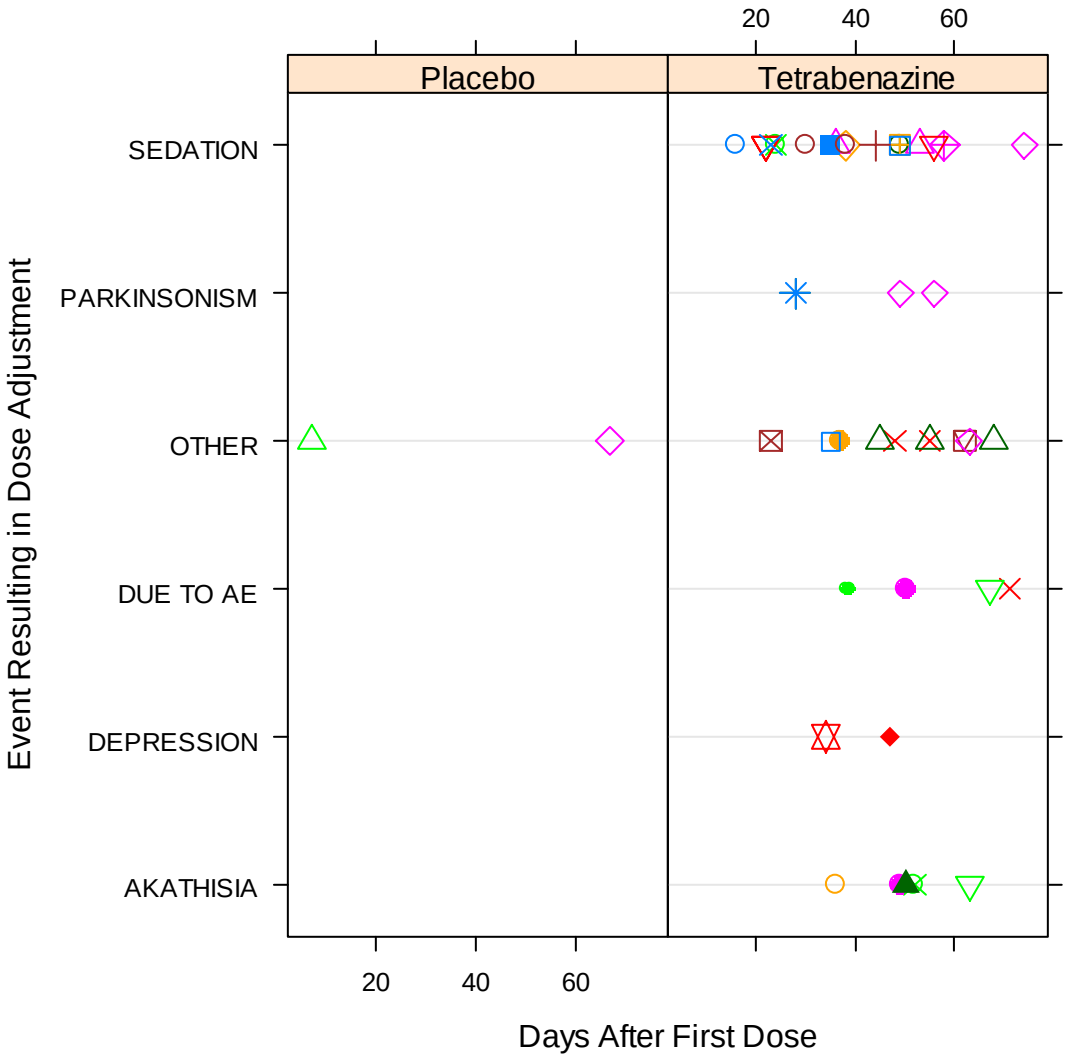


Figure 21 shows the longitudinal time course of mean (functional status score, parkinson score and HAMD scores in Study TBZ103,004. The changes in parkinson's scores are similar in placebo and tetrabenazine groups. For HAMD scores, it appears that patients in placebo group have improvement in HAMD scores. 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).

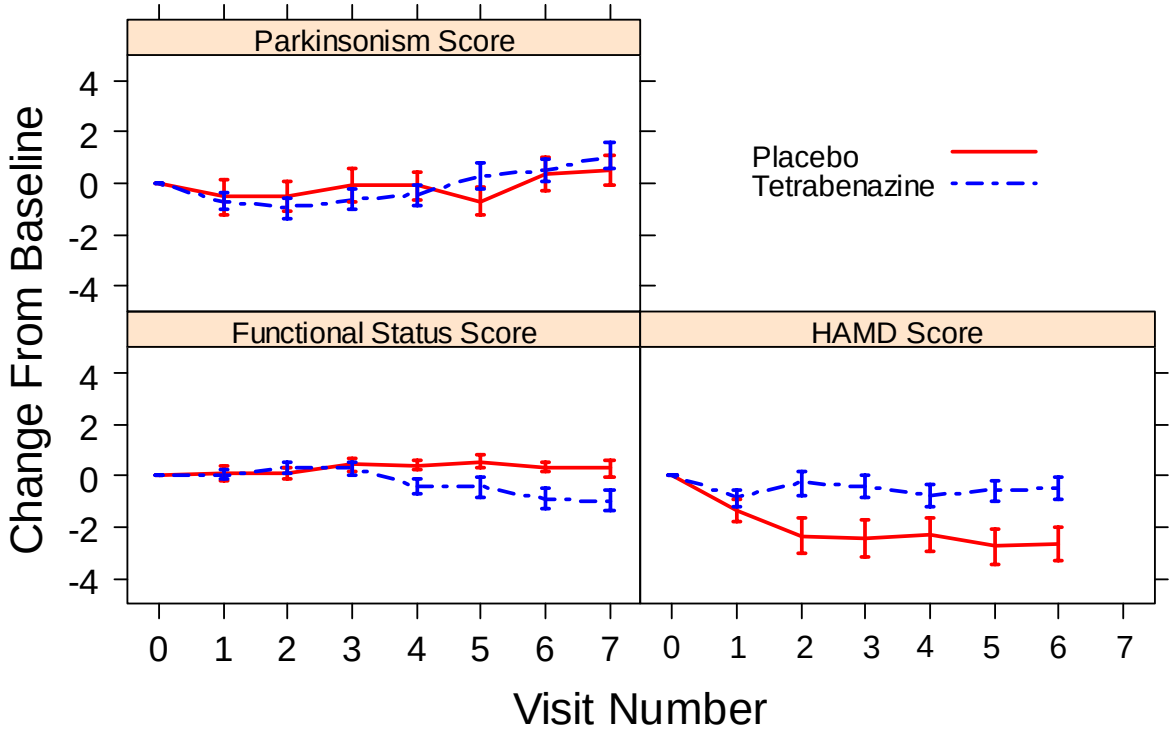
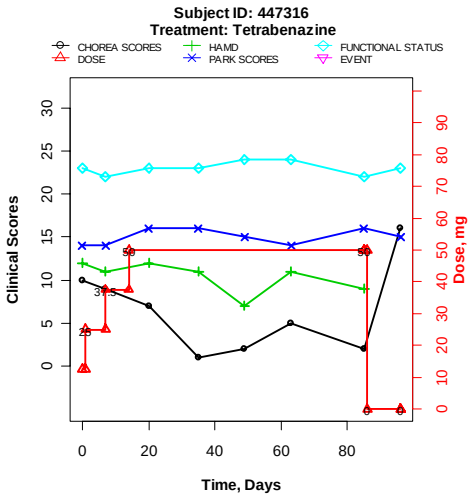


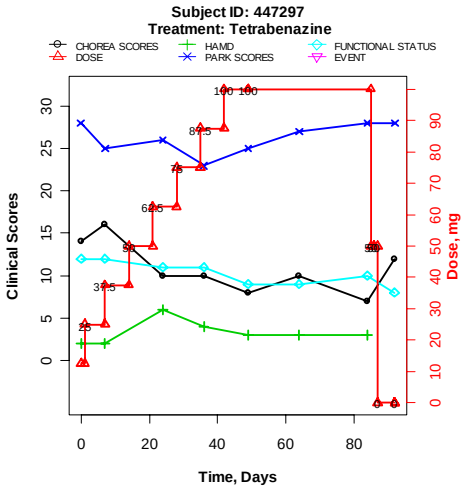
Figure 23, Figure 24, Figure 25, Figure 26, Figure **27** show the time course of clinical scores (Chorea, Parkinsonism, HAMD, Functional Status) along with dose in selected patients whose doses were either adjusted for management of sedation, akathisia, parkinsonism or depression. Also shown for reference 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.

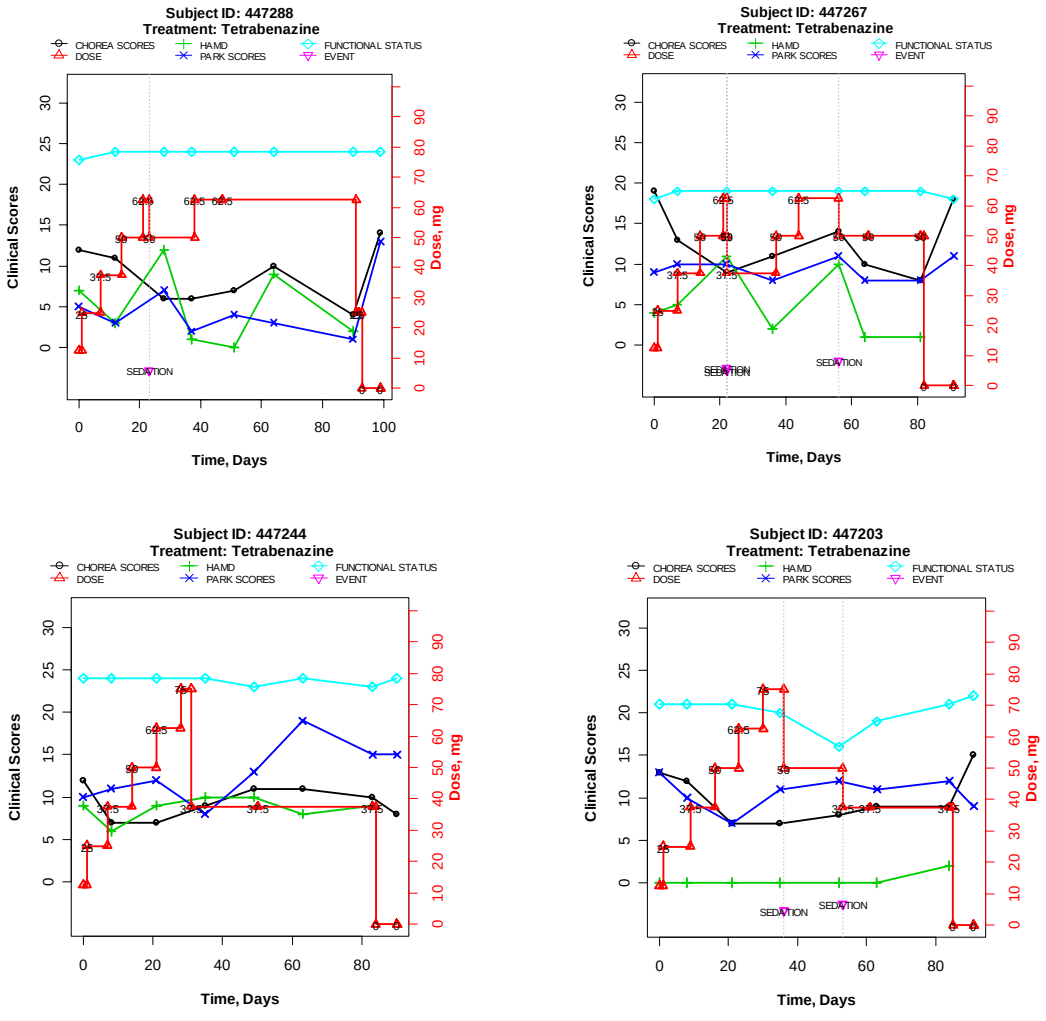




Dose Adjustment Due to Sedation in Study TBZ103,004

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.

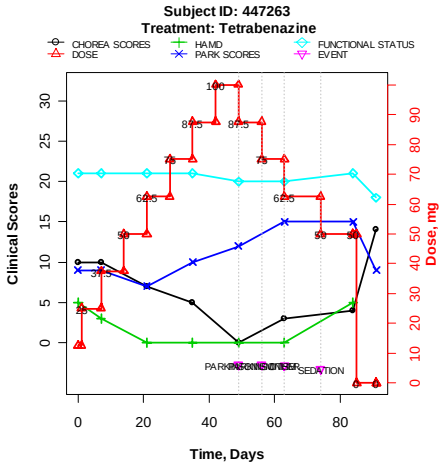
Figure 23. Changes in clinical scores (Chorea, HAMD, Parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for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

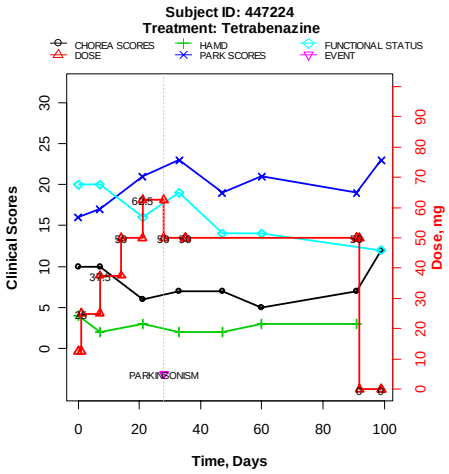


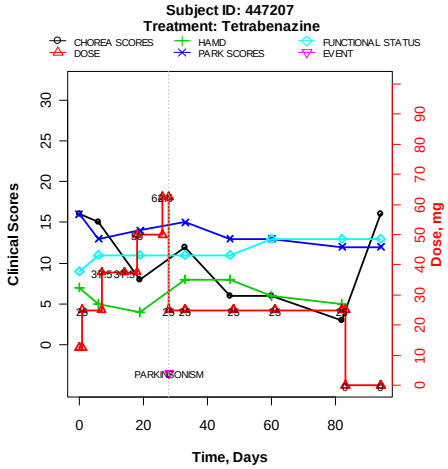
Dose Adjustment Due to Parkinsonism in Study TBZ103,004

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.



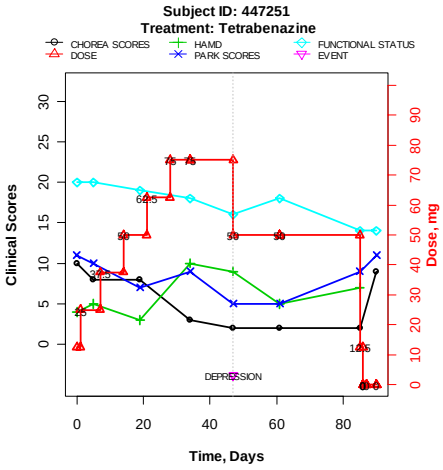


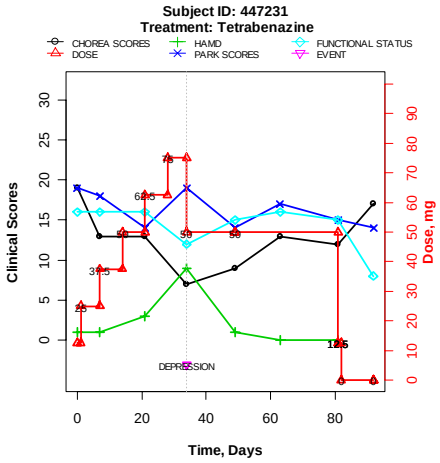


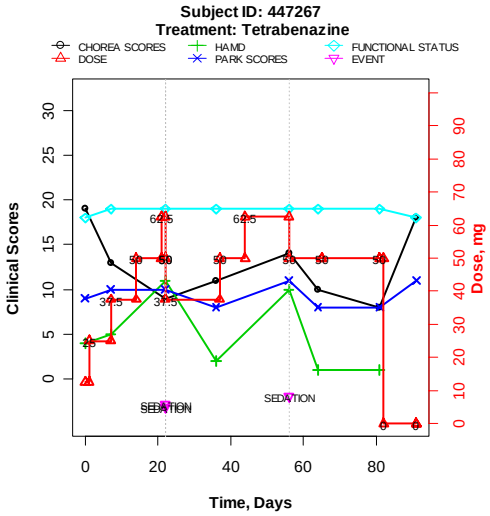
Dose Adjustment Due to Depression in Study TBZ103,004

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).



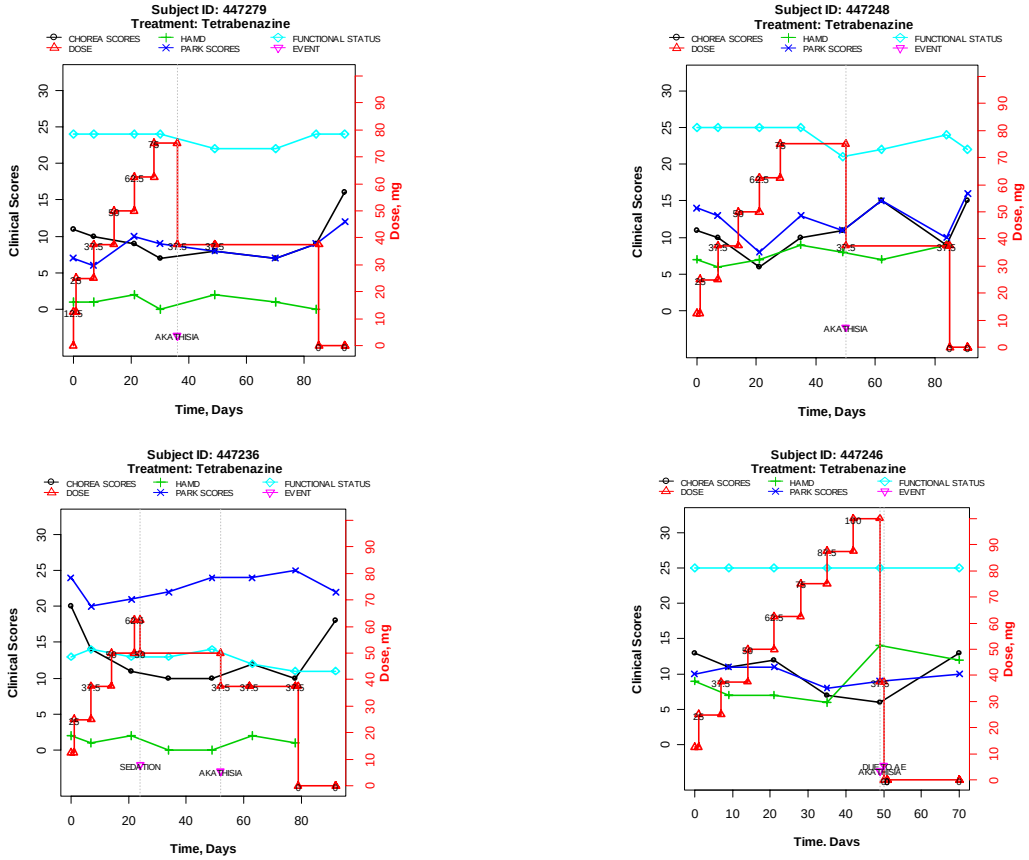




Dose Adjustment Due to Akathisia in Study TBZ103,004

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.

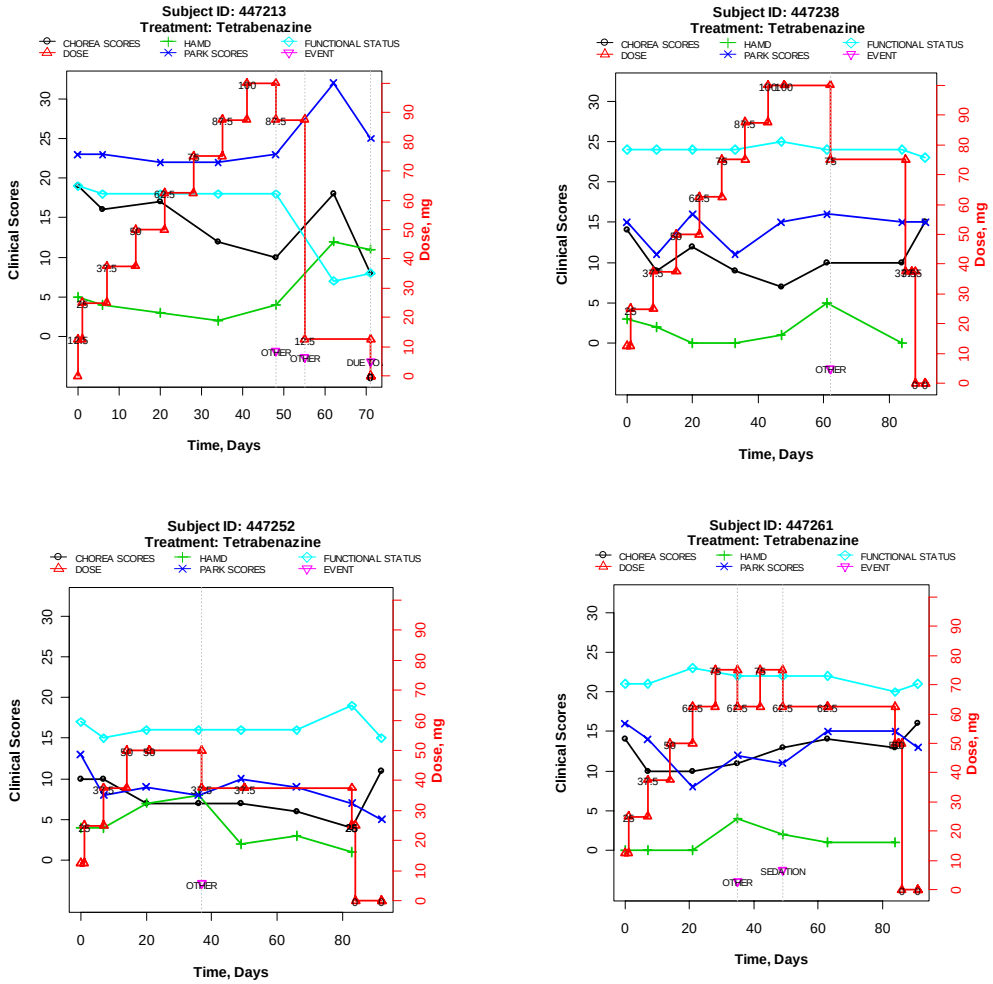
Figure 26. Changes in clinical scores (Chorea, HAMD, Parkinsonism (PARK), Functional status) versus time, days in Study TBZ103,004. Shown also are the changes in dose in the individual patient. The patients are chosen to demonstrate the time course of various scores when dose adjustments are made for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

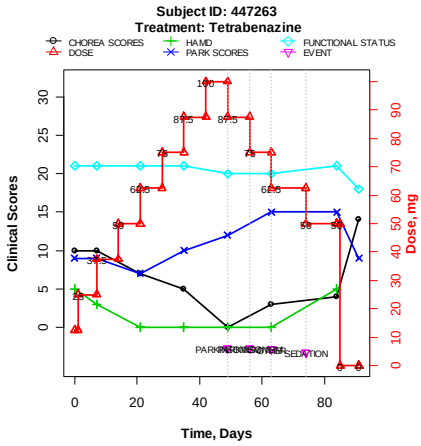


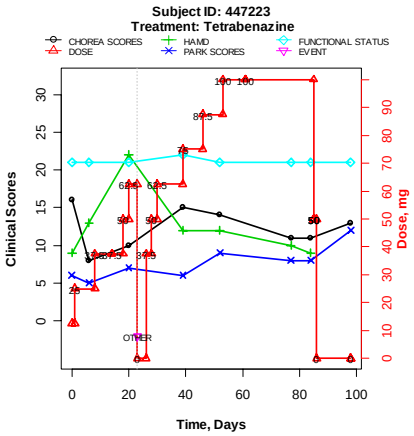
Dose Adjustment Due to Other Events in Study004

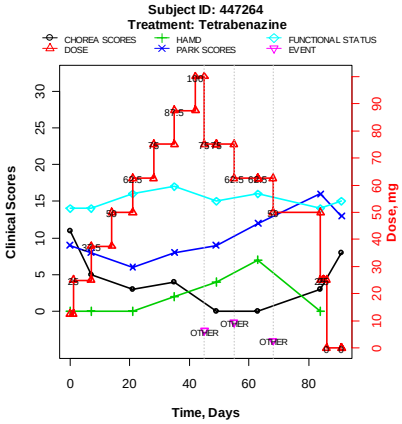
The dose of tetrabenazine was adjusted in 7 patients due to other adverse events such as agitation, anorexia, restlessness, fatigue, diarrhea, anxiety attack. In 5 out of 7 patients, a reduction of atleast 3 units in chorea score was preserved inspite of dose reductions. 1 out of 7 patients did not respond 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.




Subject ID: 447263
Treatment: Tetrabenazine
CHOREA SCORES
DOSE
HAMD
PARK SCORES
FUNCTIONAL STATUS
EVENT
Clinical Scores
Dose, mg
Time, Days
SEDATION


Subject ID: 447223
Treatment: Tetrabenazine
CHOREA SCORES
DOSE
HAMD
PARK SCORES
FUNCTIONAL STATUS
EVENT
Clinical Scores
Dose, mg
Time, Days
OTHER


Subject ID: 447264
Treatment: Tetrabenazine
CHOREA SCORES
DOSE
HAMD
PARK SCORES
FUNCTIONAL STATUS
EVENT
Clinical Scores
Dose, mg
Time, Days
OTHER

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.

CLINICAL SAFETY REVIEW
Xenazine®

NDA:	21-894
Submitted:	April 10, 2007 (& Major Amendment August 9, 2007)
Review date:	November 9, 2007
Reviewer:	Lourdes Villalba, MD, DNP Safety Team
Through:	Alice Hughes, MD, Team Leader, DNP Safety Team
Product name:	Tetrabenazine (Xenazine®)
Applicant:	Prestwick Pharmaceuticals
Dosing regimen:	25 to 100 mg daily, oral formulation
Indication :	Chorea of Huntington's Disease

Xenazine® (Tetrabenazine tablets)
Table of Contents

Table of Tables

Table of contents (cont)

Appendices

Executive summary

- Tetrabenazine (TBZ) has a beneficial effect on the chorea component of HD. In study 004, the primary efficacy analysis showed a mean change in Total Chorea Score (TCS) of -5.04 ± 0.49 among subjects receiving TBZ and -1.52 ± 0.67 among subjects receiving placebo ($p<0.0001$). In a responder analysis at 12 weeks, 38% of subjects in the TBZ treatment group had a drop of ≥ 50% in TCS as compared to no subjects on placebo and 69% had a drop of ≥ 3 points in the TBZ treatment group (which is considered to be clinically meaningful by HD experts), as compared to 23% on placebo. TCS reverted to baseline within one week after TBZ discontinuation. TBZ had no beneficial effect on the cognitive and behavioral components of HD and was associated with a small worsening in one of the functional outcome scores.

- Post-hoc analyses suggest that there is a dose response relationship in terms of efficacy, that patients who had the highest TCS at baseline showed the greatest improvements in TCS and that patients with the least functional impairment at baseline had the smallest decrease in their functional outcome scores.

- Evaluation of safety in this application is limited by the small database, the use of a flexible dose design and the fact that some of the adverse reactions associated with TBZ are also symptoms of or difficult to distinguish from the underlying disease (e.g. depression, dysphagia).

    - The application includes a 12-week placebo controlled study (Study 004, 54 subjects on TBZ and 30 on placebo) with an open label extension up to 80 weeks (study 007 that included 75 subjects), and a five-day placebo-controlled withdrawal study (Study 005, 30 subjects) with an open label extension up to 48 weeks (study 006). Altogether these studies involved 111 unique subjects exposed to TBZ. Additional information comes from chart review of patients under a non-commercial IND, of whom approximately 10% had been lost to follow up.

    - By design, the dose of TBZ was to be titrated up to desired effect (control of chorea) or to a maximum of 100 mg/day (in study 004), 150 mg/day (in study 006) or 200 mg/day (in study 007) if tolerated. The titration was to be done over a 7 week period. The flexible study design makes difficult to assess a dose-response relationship in terms of toxicity. The decision to continue titration or decrease the dose in the presence of adverse events (AEs) was based on clinical judgment. Additionally, safety analyses are confounded by time.

- The sponsor did not capture all adverse events in their analyses of incidence rates. In study 004 the FDA reviewer found 3 additional cases of parkinsonism, 2 additional cases of akathisia, 3 cases of restlessness that could have been cases of akathisia, 2 additional cases of depression, and one additional case of dysphagia, all in the active

treatment arm. Common AEs observed in study 004, the 12-week study were as follows (FDA analysis, percentage rounded):

AE	TBZ (N=54)	Placebo (N=30)
Sedation	32 %	3 %
Fatigue	22 %	13%
Insomnia	22 %	0%
Akathisia/restlessness	19 %	0 %
Depression	19 %	0 %
Falls/traumatic injury	19 %	13%
Anxiety	15 %	3 %
Parkinsonism	15 %	0 %

- This review focused on whether four events of major concern (akathisia, depression, dysphagia and parkinsonism) were recognized as drug-related AEs by the investigator, were reversible upon dose reduction or discontinuation, and on whether total chorea scores were adversely affected by the AE and/or dose reduction in the Prestwick-sponsored studies (004, 007, 005 and 006) and attempted to evaluate risk and benefits associated with the use of TBZ. The findings are summarized as follows:

  - Akathisia

  Akathisia is a known AE associated with the use of dopamine antagonists. There were seven cases of akathisia in study 004 (13%) (including one patient mentioned to have akathisia in one file [called "UH" file, submitted on September 2005] but listed as having restlessness in the AEs file, and one patient noted to have mild akathisia in the UH file but not listed in the AEs file). Including the term restlessness, there would be 10 cases of akathisia/ restlessness in 004 (19%). Altogether, there were 22 cases of akathisia in 20 out of 111 patients (20 %) enrolled in the Prestwick-sponsored studies (7 in 004, 15 in 007 and none in 006). Four of these cases were severe.

  In study 004, the median time to onset of the first event of akathisia was 43 days (range 19 to 59) and the median dose was 75 mg/day (range 50 to 100). No cases of akathisia occurred at doses < 50 mg/day in study 004, but three cases did in study 007.

  Eighteen out of 22 cases of akathisia underwent dose reduction. Of those, 11 resolved (most took 1-2 months to resolve but one case resolved after 2 days and another resolved after 11 months). Two patients whose akathisia resolved in 004, had recurrence of akathisia in 007. One patient in 004 and three patients in 007 discontinued because of akathisia. Data on recovery after study completion or early withdrawal were missing for most patients. For patients with recovery data, akathisia resolved 1-2 weeks after washout and 4 months after early withdrawal.

  A few patients who had an AE of akathisia achieved a drop in TCS ≥3 points at week 12 (2 out of 7 patients in 004 and 3/15 in 007).

- Depression/worsening depression and suicidality

Depression is common in patients with HD. TBZ can potentially increase the risk of depression, because along with dopamine depletion it causes serotonin and norepinephrine depletion.

In study 004, the 12-week placebo-controlled study, depression/worsening depression developed in 10/54 (18.5%) subjects treated with TBZ (three of whom had no history of depression), including one case of completed suicide and one suicidal ideation (both in patients with no prior history of depression). No such cases occurred among 30 placebo- treated patients (0%). The baseline risk factors for depression are not different enough to explain this striking difference between TBZ and placebo.

Altogether, 53 events of depression/worsening depression occurred in 46 out of the 111 patients enrolled in Prestwick-sponsored TBZ studies (41%). Six of these cases were severe. The reporting rate of depression in the Prestwick-sponsored studies was 2 to 7-fold higher than in the CARE-HD study (a large study in patients with HD, receiving treatments other than TBZ, referred to in more detail in Dr. Carole Davis' review).

The median dose at onset of the first event of depression in study 004 was 62.5 mg/day, although depression occurred at any time and at any dose, even at the 25 mg/day dose and as soon as 4 days of entering the study. In 004, more cases of depression/worsening depression occurred during titration (first seven weeks of the 12-week study), but cases continued to be reported thereafter. A total of 27 patients had depression/ worsening depression in study 007, 19 of whom had received TBZ for 12 weeks in study 004, however in the absence of a control arm, it is not possible to attribute causality for these patients.

Of the 53 cases with depression/worsening depression, 40% underwent TBZ dose reduction and 75% had a change in antidepressant regimen. Dose reduction and or antidepressant treatment led to resolution of the event in approximately 40% of cases.

Of the 3 patients with depression who underwent dose reduction in 004, all three recovered and had a drop in TCS of ≥ 3 points from baseline; however, one relapsed and attempted suicide in 007. Of the 12 patients with dose reduction because of depression in study 007, only two achieved a drop in TCS ≥ 3 by week 80.

- Dysphagia

Dysphagia is a known complication of advanced HD. However, it is also a potential adverse event of dopamine antagonists. In study 004, including the term "choking" there were two cases of dysphagia/choking on TBZ and one on placebo (3.7% and 3.3%, respectively). Altogether there were 11 cases of dysphagia/choking out of 111 patients in the Prestwick-sponsored studies (10%).

The dose of TBZ at the onset of the first event of dysphagia was 50 to 150 mg/day. All the cases that underwent dose reduction appeared to resolve (n=4), suggesting a dose response relationship. However, one took 6 months to resolve. The final median dose for patients who had developed dysphagia was 50 mg/day (range 25 to 150 mg/day).

Three subjects with dysphagia who did not undergo dose reduction completed the studies with impressive improvement in TCS but ongoing dysphagia, including one who was hospitalized with aspiration pneumonia, despite having a drop in TCS of 14 points.

Two of four patients with dysphagia who underwent dose reduction had a drop in TCS of at least 3 points from baseline.

Evaluation of cases in this database does not rule out an increased risk of dysphagia in patients taking TBZ.

- Parkinsonism:

Parkinsonism is associated with the use of dopamine antagonists. In study 004, there were 8 cases of parkinsonism among TBZ treated patients (15%) as compared to none on placebo. Altogether, there were 13 cases of parkinsonism in the Prestwick-sponsored studies. One was severe. No patients discontinued from 004 because of parkinsonism, however, one patient whose parkinsonism was ongoing at the end of the study was lost to follow-up within a week of entering 007, when transferred to a nursing home facility.

The median time to onset and the dose of TBZ at the time of the first event of parkinsonism in study 004 was 29 days and 62.5 mg/day respectively. Events also occurred in the long term studies, at doses of 75 to 200 mg daily. Some recurrent events occurred at doses of 25 mg and above.

Parkinsonism generally decreased or resolved after dose reduction or discontinuation, however, in some cases it took several weeks to months to resolve. Of the 11 cases, 4 resolved with dose reduction (1 day to 3 months later) and one without dose reduction (within 4 weeks). Two cases resolved after stopping TBZ during washout.

In general, despite the presence of mild to moderate parkinsonism, the final total chorea scores were lower than baseline. In study 004 five out of 8 patients with parkinsonism underwent dose reduction. Of these, four had a drop in TCS $\geq$3 by the end of the study and one did not.

- Akathisia/restlessness, depression and parkinsonism were generally recognized as probably or possibly related to study drug in this clinical program, although in some cases investigators may have preferred to tolerate mild events over decreasing the dose and losing therapeutic benefits. Six out of 53 cases of depression had neither

dose reduction nor medical treatment, and in five out of 53 cases investigators recorded a change in antidepressant regimen without recording depression or worsening depression as an adverse event. In the case of dysphagia, it appears that most investigators did not consider dysphagia as an adverse event potentially related to TBZ treatment. Only 4 out of 11 cases of dysphagia/choking in the Prestwick studies underwent dose reduction. In study 011 (Baylor Chorea report) there were 21 cases of dysphagia/choking and four of aspiration pneumonia with no reported AE of dysphagia. Of these cases, only two were recognized as possibly or probably related to study drug, and only three underwent dose reduction or discontinuation.

- In my opinion the optimal dose or the optimal HD population that would achieve the best benefit to risk ratio may have not been adequately identified for TBZ. In study 004 the median dose at onset of the first event of akathisia, depression and parkinsonism was > 50 mg/day (75 mg/day for akathisia and 62.5 mg/day for parkinsonism and depression [although some cases of depression occurred at doses <50 mg/day]). Notwithstanding the limitations of the database, based on post hoc analyses of the number of patients who at the end of the 12-week study achieved a drop in TCS from baseline ≥3 points (11 out of 21 patients at the 100 mg/day dose [52%] and 10 out of 11 patients at the 50 mg/day dose [91%], in the context of most concerning events occurring at doses above 50 mg/day, it appears that the 50 mg/day dose has a more favorable safety profile than the 100 mg/day dose.

- A Risk Minimization Action Plan (RiskMAP) offers a potential approach to reducing some of the safety concerns associated with TBZ. The Office of Surveillance and Epidemiology (OSE) is conducting a detailed review of the proposed RiskMAP.

1. Background

Huntington's disease (HD) is a hereditary, slowly progressive neurodegenerative disorder characterized by motor, behavioral and cognitive impairment. The behavioral and cognitive components of the disease appear to be more challenging than the motor component in terms of management. In advanced stages of the disease, chorea may improve, while rigidity and dystonia become more prominent. Inanition and pneumonia secondary to dysphagia are often terminal events. [1, 2]

Tetrabenazine (TBZ) inhibits the central nervous system (CNS) specific vesicular monoamine transporter-2 (VMAT-2) leading to CNS monoamine depletion, in particular, dopamine depletion (with resulting reduction of chorea), and to a lesser extent, serotonin and norepinephrine depletion. These pharmacologic effects explain common adverse effects observed with TBZ (somnolence, insomnia, anxiety, restlessness/akathisia, depression and parkinsonism).

Tetrabenazine, originally developed as a potential antipsychotic agent, was first approved in the UK in 1971 for the treatment of chorea and other involuntary movements. It is currently approved in several countries for these indications. In the U.S., there is no product approved for the treatment of HD-associated chorea (or any component of Huntington's Disease), however, antipsychotic medications (e.g. risperidone, olanzapine) are used off-label for the treatment of HD chorea.

NDA 21-894 (Xenazine®) was submitted on September 23, 2005. On March 24, 2006, the application received an Approvable (AE) action. The DNP felt that despite the documented efficacy of TBZ in the chorea component of the disease (based on Part 1 [Motor Assessment] of the Unified Huntington Disease Rate Score [UHDRS] in study 004, supported by study 005), "troubling questions remained regarding the utility and ultimate approvability of the application." There was no evidence of improvement on the behavioral/cognitive components of the disease. Moreover, some of the functional measurements favored placebo. Additionally, some of the adverse reactions associated with TBZ use might have not been adequately distinguished from the underlying disease.

In study 004, the primary efficacy analysis showed a mean change in Total Chorea Score (TCS) of -5.04 ± 0.49 among subjects receiving TBZ and -1.52 ± 0.67 among subjects receiving placebo ($p<0.0001$). In a responder analysis at 12 weeks, 38% of subjects in the TBZ treatment group had a drop of ≥ 50% in TCS as compared to no subjects on placebo and 69% had a drop of ≥ 3 points in the TBZ treatment group, as compared to 23% on placebo. TCS reverted to baseline within one week after TBZ discontinuation.

The medical officers who reviewed the original application (Drs. Davis, McNeil and Feeney) initially recommended that an additional study be conducted. However, given the robust favorable effect of TBZ on the chorea component of the disease, it was decided

[1] Walker. Huntington's disease. Seminars in Neurology, 2007 (7).
[2] Bonelli et al, International Clinical Pharmacology, 2004 (19).

that additional analyses of the available data might be sufficient to address the questions raised during the review, which are detailed below.

Clinical deficiencies cited in the March 24, 2006 AE letter, were as follows (verbatim language):

- "There is a consistent tendency for the results of the analyses of multiple secondary outcomes (UHDRS Parts 2, 3, 4, 5 and 6) to favor placebo in study 004. Specifically,

  the between-treatment comparisons on the Cognitive Assessment (UHDRS Part 2), the Behavioral Assessment (UHDRS Part 3), the Functional Assessment (UHDRS Part 4), the Independence Scale (UHDRS Part 5), the Functional Capacity (UHDRS Part 6) all numerically favored placebo, and the comparisons on the Cognitive Assessment (UHDRS Part 2) and the Functional Assessment (UHDRS Part 4) actually achieved nominal statistical significance in favor of placebo (p=0.025 and p=0.018, respectively).

- There are no patient-rated measures of overall benefit in study 004.

- These results raise serious questions not only about the overall utility of Xenazine's effect on chorea but also, about Xenazine's capacity to cause harm in these patients.

  There is concern with Xenazine's capacity to cause serious adverse events, such as parkinsonism, akathisia, depression and dysphagia (with associated aspiration pneumonia). Some of these events have substantially greater incidence in drug-treated patients as compared to placebo (depression: 15% vs. 0; akathisia: 9% vs. 0). It is not clear whether other terms coded differently from akathisia do not in fact, represent the same phenomenon (e.g. agitation, anxiety, irritability). All of these events are consistent with the pharmacologic effects of the drug, and the incidence of these events increases with increasing duration of use. We acknowledge, of course, that the long-term safety data were collected in an open-label, uncontrolled setting, and also that these can themselves be manifestations of progressive HD. For these reasons a definitive conclusion about causality clearly can not be made at this time. Nonetheless, we are concerned that these events may be drug-related.

  We are particularly concerned about the ability of practitioners to readily identify these events and consider the possibility that they may be drug -related. We would agree that, should these events occur relatively acutely after treatment initiation (or dose increase), the prescriber might consider them drug related (and take the appropriate action). However, to the extent that they might be drug-related, but occur slowly over time, it is less likely that they will be considered potentially drug-related and more likely to be considered related to disease progression. In such a scenario, the possibility that the specific symptom might reach a severe stage (with the possibility that it may become irreversible), or result in a serious outcome even if reversible (e.g., depression leading to suicide), is raised.

Also, in regard to dysphagia specifically, we note the disturbing finding that one investigator did not systematically record episodes of dysphagia in many of his patients because he considered it to be a symptom of progression of the underlying HD. Because his experience represents a large portion of the clinical experience submitted in this application, we are concerned that the incidence of dysphagia (which can have devastating clinical consequences) may be significantly underestimated.

We are not sure that Xenazine can be used safely, even with labeling that describes as accurately as possible, the known risks of its use".

2. Current application

The current application (submitted April 10, 2007, with a Major Amendment submitted August 19, 2007) is a Complete Response to the March 24, 2006 AE letter. To address the concerns raised in the FDA AE letter, the sponsor:

- Conducted several exploratory efficacy analyses (which are being reviewed by Dr. Carole Davis)
- Developed a comprehensive list of investigator verbatim terms to define each of the AEs mentioned in the letter (parkinsonism, akathisia, dysphagia and depression) and reviewed investigator verbatims to determine if the terms were correctly coded
- Analyzed the incidence, timing and reversibility of these AEs following TBZ dose reduction or discontinuation
- Compared the rate of dysphagia in the Prestwick development program with that of patients with HD treated with drugs other than TBZ.
- Developed a Risk Minimization Action Plan (RiskMAP) to enhance monitoring and minimize the risk of suicide (reviewed in detail by the OSE RiskMAP review team).
- Provided responses to chemistry, non-clinical and clinical pharmacology issues raised in the AE letter (these topics are being addressed by different reviewers).

A detailed review of the safety of TBZ in the original NDA was conducted by Dr. Elizabeth McNeil during the first review cycle (date March 15, 2006). My review will focus on the sponsor's response to the deficiencies pertaining to safety (parkinsonism, akathisia, depression and dysphagia) and on trying to better understand the dose/response relationship and risk/benefit ratio of this drug.

A summary of the studies referenced to in the TBZ development program is presented in Table 1.

Table 1. Sources of Clinical Data in the TBZ development program

Protocol #	Design (duration)	Type of patients	N TBZ/Pla	Dose of TBZ (mg/day)	Study sites
Prestwick-sponsored studies of TBZ					
TBZ 103,004 (Study 004)	R, DB, PC (12 weeks)[1]	HD Chorea	54/30	Titrated to best dose 12.5 - 100	16
TBZ 103,007 (Study 007)	Open label extension to 004 (up to 80 wks)	HD Chorea	75[2]/0	Titrated to best dose 12.5 - 200	16
TBZ 103,005 (Study 005)	R, DB, PC, staggered withdrawal (5 days)	HD Chorea	30/24	Withdraw from up to 150 mg	1
TBZ 103,006 (Study 006)	Open label extension to 005 (up to 48 wks)	HD Chorea	29/0	Not titrated 12.5 - 150	1
Data compiled by retrospective record review of TBZ studies [3]					
Baylor Chorea report (Study 011)	Prospective, OL, dose-titration study (up to several years)	HD Chorea Non HD Chorea	98/0 47/0	Titrated to best dose 12.5 – 200	1
Baylor Non-chorea report	Open label, compassionate use	Hyperkinetic mov. disorders	247/0		
Other Clinical studies of HD (not TBZ) used for safety comparisons					
CARE-HD[4]	R, DB, PC (30 months)	Early HD	0	NA	23

TBZ= tetrabenazine. HD= Huntington's Disease. [1] In 004, there was a titration phase during the first 7 weeks, and a maintenance phase, for 5 weeks, followed by 1 week washout. Of the 30 patients on placebo, 27 entered study 007 (Appendix 1). [2] A list of patients who had been on placebo in 004 is presented in Appendix 1. [3] Previous to Prestwick's involvement, patients were treated with TBZ at Baylor College of Medicine since 1979. Data from clinical records from patients with chorea were entered into case report forms (CRFs) in 2003-2004 to support the current application. Serious AEs were not prospectively reported but retrospectively defined. CRFs were not created for the Baylor non-chorea database. Included 162 patients with chorea (of these 17 were not available), and 280 with hyperkinetic movement disorders other than chorea (of these, 33 were lost to follow up). Therefore, data are missing from approximately 10% of patients. [3]CARE-HD enrolled 347 patients randomized to interventions other than TBZ (remacemide, coenzyme Q10, remacemide+ coenzyme Q10 or placebo). The sponsor used CARE-HD as a control for some of the efficacy and safety analyses.

The original submission also refers to other sources of safety information collected by Roche prior to Prestwick's involvement: the Nitoman database and a safety database from the schizophrenia development program. The Nitoman database is old and missing one third of the records. The schizophrenia database was not submitted.

Therefore, the source of safety data prospectively collected in TBZ clinical studies in patients with HD is limited to 111 patients on TBZ, of whom 54 were involved in head to head placebo-controlled studies.

2.1 Evaluation of akathisia, depression, dysphagia and parkinsonism

In response to the April 2006 AE letter, to ensure the adequacy of AE identification of parkinsonism, akathisia, depression and dysphagia in the NDA, the sponsor developed a comprehensive list of investigator verbatim terms defining each of the AE of interest. Then they reviewed if the verbatim terms were adequately coded across the development program. Of note, the Prestwick development program used different coding dictionaries. For studies 004, 005, 006 and 007 verbatims were coded using the WHO 1999 4th Quarter dictionary. For study 011, verbatims were coded using COSTART 5.0. The Baylor non-chorea study used only verbatims.

By using the expanded definitions, the sponsor found a few additional cases of parkinsonism and dysphagia but no new cases of akathisia and depression. By reviewing the adverse event listings, the concomitant medication listings and the comments' column included in some of the datasets for studies 004 ("UH file"), 007 and 006, I found two additional cases of akathisia, six of restlessness that could have been cases of akathisia, two of depression, one of dysphagia and three of parkinsonism. For explanations about the sources of these newly identified events, see Table 2. I did not review study 005 (the five-day withdrawal study) and study 011 (the Baylor chorea database), except for events of dysphagia.

Table 2. Patients with akathisia, depression, dysphagia & parkinsonism in the TBZ treatment group, in studies 004, 006 and 007 (original NDA application and current application).

	004 N= 54			007 N= 75			006 N= 29			All N=158
	Original NDA	4/10/07 CR		Original NDA	4/10/07 CR		Original NDA	4/10/07 CR		4/10/07 CR
	Sp	Sp	**FDA**	Sp	Sp	**FDA**	Sp	Sp	**FDA**	**FDA**
Akathisia	5	5	**7**[1,2]	11	15	**15**	-	-	**0**[2]	**20***
Depression	8	8	**10**[3]	18	24	**27**[4]	4	9	**10**[4]	**46***
Dysphagia[5]	1	1	**2**[6]	2	3	**6**[7]	2	3	**3**	**11**
Parkinsonism	3	5	**8**[8]	2	2	**2**	1	3	**3**	**13**

N= number of patients randomized to TBZ. Sp= sponsor analysis. [1] Two additional cases of akathisia in 004. [2] Additionally, 3 cases of restlessness in 004 and 2 in 006 are potential cases of akathisia. [3] Includes one patient who was depressed before committing suicide but did not report the AE to the investigator and one patient who was not listed in the AE dataset but started mirtazapine for depression (as per dataset of concomitant medications). [4] Includes patients not listed in AE dataset whose antidepressant medication was initiated or changed for an indication of depression. [5] One case of dysphagia occurred on placebo in study 004. [6] Includes 1 case of choking. [7] Includes 3 cases of choking. [8]Includes one case of "stiffness when walking", one "coordination abnormal, balance difficulty" that improved with dose reduction and one case of bradykinesia that was not in the AE listing. *Some patients had more than one event. Source: Table 9 of Dr. McNeil's March 15, 2006 review of original NDA application; AE listings and datasets in the February 2007 Complete Response; UH file for study 004 submitted September 2005.

At the FDA's request, the sponsor provided summary tables that included the relative day of onset of the AE, the action taken (dose reduction or discontinuation, medical treatment), the outcome (resolved or not) and the dose of TBZ and total chorea scores (TCS) at the time of the adverse event, after the onset of the adverse event and at subsequent visits for all cases of akathisia, depression, dysphagia and parkinsonism in studies 004, 007 and 006. Although these tables are somewhat difficult to follow, it is the best way I found to summarize all cases, rather than writing narratives for each of them. Detailed information on dates, doses and TCS scores are missing from most cases identified by FDA.

For each one of these adverse events of interest, I tried to answer the following questions:

- Was the event dose-related? Did it resolve with dose reduction/discontinuation?
- Was the event recognized as an adverse event potentially related to TBZ?
- What happened with the total chorea scores (TCS) after dose reduction?

2.1.1. Akathisia

Akathisia, which is defined as a sensation of motor restlessness with a subjective desire to move, is a common adverse reaction associated with dopamine antagonist use. The preferred terms chosen by the sponsor to analyze events suggesting akathisia during the TBZ development program were "akathisia" and "hyperkinesia." The sponsor analysis did not include "restlessness." Some of the patients listed as having restlessness could have had akathisia.

In response to the FDA request to assess whether akathisia was adequately captured in the program, the sponsor evaluated whether adverse events coded as anxiety, anxiety aggravated, anxiety attack, increased anxiety, restlessness, restlessness aggravated, agitation, nervousness and irritability included verbatim terms that should have been coded as akathisia or hyperkinesia. Review of these terms in the adverse event listings by a neurologist consulted by the sponsor "revealed none that should have been coded to akathisia based on the available data."

Additionally, to evaluate whether investigators recognized akathisia and could differentiate it from anxiety and related symptoms, the sponsor conducted a post hoc analysis of maximal on-treatment BARNES (akathisia) scores in studies 004, 007 and 006, in patients having the following AEs: akathisia, anxiety, or restlessness/agitation (restlessness, restlessness aggravated, agitation, nervousness and irritability). (Appendix 2 of this review).

> *Comment: As per the August 1, 2007 response to an FDA informational request, the sponsor clarified that the neurologist's conclusions were based on the AE listings. The sponsor reported that they are confident that adverse event information in the CRFs is accurately reflected in the databases and AE listings, and that no verbatim terms were miscoded for studies 004, 006 and 007.*

However, if akathisia was incorrectly recorded as restlessness in the CRF, it would appear as restlessness in the listings.

Of note, a case coded as restlessness in the adverse event listings of study 004, was listed as akathisia among the comments in the UH file (a file that includes UHDRS scores) submitted with the original application in September 2005 (subject 447-236). The event reappeared in study 007 and this time it was coded as akathisia. Another patient who was reported to have sedation and depression in the adverse event listings, was reported to have mild akathisia in the UH file of September 2005 (447-267). Additionally, one patient with restlessness/agitation had a BARNES score of 4 (consistent with significant akathisia). On the other hand, several patients with an AE of akathisia had a BARNES score of 0 (see Appendix 2).

Comment: There is a disconnect between the BARNES scores and the reporting of adverse events of akathisia. In the absence of a more specific description of the adverse event, based solely on the listings and the analysis of BARNES scores, it is challenging to differentiate pure motor restlessness from true akathisia. In my opinion all cases that include the term restlessness should be considered potential cases of drug-induced akathisia.

As per the sponsor analysis presented in the Complete Response, twenty patients taking TBZ developed akathisia (5 in 004 and 15 in 007); none on placebo and none in study 006 developed akathisia. As per my analysis - that includes the two cases of akathisia listed in the UH file - a total of 20 patients had akathisia in studies 004, 007 and 006, including two patients who had events in both, 004 and 007 (ID# 236 and ID# 248). Four of these AEs were severe. Including the cases of restlessness as potential cases of akathisia, there would be 27 events in 25 patients.

The following table shows a summary of cases of akathisia and restlessness, along with the action taken, the outcome of the adverse event, and course of chorea scores in these patients in study 004. Cases found by the FDA reviewer are in *Italics.*

Table 3. Patients who developed akathisia or restlessness in study 004 (Total n=10)

ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])		
	Rel. day	Dose		Base line[1]	At week 7	At week 12
a. Akathisia (n=7)						
447-208	59	100	None / None / Recovered after washout on Day 92	12	14 (100)	16 (100)
447-229	19	50	None / None / Recovered after washout on Day 88 (also had AE of depression)	14	14 (87.5)	15 (100)
447-246	43	100	Drug d/c on Day 50 / Valium and Propranolol started on Day 50 / Pat. prematurely d/c due to akathisia. Recovered Day 71. Did not enter 007.	13	6 (37.5)	NA
447-248	50	75	Dose reduced / None /Recovered on Relative Day 63. Akathisia reappeared during 007 requiring withdrawal.	11	11 (75)	9 (37.5)
447-279	36	75	Dose reduced / None [Valium] / Recovered on Relative Day 38 (also had AE of depression)	11	8 (37.5)	9 (37.5)
447-236	*40*	*50*	*Dose reduced/Coded as restlessness in the AE listings, but recorded as akathisia in a different file.[2] Also had sedation. Restlessness resolved but reappeared in 007 and was coded as akathisia.*	*20*	*10 (50)*	*10 (37.5)*
447-267	*51*	*62.5*	*Dose reduced (for depression)/None/ Outcome of akathisia unknown. Not listed in AE file. "Mild akathisia" recorded in a different file.[2] Also had sedation.*	*19*	*14 (62.5)*	*8 (50)*
b. Restlessness (n=3)						
447-213	*47*	*87.5*	*Serious "restlessness/agitation" Dose reduction &hospitalization & multiple meds(including klonopin and restoril, aprazolam, lorazepam, beta blockers, bupropion and, secobarbital). Did not resolve. Patient discontinued because of psychosis, paranoid reaction and thoughts of self harm (as per concomitant med. file, he was treated for depression). Did not enter 007. Restlessness resolved 4 weeks after d/c.*	*19*	*10 (100)*	*NA*
447-217	*52*	*100*	*Dose reduction/Restlessness resolved day 75.*	*13*	*?*	*8 (87.5)*
447-238	*48*	*100*	*Dose reduction/Restlessness resolved day 68.*	*14*	*?*	*8 (75)*

Additional cases found by FDA reviewer are in Italics. ?= unknown. Rel. Day = Day relative to dosing Rel. day: relative day. Week 12: Rel. day 84; Week 24: rel. day 168; week 48: rel. day 336. d/c: discontinuation. NA: data not available; patient no longer in study. [1]For the baseline visit= 0 mg. Source: Modified from Table 11 submitted July 23, 2007 in response to June 14, 2007 FDA informational request, UHDRS file submitted September 2005 and Listing 1.2 and 1.16 of Appendix 4 of Complete Response.

Not included in Table 3 are two additional patients receiving TBZ:

- One patient who presented an AE of restlessness that resolved the same day, with no intervention and was able to continue titration up without further restlessness (447-275). This is clearly not a case of true drug-induced akathisia.

- One patient listed as having "restlessness inside", who was also noted to have apathy, be withdrawn from social contacts and obsessed with certain thoughts (447-285) and sounds more like a case of depression.

Patients who developed akathisia in study 007 are presented in Table 4.

Table 4. Patients who developed akathisia in study 007 (n=15)

Pat ID	AE Onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])					
				Base line[1]	After AE	At week			
	Rel. day	Dose				12	24	48	80
747-202	99	75	Dose reduced / None / Recovered on Day 142.[2] Treated with paroxetine for irritability and anxiety. D/c on Day 215 because of "exclusionary med" (aripiprazole) after a fall	15	7 (75)	12 (75)	7 (75)	NA	NA
747-207	29	50	Dose reduced / None / Recovered on Day 353	16	15 (37.5)	12 (12.5)	12 (25)	5 (12.5)	7 (12.5)[3]
747-219	151	200	Dose reduced / None / Recovered on Day 168	12	4 (150)	6 (200)	4 (150)	5 (150)	4 (50)
747-222	46	100	Dose reduced 4x between Days 46 and 55; dose suspension on Day 56/ Buspar increased on Day 53 / Following dose suspension x 10 days, Recovered on Day 65	21	10 (37.5)	19 (50)	14 (50)	8 (125)	25 (25)[4]
747-223	60	125	None[4] / None / Intensity increased to severe on Day 68. (also had depression)	15	11 (62.5)	11 (62.5)			NA
	68	150	Dose reduced / None / Recovered on Relative Day 171. Pat d/c early at request of caregiver	15	11 (62.5)		11 (75)	15 (50)	NA
747-225	515	50	Dose reduced / None / Recovered after washout on Day 589	16	16 (50)	4 (75)	7 (75)	9 (75)	16 (25)
747-236	26	25	None /None/ Recovered on Relative Day 358[2]	18	12 (37.5)	11 (50)	8 (50)	3 (62.5)	11 (37.5)
747-239	25	150	Dose reduced / None / Recovered on Relative Day 89	20	8 (125)	9 (62.5)	13 (62.5)	13 (50)	11 (62.5)
747-245	142	75	Dose reduced [5]/ multiple meds[6] / Ongoing at study end. Pat d/c Day 153 due to consent withdrawal. Akathisia resolved after 4 mo. (also had depression)	17	NA[7]	14 (62.5)	NA[7]	NA	NA
747-247	113	37.5	Drug discontinued on Day 114 / None / Ongoing at study end. Pat d/c due to depression and akathisia. Patient was lost to follow up after 1 week in 007.	14	10 (37.5)	7 (62.5)	10 (37.5)	NA	NA

Table 4 (cont). Patients who developed akathisia in study 007 (n=15)

ID	AE onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])				
	Rel day	Dose		Baseline	At week			
					12	24	48	80
747-248	163	50	Drug discontinued on Day 175/ Seroquel 25 mg started Day 175/ Ongoing at study end. Pat d/c on Day 175 due to akathisia and exclusionary med. Final BARNES scores= 3.	15	10 (50)	16 (50)	NA	NA
747-267	8	37.5	None / None /Recovered on Relative Day 39. Pat d/c on Day 459 due to obsessive reaction and depression.	21	13 (62.5)	7 (50)	12 (50)	NA
747-272	267	137.5	Drug stopped for akathisia on Day 280/ None/ Pt d/c due to moving out of state (last dose: Day 280)5, 7 (This patient also had depression) Recovered on Relative Day 332.	16	10 (125)	18 (125)	11 (137) (Day 280)	NA
747-273	32	87.5	Dose reduced/Alprazolam 0.25 mg PRN added/ Intensity reduced to mild on Day 60	15	14 (112)	13 (87.5)	13 (87.5)	NA
	80	125	Dose reduced/none/recovered on day 88. Pt d/c due to site unable to continue protocol past week 48.					
747-287	62	87.5	None/none/recovered on rel day 69	10	4 (200)	1 (150)	18 (150)	25 (75)

Rel. day: relative day; d/c: discontinuation. Week 12: Rel. day 84; Week 24: rel. day 168; week 48: rel. day 336. NA: not available; patient no longer in study. [1] Baseline dose = 0 mg. [2] Patient 747-202 and 747-236 Month and year but specific stop date for adverse event not specified. [3] Patient 747-207 experienced an AE of anxiety overlapping with akathisia. Patient discontinued study drug 1 day prior to Week 80 visit. [4] Patient 747-222 also discontinued study drug 1 day prior to Week 80 visit. [5]There were four severe cases: 747-223-, 245, 272 and 273. [6] Patient 747-245 was treated with Inderal, Amantadine & Klonipin; withdrew while event ongoing AEs. [7]Patient 747-272 stopped taking study medication after week 36 because of akathisia, but also had to move out of state and was unable to participate in the study. Source: Modified from Table 6, July 18, 2007 response to June 14, 2007 FDA request, UHDRS file of September 2005 and Listing 1.2 of Appendix 4 of CR.

Of note, five of the 15 patients who developed akathisia in study 007, also had depression during the study (ID# 747-223, 239, 245, 247, 267 and 272).

Not included in Table 8 is one case of restlessness/agitation (ID# 747-263) coincident with worsening chorea and insomnia on day 563 & 564 while on the 12.5 mg /day dose during the washout period. This was clearly not a case of drug-induced akathisia.

As per the AE listings of study 006, there were two cases of restlessness and no cases of akathisia in this study. It is unclear whether they underwent dose reduction or not; one resolved within 2 months (647-429), and one did not resolve (647-242).

- Analysis of response of akathisia/restlessness to dose reduction

A summary of the course of the 27 cases of akathisia/restlessness (10 in 004, 15 in 007 and 2 in 006) (in 25 patients) is presented in Table 5. In this table, patients who had an event that resolved in 004 and relapsed in 007 are counted twice.

Table 5: Course of akathisia/restlessness in studies 004, 007 and 006 (n= 27 events in 25 patients)[1]

Dose reduction	**20/27**	Patient ID
Resolved (2 days to 11 months after dose reduction)	**13**	*447*-279, 217*, 236, 238* & 248, *747*-202, 207[2], 219, 222, 223, 236, 239, & 273[3]
Did not resolve while on treatment	**7**	
Withdrew because of akathisia	4	*447*-246, *747*-247, 248 & 272
Withdrew because consent withdrawal	1	*747*-245
Withdrew because additional AE of psychosis and depression (restlessness resolved 4 months after discontinuation)	1	*447*-213*
Recovered after washout	1	*747*-225
No dose reduction	**5/27**	
Resolved one week to 11 months after onset of the AE	3	*747*-236[4], 267, & 287
Did not resolve while on treatment (Resolved within 1-2 weeks after washout)	2	*447*-208 & 229
Unknown action	**2/27**	
Resolved within 2 months	1	647-429*
Did not resolve	1	647-424*

[1] Events from two patients who recovered in 004 and reappeared in 007 (patient 236 and 248) are counted as separate cases. [2]Event started on day 29 and resolved on day 353. [3] This patient later discontinued because site unable to continue protocol past week 48. [4] Event started on day 26 and resolved on day 358.
* Cases coded as restlessness. Source: Table 6, July 18, 2007 response to June 14, 2007 FDA request, UH file of September 2005 and Appendix Listing 1.2 of Appendix 4 of CR.

Conclusions regarding akathisia:

- **Was akathisia dose related? Did it respond to dose reduction?**

The data suggest that akathisia was dose related but was not easily controlled with dose reduction.

The median dose at onset of the first event of akathisia/restlessness in 004 was 75 mg/day (range 50 to 100). The median time to onset was 48 days (range 19 to 59). No cases of akathisia/restlessness were seen at doses < 50 mg/day in study 004, however, there were three cases at doses < 50 mg/day in study 007 (one of whom had been on placebo in

study 004). The median dose at onset in 007 was 87.5 mg/day (range 37.5 to 200) mg daily. The final dose among patients who had developed akathisia in study 004 was 12.5 to 87.5 mg daily and in study 007 was 12.5 to 125 mg daily.

As per Table 5, 17 out of 22 cases of akathisia underwent dose reduction. Of those, 11 resolved (most took 1-2 months to resolve but one case resolved after 2 days and another resolved after 11 months). Two of these patients whose AE resolved in 004 (447-236 and 447-248) presented akathisia again in study 007. Of these two patients, akathisia resolved without dose reduction in patient 747-236 (although it took approximately 11 months to resolve) and led to study withdrawal in patient 727-248.

One patient in 004 and three patients in 007 discontinued because of akathisia. In addition to these four patients, two patients with ongoing akathisia discontinued because of consent withdrawal (747-245) and psychosis and depression (747-213); and three patients whose akathisia had resolved, withdrew before study completion for various reasons (patient 747-223 at the request of the caregiver; 747-273 because the site was unable to continue protocol past week 48 and 747-267 because of an obsessive reaction and depression with attempted suicide). Data on recovery after study completion or early withdrawal were missing for most patients. For patients with recovery data, akathisia resolved 1-2 weeks after washout and 4 months after early withdrawal.

- **Was akathisia recognized as a drug related AE**?

Some cases recorded under the verbatim term of "restlessness" were coded under the WHO term "akathisia" and others were not. One case of akathisia was coded as restlessness in the AE file and as akathisia in another file. Akathisia and restlessness were usually considered probably or possibly related to study drug. However, several cases did not undergo dose reduction. It could be that the investigators did not think of the possibility that the adverse event could get better with dose reduction or that they chose to tolerate some degree of akathisia in order to improve chorea.

- **What happened with chorea scores in patients with akathisia?**

It is hard to draw conclusions regarding the impact of dose reduction on the TCS of patients with akathisia/restlessness. In study 004 four out of seven patients who underwent dose reduction had a drop in TCS of ≥3 points, two had a drop of <3 points and one required discontinuation and is missing week 12 data. Two patients who did not undergo dose reduction had a worsening of their TCS at 12 weeks. Of the patients who underwent dose reduction and had 80-week data in study 007 (n=6), three had a drop in TCS of ≥3 points and three had a worsening TCS. Nine patients discontinued before week 80 for different reasons (Table 5). A few patients who developed an AE of akathisia achieved a drop in TCS ≥3 points at week 12 (2 out of 7 patients in 004 and 3/15 in 007).

> *Comment: The sponsor has proposed a RiskMAP to ensure appropriate titration to reduce the risk of "restlessness." I believe it is important to make clear that*

akathisia is an adverse event known to occur with dopamine antagonists that might be controlled with dose reduction but sometimes requires discontinuation.

2.1.2. Depression/worsening depression and suicidality

Depression and suicidality stand out as the most concerning adverse events associated with TBZ use. A total of 53 events of depression/worsening depression occurred in 47 patients enrolled in the Prestwick sponsored studies (47/111, 42%). Most cases were mild to moderate. Six of the 53 cases of depression/worsening depression were severe.

- In study 004, based on reported adverse events, the sponsor identified 8 patients who developed new (n=1) or worsening (n=7) depression in study 004. I identified two additional cases: Patient ID# 447-721, who had symptoms of depression before committing suicide, and patient ID# 447-213 who initiated mirtazapine for an indication of depression. Therefore, in study 004, a total of 10 out of 54 patients on TBZ had depression/worsening depression on TBZ (18.5%) versus no patients on placebo (0/30). In addition to the patient who committed suicide (447-271) and one had suicidal ideation (474-213).

The narrative of the subject who committed suicide is as follows:

> Participant 447-271. 40 year-old male randomized to TBZ. A diagnosis of HD had been made approximately 10 years earlier. He had no history of depression but reported suicidal ideation in the past. No concomitant meds at the time of enrollment. Seen for study visit #2 (week 3), he was taking TBZ 62.5 mg/day. TCS had dropped 14 points (from an initial score of 22). Total HAM-D score was 0, including 0 suicidal thoughts. Patient was seen for study visit #4 (week 7). He was taking TBZ 87.5 mg/d. Chorea score increased by 2 points but was still -12 points from baseline. HAM-D score was 1 due to early morning awakening. After this visit the patient decided to stop working because of his disability. After this decision his family noted that his mood and behavior changed dramatically; he was spending most of his time at home in his room and sometimes did not come out for meals. The study personnel were contacted by a family member to report his death by drowning. The investigator judged that the AE was possibly related to study drug.
>
> *Comment: despite the fact that depression was not reported to the site, the patient had signs of depression (being most of the time in his room and not coming out for meals) before committing suicide. Of note, the patient decided to stop working and apply for disability despite the fact that the chorea scores had markedly improved (from 22 to 10).*

Additionally, three TBZ patients received antidepressant treatment for the indications other than depression (ID# 447-248 received mirtazapine and 447-236 received trazodone for insomnia; ID# 447-313 received trazodone for anxiety) which could have masked symptoms of depression. One placebo patient received escitalopram for exacerbation of OCD, starting on day 29 (ID# 447-281).

A summary of the 10 patients who developed depression in study 004 is presented in Table 6.

Table 6. Patients who developed Depression in study 004 (n=10)*

ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])		
				Base line[1]	At week	
	Rel. Day	Dose			7	12
447-206[2]	4	25	None / Continued Celexa 20 mg from entry/ Ongoing when patient prematurely d/c due to subarachnoid hemorrhage. HAM-D one week after last dose was 5. Depression resolved one month after drug d/c.	14	NA	NA
447-228	62	50	None/ Re-start Paxil 40 mg on Day 65 (unclear why had been d/c) / recovered on day 85. [3]	11	8 (50)	8 (50)
447-229	82	100	None/ None / Recovered after washout on Day 92. (No prior hx of depression.)	14	14 (87.5)	15 (100)
447-231	24	62.5	Dose reduced (also had bradykinesia)/Continued Prozac 20 mg from entry/ Recovered on Day 40	19	9 (50)	12 12.5) [4]
447-244	50	37.5	None / Started Paxil 12.5 mg / Recovered after washout on Day 91	12	11 37.5)	10 37.5)
447-251	31	75	Dose Reduced / Increased Paxil from 20 to 40 mg on Day 36 / Recovered Day 62	10	2 (50)	2 (12.5) [3]
447-267	51	62.5	Dose reduced / Continued Paxil 40 mg from entry/ Recovered on Relative Day 58. Patient also had mild akathisia.[3] He later attempted suicide during extension study 007.	19	14 (50)	8 (50)
447-274[4]	7	37.5	None / Stopped Trazadone 200 mg on Day 16, restarted Trazadone (100 → 250) on Day 20 / Recovered on Relative Day 33	12	8 (87.5)	8 (62.5)
447-271	*50*	*87.5*	*None/No hx of depression but Hx of suicidal ideation. Patient committed suicide. Retrospective diagnosis of depression.*	*22*	*16 (87.5)*	*NA*
447-213	*69*	*12.5*	*None/ No hx of depression. Suicidal ideation listed in AE dataset. Dose had been reduced due to akathisia and later d/c due to paranoid reaction & thoughts of self harm. As per concomitant medication dataset, mirtazapine dose was started for depression on day 69, and increased on day 78 Outcome of depression is unknown.*	*19*	*10 (100)*	*NA*

- Cases identified by FDA are in *Italics.* Rel. Day = Day relative to dosing. d/c: discontinuation. [1] For the baseline visit, dose= 0. [2] Patient 447-206 was prematurely withdrawn due to an SAE of fall and subarachnoid hemorrhage. [3]Patients also had sedation. Source: Tables submitted July 18 and July 31, 2007 in response to FDA informational request of June 14, 2007.

Of note, three out of 10 patients who developed depression/worsening depression withdrew prematurely from the study (due to fall & subarachnoid hemorrhage, suicide and suicidal ideation). Three out of three patients who underwent dose reduction improved within 1 to 4 weeks after dose reduction (one of them also had an increase in the dose of antidepressant).

Not included in Table 6 is patient ID# 447-285, also on TBZ, who had symptoms suggestive of akathisia and depression/obsessive compulsive disorder. As per UH file submitted 9/05 she felt "restlessness inside" and apathetic, withdrawn from social contacts and "obsessed with certain thoughts." In the AE file, she was reported to be "listless" and "withdrawn." These AEs started 12 days into study 004 at the 100 mg/d dose and resolved 3 weeks after dose reduction.

- In study 007, 27 out of 75 (36%) patients had depression/worsening depression (seven of whom had no prior history of depression). One patient who had presented an AE of depression that resolved in study 004, attempted suicide in study 007 (ID# 747-231).

  Of the 27 cases of depression, 24 had a reported AE of depression/worsening depression and three had a change in antidepressant regimen (antidepressant started, added, dose increased, or switched) for an indication of depression (n=3, ID# 747-279 [Paxil on day 225]; ID# 747-314 [Trazodone on day 399] and ID# 747-225 [Zoloft on day 586 for OCD/depression]) even though there was no report of depression in the AE listing.

  Additionally, seven patients (9%) received antidepressant changes for indications other than depression as follows: OCD (ID# 747-227 [clormipramine]), irritability (ID# 747-299 [Zoloft]) and anxiety (ID# 747-202, 747-238, 747-249, 747-250 and 747-252 [Paxil]).

- In study 006, ten out of 29 patients (35%) had an adverse event of depression and two received antidepressants for indications other than depression.

  Of the ten cases of depression in 006, nine TBZ patients had a reported AE of depression and one underwent a change in antidepressant regimen for the indication of depression (ID# 647-403 increase in dose of amitriptyline) but it was not reported in the AE listing.

  In addition to these patients two TBZ patients received antidepressant treatment for indications other than depression (sleep disturbance [ID# 647-405], anxiety [ID# 647-425 on day#83]).

Summary tables of the cases of depression/worsening depression in studies 007 and 006 (with a format similar to Table 6) are presented in Appendix 3 and 4 of this review.

2.1.2.1 Discussion about depression and suicidality

In addition to one patient who committed suicide and one with suicidal ideation in 004, one patient who had depression in 004 attempted suicide in 007 (747-267) and two had suicidal ideation (647-430 and 747-262). Additionally, a suicidal gesture (00058 in study

011) and two cases of suicidal ideation (011/00557 and 011/00089) were reported in the Baylor Chorea studies (011). Additionally, a recent case of suicidal ideation has been reported to the IND, for a young patient enrolled in a TBZ protocol, after one dose of TBZ.

Depression is one of the cognitive/behavioral manifestations of HD. The lifetime prevalence of depression in patients with HD has been reported to be 39%,[3] with a rate of suicide between seven and 200 times (depending on the methodology) more often than in the general population.[4] Autopsy studies have reported suicide rates up to 13%,[5] although the most frequently cited average percentage is 5.7%.[6] Studies suggest that the risk of suicide in patients with HD is greatest at the time around the onset of HD and right after diagnosis of the disease, in stages 1 and 2. One study found that the rate of suicidal ideation was approximately 17% and 21% in stage 1 and 2 of the disease, respectively, but the rate seemed to diminished with advancing disease.[6] The nature of depression and suicidality in HD are poorly understood. It is unknown what proportion of persons with HD experience symptoms of depression secondary to biological changes in the basal ganglia and what proportion of persons are experiencing depression secondary to life stressors.[6]

The remarkable difference between the incidence of depression in the TBZ (18.5%) and placebo-treated groups (0%) is of concern.

To explore whether differences in baseline characteristics could have predisposed patients to a greater incidence of depression in the TBZ group, the sponsor evaluated the risk of depression in four different ways: history of depression; response of Yes on UHDRS question 38 at study entry ("Does the examiner believe that the patient is depressed?") which is considered indicative of "stable" depression (patients with unstable depression were not admitted into the study); Hamilton Depression Scale (HAM-D) score; and treatment with antidepressant at study entry (see Table 7).

Although at entry more patients had a reported history of depression, the HAM-D score at entry was similar for both groups (4.5 and 5.1 for TBZ and placebo group, respectively). Additionally, the number of patients taking antidepressant medications at entry was 56% for the TBZ group and 67% for the placebo group, which suggests that the previous/ current history of depression may have been under-reported in the placebo group. The list of antidepressant medications at entry in 004 is presented in Appendix 5.

[3] Shiwach. Psychopathology in Huntington's disease patients. Acta Psych Scand. 1994 (90).
[4] Paulsen et al. Critical periods of suicide risk in Huntington's disease. Am J Psychiatry, April 2005; 162:4
[5] Shoenfeld et al. Increased rate of suicide among patients with Huntington's disease. J Neurol Neurosug Psychiatry, 1984 (47).
[6] Hayden et al. Huntington's chorea on the island of Mauritius. S Afr Med J 1981 (60).

Table 7. Baseline measures of depression in Study 004

Baseline measure of depression	TBZ (N=54)	Placebo (N=30)
HAM-D score[1] Mean (SD) range	 4.5 (3.4) 0-14	 5.1 (3.9) 0-14
Patients treated with antidepressants at study entry[2]	30 (56%)	20 (67%)
Patients with past history of depression	34 (63%)	14 (47%)
Patients with Yes on UHDRS 38 at study entry[3]	8 (15%)	2 (7%)

[1]HAM-D: 17-item Hamilton Depression Scale; [2]Participants taking more than one medication are counted for each medication in the table. [3]UHDRS: Unified Huntington's Disease Rating Scale: a "yes" answer to this question ("Does the examiner believe that the patient is depressed?") is considered indicative of "stable" depression. Source, Table11, 004 CSR (Page 86 of 5596).

Given the known pharmacologic effect of TBZ (serotonin/norepinephrine depletion, although to a lesser degree than dopamine depletion), an increase in the rate of depression in patients taking TBZ as compared to placebo is not unexpected. The baseline characteristics regarding the risk of depression do not appear to be different enough to explain the dramatic difference in the incidence of depression and suicidality between the TBZ and placebo groups in study 004. In this study, seven of the 34 patients with prior history of depression developed worsening depression (21%), as compared to none of the 14 patients with history of depression randomized to placebo (0%).

- Dose and time at which patient developed depression

The doses associated with onset of depression were 25 daily and above. Evaluation of the course of depression during TBZ trials is difficult because in addition to decreasing the dose for depression or other AEs, the protocol allowed changes in dosing of concomitant medications and addition or change in antidepressant medications.

In study 004, events occurred 4 to 82 days into the study. The median time to onset of a first event of depression/worsening depression in study 007 was approximately 2 ½ months; however, some of these patients had been on TBZ and some had been on placebo in study 004. In study 006, the median time to onset of first event was 158 days. Therefore, the risk of depression goes beyond the first 12 weeks of treatment.

- Response to dose reduction/medical treatment

The course of cases of depression in studies 004, 007 and 006 are presented in Table 8. It is difficult to evaluate and summarize the response to TBZ dose reduction and medical treatment because the management of depression/worsening depression did not follow a pre-determined algorithm. Different investigators used different approaches. Even in the same patient, the approach was not always the same. In analysis presented in Table 8, patients who had one event that resolved but relapsed are counted twice.

Table 8. Course of cases of depression in studies 004, 007 and 006 (n=53[1]) (all on TBZ)

TBZ Dose reduction alone	**5 (9%)**	
Resolved while on TBZ (1-2 weeks)	**5**	*447*-231[3], 267[4], *747*-231[3], 237[5], 239
Change in antidepressant regimen alone	**28(53%)**	
Resolved while on TBZ treatment (within 1 week to 5 months after AE onset)	**8**	*447*-228, 274, *747*-217, 230, 252[3], 272[4], 316
Did not resolve	**14**	
Completed study (no recovery data)	11	*747*-207, 208, 210, 279, 209[3], 266[3], 288[3], 291[3,5] *647*-426, 428, 402
Completed study and recovered after washout (1 week)	1	*447*-244
Withdrew due to need for exclusionary meds and AE of chorea	1	*747*-203
Withdrew after suspension for delusional suicidal ideation	1	*647*-430
Unknown course[6]	**5**	
For indication of depression	4	*447*-213, *747*-225, 279, & *647*-403
For indication of OCD/depression	1	*747*-314
TBZ dose reduction + change in antidepressant regimen	**13(25%)**	
Resolved while on TBZ [2] (1 week-7 months)	**6**	*474*-251, *747*-243[7], 209, 266, 288 & 291
Did not resolve despite change in antidepressant Rx.	**7**	
Completed study	1	*747*-313
Withdrew because of adverse events or other reasons	6	
Withdrew consent (after 1 week of onset of depression)	1	*747*-245
Withdrew for depression and akathisia (after 2 months)	1	747-247
Withdrew for depression & suicidal thoughts (after 2.5 mo.)	1	*747*-262,
Withdrew for depression and psychosis (after 4.5 months)	1	*747*-267
Withdrew for akathisia/paranoid reaction/suicidal ideation	1	474-213
Withdrew because of caregiver preference (after 3 months)	1	747-223
Neither TBZ dose reduction nor change in regimen	**7(13%)**	
Resolved while on TBZ treatment (3-5 months after AE onset)	**3**	*647*-401, 418 & 419
Did not resolve while on TBZ	**4**	
Completed study (no recovery data)	1	*647*-414
Completed study and recovered after washout (1 week)	1	*447*-229,
Withdrawn due to fall & subarachnoid hemorrhage (resolved one month after drug discontinued)	1	*447*-206
Patient committed suicide (Retrospective diagnosis of depression)	1	447-271

[1] In 46 patients. Events from patients who recovered and relapsed are counted as separate cases. [2] Antidepressant regimen change: increase dose, start, add or switch to new antidepressant. [3]Subjects 447-231,747-209, 266, 288, 291 and 747-252 had events that resolved within 1 to 7 months but reappeared 3 to 7 months later. [4] 747-272 Later withdrew because of akathisia and moving out of state. [5] Recovery is after week 80 visit; unclear he was still on treatment or not. [6]Change in antidepressant regimen recorded in medication file but not in AE dataset. Duration and outcome for these events are unknown. [7] Later withdrew because of increased transaminases.

Of the 53 cases of depression/ worsening depression evaluated in this review, 9 % underwent TBZ dose reduction alone, 53 % underwent change in antidepressant regimen alone, 25% underwent both and 13% neither. Approximately 40% of the cases (21/53) resolved with dose reduction and or medical treatment, and the time to resolution was 1 to 7 months.

Five out of six patients who had depression/worsening depression that resolved with dose reduction and change in antidepressant regimen, relapsed 3 to 7 months later. One of these five patients was treated with the same approach (447-231) and recovered again, and four were treated with medical treatment and no dose reduction, with no resolution of the event (747-209, 266, 288 and 291). One patient who had two separate episodes of depression responded both times to dose reduction alone (747-252).

Approximately half of the patients who developed depression/worsening depression (25/46) had an ongoing AE of depression at the end of the studies and one fourth (12/46) had withdrawn for various reasons (mostly adverse event of depression). Of these patients (25+12), all but two (447-271 and 447-213, the patient who committed suicide and the patient with suicidal ideation, respectively) had a prior history of depression before entering the studies.

For the few cases with available data, recovery occurred 1 to 4 weeks after drug discontinuation. However, adverse event outcome after study completion or study withdrawal is not available for most patients.

> *Comment: TBZ dose reduction and/or change in antidepressant regimen appeared to be useful in the management of TBZ-associated depression. However, less than 50% resolved with dose reduction/treatment/ discontinuation. This analysis includes patients in the open label studies. Without a control arm it is impossible to distinguish whether these cases are part of the underlying disease or are drug related. Some experts recommend concomitant use of an antidepressant for prevention of depression/worsening depression in patients taking TBZ. However, the efficacy and safety of this approach has not been adequately studied.*

- Evaluation of HAM-D SCORES over time

During the course of the study, TBZ showed worsening of HAM-D scores as compared to placebo. Although both groups had a slight <u>decrease</u> on the 17-item HAM-D, those in the placebo group did so more.

Table 9. Mean change from baseline in total scores on the 17-item HAM-D in study 004

	Change from baseline to Average Wk 9 and 12 (SD)		P value
	TBZ	Placebo	
17-item HAM-D	- 0.48 (2.8)	-2.55 (3.56)	0.0031

Source: Table 62, study 004 CSR.

> *Of note, the difference in HAM-D scores was driven by the insomnia, agitation and anxiety components. Results of HAM-D scores are difficult to interpret in this application. Several patients underwent initiation or changes in their antidepressant regimen during the trial. Four patients initiated antidepressant medications for an indication of depression or other adverse events (e.g. anxiety or insomnia) in the TBZ group, as compared to one in the placebo group (for OCD). Additionally, the HAM-D has been validated for classifying disease severity in patients with Major Depressive Disorders. It may be inadequate to try to apply this score to patients with Huntington's disease.*

- Comparison of the rates of depression in patients with HD

I estimated the rate of depression in the Prestwick development program using the number of events found in my review as the numerator, and exposure data provided by the sponsor as the denominator (See Table 10). The rate of depression among HD patients treated with TBZ across studies was 2-7 fold higher than that of HD patients not treated with TBZ in the CARE HD study.

Table 10: Rate of depression/worsening depression in patients with HD in Prestwick-sponsored TBZ studies as compared to non-TBZ treatment.

Study Treatment Duration	**No. Patients**	**Treatment**	**Person-years**	**Sponsor's analysis**		***FDA analysis***	
				n	**n/ 100 PYRs**	***n***	***n/ 100 PYRs***
004 *12 weeks*	54	TBZ	12.2	8	65.5	*10*	*82.0*
	30	Placebo	7.0	0	0	*0*	-
007 *Up to 80 weeks*	75	TBZ	96.8	24	24.8	*27*	*27.9*
006 *48 weeks*	29	TBZ	25.5	9	35.3	*10*	*35.3*
CARE-HD[1] *Up to 3 years*	347	No TBZ	817	93	11.4	*93*	*11.4*

CARE-HD: Non-Prestwick study with the following treatment arms: Remacemide, Co $Q_{10,}$ placebo, Remacemide+ Co Q_{10}. PYRs: person years of exposure. Source: Modified from sponsor's analysis: Table 70 CR of April 2007. Exposure in PYRs: August 17, 2007 submission, upon FDA request for information.

In summary:

- **Was depression recognized as an AE?**

In general, depression was recognized by the investigators as potential TBZ-related AE. TBZ dose reduction was done in less than half of the cases and medical treatment was instituted in approximately 75% of cases. Six patients with a reported AE of depression/worsening depression had neither dose reduction nor medical treatment. Investigators may have preferred to tolerate mild depression over to decreasing the dose of TBZ and losing therapeutic benefit. However, in five of 53 cases, investigators initiated or increased doses of antidepressants for an indication of depression, without recording depression as an AE (one case in 004, three in 007 and one in 006). Occasionally, depression was considered by the investigator to be unlikely to be related to study drug (e.g. 447-228 and 244).

- **Was depression dose related? Did it respond to dose reduction?**

The median dose at the onset of the first AE of depression was 62.5 mg/day, in study 004 (excluding one patient who had undergone multiple dose reductions because of akathisia and was recorded to start treatment for depression at the 12.5 mg dose) and 75 mg/day, in study 007. However, worsening depression was observed at any dose, including the 25 mg dose, and as early as 4 days into the study.

Of the 53 cases identified in studies 004, 006 and 007, approximately 9% underwent dose reduction alone, 53% underwent medical treatment alone and 25% underwent both. Overall, 22 cases (40%) had resolution of the event with either dose reduction/change in antidepressant regimen or no intervention. The outcome is unknown for five patients who were recorded to have a change in antidepressant regimen for an indication of depression but not recorded to have an AE of depression.

Resolution took 1-7 months after dose reduction. Information on duration of the event after drug discontinuation (either because of completion of early withdrawal) is missing for most patients.

For patients with depression/worsening depression, the final dose by the end of week 12 in study 004 was 12.5 to 100 mg daily; three patients had discontinued (one subarachnoid hemorrhage, one suicide and one suicidal ideation). In study 007 by week 48, the doses ranged from 12.5 to 150 mg daily, but only 3 of the 24 patients with a reported AE of depression were taking doses above 100 mg/day. By week 80, 13 of these 24 patients had discontinued prematurely from the study.

- **What happened to chorea scores in patients with depression?**

Upon development of an adverse event of depression with or without dose reduction, chorea scores varied. Some patients had a small increase in chorea scores but others

stayed the same as before the event or continued to improve. Of the 3 patients with depression who underwent dose reduction in 004, all three recovered and had a drop in TCS of ≥ 3 points; however, one relapsed and attempted suicide in 007. Of the 12 patients with dose reduction because of depression in study 007, seven recovered and only two achieved a drop in TCS ≥ 3 by week 80.

The sponsor has proposed a draft RiskMAP to address the issue of suicidality. Briefly, they propose restricted distribution (only certain pharmacies with pharmacist specifically trained on the use of TBZ would be allowed to sell it); prescriber and patient registration; routine patient counseling and monitoring during titration; routine prescription surveillance during titration (with pharmacists' follow-up phone calls every four weeks for the first three months) and targeted education for physicians, special pharmacy staff, patient and caregivers, to assure slow titration and early identification of adverse events, including depression and suicidality.

The current proposal does not adequately address this issue, as the risk of depression might increase earlier than 4 weeks and extend beyond 12 weeks. Additionally, it is difficult to assess depression over the phone, and it is unclear who will be deciding whether titration should be continued or not. The Office of Surveillance and Epidemiology is conducting a detailed review of the proposed RiskMAP.

2.1.3. Dysphagia

Dysphagia is a complex syndrome involving oral, lingual and esophageal muscles. In HD patients with chorea, lingual, respiratory and laryngeal chorea as well as swallowing incoordination and esophageal dysmotility contribute to dysphagia. To ensure that all cases of dysphagia events were captured, the sponsor used an "expanded" definition of dysphagia which included "dysphagia" and "swallowing difficulties". Additionally, listings of events that could potentially be related to dysphagia such as choking, coughing and pneumonia were examined. However, these terms were not included in the analysis, if they were not accompanied by the term dysphagia or swallowing difficulty. With this approach, the sponsor found no new cases of dysphagia. I reviewed the verbatim terms that could suggest dysphagia or swallowing difficulties in the AE datasets for studies 004, 006, 007 and 011. (Datasets for 004 and 011 were submitted with the original application, September 2005; datasets for 006 and 007 were re-submitted on February 9, 2007 as part of the CR.) As per my review of AE listings and of 004 UH file, there was one additional case of choking in study 004 and three in study 007 that should have been accounted as swallowing difficulty.

Table 11. Patients who developed Dysphagia in study 004 (n=2 on TBZ ; 1 on placebo)

Patient ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])		
	Rel. Day	Dose (mg/day)		Baseline[1]	At week 7	12
447-240	23	62.5	Dose reduced / None /Recovered on Day 84, at 25 mg day dose (before down-titration began). Other AE's: decrease dexterity and balance difficulties, dysarthria, fatigue, lethargy. Did not enter 007.	15	18 (50)	17 (25)
447-224	*32*	*50*	*None/none/unknown. Not listed in the AE listings but it is a comment in the UH file of 9/05, coincidentally with a change in Dysphagia score from 1 to 2. Pt reported poor coordination & gait unsteady on day 25. Eventually, this patient was lost to follow up on day 7 of study 007, due to transfer to skilled nursing home.*	10	?	7 (50)
447-273	96	Placebo	None / None / Recovered on the same day. It was preceded by dyspepsia, nausea, vomiting, diarrhea and ulcerative stomatitis.	16	13 (Placebo	14 (Placebo)

** Case found by FDA reviewer.* [1] Baseline is 0. [2]On 12/09/03 (day 32) the investigator commented that the patient had "occasional choking that did not yet require swallowing studies or soft food." Source: sponsor's table 10, July 23, 2007 response to June 14, 2007 FDA request. UH file submitted September 9, 2005.

Of note, the dysphagia in the placebo case was a one day episode associated with other upper gastrointestinal symptoms (nausea, vomiting, dyspepsia, mouth ulcer) of unclear etiology. The cases in patients 447-224 and 447-240 were associated with other signs of TBZ toxicity; 447-240 lasted for a couple of months and resolved with dose reduction.

Patients who developed dysphagia in study 007 are presented in Table 12.

Table 12. Patients who developed Dysphagia in study 007 (n=6)

Pat ID	AE Onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])				
	Rel. Day	Dose		Baseline	At week 12	24	48	80
747-241	32	100	Dose reduced /None/ Recovered on Day 32. Patient completed chose to discontinue because of mild lethargy.	10	2 (87.5)	4 (87.5)	4 (50)	NA
747-249	335	75	Dose reduced /None/ Recovered on Day 358 (Week 48 visit).	10	3 (87.5)	2 87.5)	6 (37.5)	4 (25)
747-257	198	50	None / None / Ongoing. Hospitalized, feeding tube, pneumonia.	21	18 (50)	8 (50)	9 (50)	7 (50)

Table 12. (cont) Patients who developed Dysphagia in study 007 (n=6)

ID	AE onset			Total Chorea Score (dose [mg/day])				
	Rel day	Dose		Baseline	At week			
					12	24	48	80
747-242	*?*	*150*	*None (single episode of choking)*	?	? (150)	? (150)	? (100)	? (150)
747-265	*210*	*87.5*	*None. Choking started 7 months into TBZ treatment; no resolution patient also had worsening chorea*	?	? (87.5)	? (87.5)	? (87.5)	? (75)
747-273	*?*	*87.5*	*None/ This patient had several episodes of choking and saliva increased, starting on day 6. Dose was titrated down and up for other AEs (akathisia) (up to 125 mg at some point)*	*?*	*? (112.5)*	*? (87.5)*	? (87.5)	? NA[1]

Cases identified by FDA reviewer in the AE datasets are in Italics. Rel. Day = Day relative to dosing. Week 12: Rel. day 84; Week 24: rel. day 168; week 48: rel. day 336) Modified from Table 12, July 23, 2007, response to FDA June 14, 2007 informational request and Listing 1.2, Appendix 4 of CR. [1] As per Listing 1.2, the dose of TBZ was 0 at Week 49.

Of note, ID# 747-257 had a drop in TCS of 14 points, however, the patient developed dysphagia on day 198 and by the end of the study the dysphagia was ongoing, with the patient hospitalized with a tube feeding and pneumonia. Given the impressive improvement in TCS it is unlikely that dysphagia was due to worsening HD. A similar observation applies to ID# 647-403 and ID# 647-245. Both cases had an ongoing event of dysphagia along with a large drop in TCS scores at week 48 (17 and 9 points, respectively, See Table 13). Possible explanations for this observation are that despite a meaningful impact on peripheral disease TBZ has no effect on the progression of dysphagia, or that TBZ may actually induce/worsen dysphagia.

Table 13. Patients who developed Dysphagia in study 006

Patient ID	AE onset Rel. Day	Dose	Study drug action/medical Rx/AE outcome	Total Chorea Score (dose [mg/day])				
				Baseline				
				005[1]	006[2]	12	24	48
647-403	54	75	None / None / Ongoing at end, UPDRS dysphagia score was 1 (rare choking).	11	22 Off TBZ 4 days	13 (125)	10 (125)	5 (150)
647-424	−1	0	Dose reduced / None / Recovered on Relative Day 214. "Swallowing difficulty" began 3 days following withdrawal of tetrabenazine in Study 005 and was present at baseline in Study 006 (no change in severity).	15	22 Off TBZ 4 days	12 (37.5)	8 (37.5)	12 (37.5)
647-425	335	50	None / None / Reported on last day of study treatment and ongoing at study end. UPDRS dysphagia score was 2 (occasional choking)	7	14 Off TBZ 2.5 days	5 (37.5)	5 (50)	5 (50)

Rel. Day: relative day of onset. Week 12: Rel. day 84; Week 24: rel. day 168; week 48: rel. day 336) Modified from Table 11 of July 23, 2007, response to FDA June 14, 2007 informational request. Of note, dysphagia in patient 647-424 started during study 005; resolved 6 month after dose reduction in 006.

Subject # 647-424 actually developed dysphagia during TBZ withdrawal, in study 005. Dysphagia was present at baseline in 006. Dysphagia recovered seven months after dose reduction.

- Review of Dysphagia in study 011

To address concerns raised in the AE letter of March 2004, Prestwick asked Baylor to review "all sources documents for patients with documented dysphagia." Baylor confirmed that "dysphagia was reported as an AE in 22 out of 145 chorea patients in study 011."

> *This response does not adequately address the lack of systematic recording of episodes of dysphagia in the CRFs. Data on AEs from the Baylor Chorea study was collected retrospectively from chart review. There is no way to capture adverse events of dysphagia if they were not reported in the CRF.*

I conducted a review of potential cases of dysphagia in **Study 011 datasets** (submitted September 2005, data not shown). There were:

- 21 cases of dysphagia or choking – including 4 associated with pneumonia or aspiration pneumonia and 5 associated with sialorrhea/increased salivation. Thirteen of these cases had preexistent dysphagia and nine were severe.
- 4 cases of aspiration pneumonia with no report of dysphagia
- 1 case of pharyngeal spasms

Additionally, there were 7 cases of sialorrhea/increased salivation with no report of dysphagia.

Of the 21 cases of dysphagia, only two were considered possibly or probably related to TBZ and only three underwent dose reduction (n=1, reported recovery after 2 weeks) or discontinuation (n=2, no data on recovery). In the other 18 cases, dysphagia was thought to be either primary disease or concomitant disorder and did no undergo dose reduction. Some of these cases recovered and others relapsed. Data on starting and ending dates for the adverse event of dysphagia are missing in several cases in this database. (My analysis does not address the problem of lack of capture of dysphagia in the CRFs, but confirms that investigators rarely identified dysphagia as a potential drug-induced AE.)

- Cases of increased salivation/sialorrhea/drooling in TBZ studies:

Patients 447-274 (study 004), 647-425 and 647-410 (study 006), and seven patients in study 011 had adverse events of saliva increased/sialorrhea/sialorrhea increased. These terms suggest swallowing difficulty (of note, in study 011 several patients had and AE of sialorrhea along with dysphagia or choking), however, these terms could be symptoms of parkinsonism (dysphagia and drooling affects many patients with PD), worsening chorea, or drug effect (increased salivation is in the labeling for haloperidol, clozaril, quetiapine and olanzapine).

- Evaluation of Dysphagia Scores in study 004

For evaluation of dysphagia, in study 004, the sponsor used the UPDRS (Unified Parkinson's Disease Rating Scale) part II, dysphagia score. The score is as follows: 0= normal swallowing; 1= rare choking; 2=occasional choking; 3= requires soft food, and 4= requires NG tube or gastrostomy feeding.

The change from baseline for the UPDRS for TBZ (LOCF) was -0.27 +- 0.06 for TBZ and -0.12 +- 0.08 for placebo. (Data submitted August 1, 2007 upon FDA request). Additionally, I conducted a post-hoc shift analysis evaluating how many patients improved, got worse or had no changes in dysphagia scores in study 004. Most patients' scores fluctuated during the study. Of the patients on placebo, 6 (20%) got a worse score and 16 (53%) had a better score at some point during the study as compared to baseline. Of the patients on TBZ, 10 (18.5%) had a worse score and 27 (50%) had a better score at some point during the study as compared to baseline. Only 8 patients in the placebo group (26.7%) and 17 in the TBZ group (31.5%) maintained the exact same score during the 12 week study. Table 14 shows the shift analysis in dysphagia scores at the 12 week endpoint.

Table 14. Dysphagia scores in study 004

Dysphagia score	Baseline n(%)	At 12 weeks n(%)
TBZ		
0	20 (37)	33 (61)
1	32(59)	15 (28)
2	2 (2)	1 (2)
Missing	0	5 (9)
Placebo		
0	9 (30)	12 (40)
1	20 (67)	16 (53)
2	1 (3)	1 (3)
Missing	0	1 (3)

Source: Estimated from listings submitted on 8/1/07 upon FDA request.

As noted in Table 14, a slightly greater percentage of patients had a UPDRS dysphagia score of ≥1 in the placebo group (70%) as compared to the TBZ group (61%) at entry. The analyses of changes in the UPDRS dysphagia scores in study 004 suggests that TBZ did not have a deleterious effect on dysphagia; however, definitive conclusions can not be drawn, as patients were being tapered down and up according to other adverse events and final dysphagia score data are missing from five patients in the TBZ group.

Only two of the 16 patients who had worsening dysphagia scores (form 0 to 1 or from 1 to 2) were listed as having an adverse event of dysphagia (447-240 on TBZ and 447-273 on placebo). Additionally, one patient who had a change in score from 1 to 2 was recorded to have occasional choking in one of the datasets (UH file) but was not listed as an AE (447-224). This patient entered study 007 but was lost to follow up at week 7. As observed with other clinical scores, there was a disconnect between the dysphagia score and the reporting of dysphagia as an adverse event.

- Response to dose reduction

The course of the cases of dysphagia in the Prestwick-sponsored studies is presented in Table 15.

Table 15. Course of cases of dysphagia in studies 004, 007 and 006 in patients taking TBZ (n=11)

TBZ Dose reduction	**4**	
All resolved while on TBZ (1 day-7 months after dose reduction)	**4**	*474*-240[1], *747*-241[2], 249, *647*-424
No TBZ dose reduction	**7**	
Resolved while on TBZ treatment (single episode of choking)	**1**	*747-242*
Did not resolve	**5**	*747*-257[3], 265, 273 *647*-403, 425[4]
Unknown course		
Completed 004 but was lost to follow up in 007	**1**	*447*-224[5]

[1] Dysphagia lasted 1 ½ months and resolved on the last day of the 12 week study. Patient also had dysarthria, fatigue, lethargy, decreased dexterity and balance difficulties. [2] Recovered but chose to withdraw because of lethargy. [3] Event ongoing, patient had feeding tube and pneumonia at end of study. [4] Reported on last day of study. Outcome unknown. [5]Listed in UHDRS comment file; patient also had poor coordination and gait unsteady. Patient eventually lost to FU on day 7, upon entering study 007.

- Reporting rate of dysphagia with TBZ

Similar to the analysis of depression, the sponsor estimated the reporting rate of dysphagia in their development program and compared it with the rates in the CARE-HD study. Analyses of the rate of dysphagia in the Prestwick's development program are presented in Table 16.

Table 16. Rate of dysphagia in Prestwick-sponsored TBZ studies

Study Treatment Duration	**No. Patients**	**Treatment**	**Person-years**	**Sponsor's analysis**		***FDA analysis***	
				n	**n/ 100 PYRs**	***n***	***n/ 100 PYRs***
004 *12 weeks*	54	TBZ	12.2	1	8.2	*2*	*16.4*
	30	Placebo	7.0	1	16.2	*1*	*14.3*
007 *Up to 80 weeks*	75	TBZ	96.8	3	3.1	*6*	*6.2*
006 *48 weeks*	29	TBZ	25.5	3	11.8	*3*	*11.8*
CARE-HD *Up to 3 years*		No TBZ		32	3.9	*32*	*3.9*

PYRs: person years of exposure. Source: Sponsor's analysis: Table 70 CR of April 2007. Exposure in PYRs: August 17, 2007 submission, upon FDA request for information. FDA analysis: FDA review of dysphagia/swallowing difficulty/choking in studies 004.007 and 006 datasets submitted September 2005.

As per the sponsor's analysis, in study 004 the rate of dysphagia was higher in the placebo group as compared to the TBZ-treated group. As per my analysis, including the case of choking, the rates of dysphagia are about the same for TBZ and placebo groups.

The rate of dysphagia in patients taking TBZ in all Prestwick sponsored studies was higher than in the CARE HD study.

In summary:

- **Was dysphagia dose related? Did it respond to dose reduction?**

From the available literature the sponsor had identified that TBZ at doses >100 mg/day is associated with an increased risk of dysphagia. Because of the small number of cases in the placebo-controlled study and the lack of comparative data in the long term studies, it is difficult to determine whether the cases of dysphagia observed in this clinical program were drug-related.

Time to first episode of dysphagia/choking in 004 was 3-4 weeks for TBZ and 3 months for the case on placebo. In 007, dysphagia started 32 to 335 days into the study, at doses of 50 to 150 mg/day. No episodes of dysphagia or choking occurred at doses < 50 mg.

Four of the 11 patients with dysphagia/choking had dose reduction in the Prestwick sponsored studies. Dysphagia/choking resolved on the same day in one case (747-241), 1 month (747-249), 2 months (447-240) and 6 months (667-424) after dose reduction. For patients with available data, the final dose at which event resolved was 25 to 150 mg/day.

- **Was dysphagia recognized as a potential TBZ-related event?**

A total of 11 cases of dysphagia/choking were identified by the FDA reviewer in the Prestwick sponsored studies (2 on TBZ, one on placebo in study 004; 6 in 007 and 3 in 006). None of the cases of choking underwent dose reduction. Four of the cases of dysphagia underwent dose reduction and resolved (although it took up to 6 months to resolve for one case). Because of the concern raised in the AE letter of March 2004, I specifically evaluated potential AEs of dysphagia in 011. Dysphagia was rarely considered to be a drug related AE in study 011. Only 2 out of 21 cases of dysphagia/choking were considered to be possibly or probably related to study drug and only 3 underwent dose reduction. Moreover, there were four cases of aspiration pneumonia likely related to dysphagia without recorded dysphagia as an AE in these patients.

- **What happened with chorea scores after dose reduction?** It varied. Of the four cases with dose reduction, two had a drop in TCS of at ≥ 3 by the end of the study.

> *Comment: The sponsor acknowledges that dysphagia is a component of HD that it can also be caused by medications that reduce dopaminergic activity. However, the sponsor concludes that TBZ is not associated with an increased rate of dysphagia. Overall, it appears that dysphagia was not consistently recognized as a potential TBZ-related event by the investigators in this development program. The data in this application do not rule out an increased risk of dysphagia in patients treated with TBZ.*

2.1.4. Parkinsonism

By using an expanded definition of parkinsonism that included bradykinesia, parkinsonism and extrapyramidal disorder, the sponsor identified a total of five cases in study 004, two in 007 and three in 006. By reviewing the datasets for study 004, I identified three more cases, making a total of 8 cases of parkinsonism in study 004 (ID# 447 231, 447-233 and 447-240). I did not identify new cases from studies 006 and 007. Tables 17, 18 and 19 summarize the cases of parkinsonism in study 004, 007 and 006, respectively. The cases that I identified are presented in *Italics.*

Table 17. Patients who developed parkinsonism in study 004.* (n=8)

ID	AE Onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])		
	Rel. Day	Dose (mg/d)		Base line[1]	At week 7	At week 12
447-203	17	50	None / None / Intensity increased from Mild to Moderate D 24 and to Severe D 32	13	8 (50)	9 (37.5)
	32	75	Dose reduced (for sedation) / None / Intensity reduced to Mod on D 56	13		
	56	37.5	None / None / Recovered after washout on Day 90	13		
447-207	28	62.5	Dose reduced / None / Recovered on D 29. Developed akathisia during 007.	16	6 (50)	3 (25)
447-224	25	62.5	Dose reduced / None / Ongoing. AE was ongoing upon enrollment into Study 007. Patient was lost to follow-up after 7 days due to skilled nursing home placement.	10	6 (62.5)	7 (50)
447-236	18	50	None / None / Recovered on Day 45 (patient also had some akathisia & sedation)	20	10 (50)	10 (37.5)
447-263	50	87.5	Dose reduced / None / Recovered on Day 71	10	0 (87.5)	4 (50)
447-231	*?*	*?*	*None/none/"Bradykinesia worse" noted in UH file but not in AE listing. Dose reduced because of depression. Outcome unknown.*	*19*	*?*	*12 (50)*
447-233	*36*	*75*	*None. Patient had "increased stiffness when walking." that resolved after TBZ was stopped during washout. As per US file, pt was given a rolling walker. He was re-started on TBZ at doses up to 125 mg/day in 007, with no reported parkinsonism.*	*20*	*19 (100)*	*22 (87.5)*
447-240	*29*	*75*	*Dose reduced/none/resolved after dose reduction. Patient had "decreased dexterity" and "coordination abnormal" coded as "clumsiness" and "balance difficulty" along with dysphagia, fatigue and worsening dysarthria in AE listing. Did not enter 007.*	*15*	*18 (50)*	*17 (50)*

*Cases identified by FDA reviewer are in Italics (?= information not available). Rel day= relative day to dosing; d/c: discontinuation. Week 12: Rel day 84; Week 24: Rel day 168; Week 48: rel day 336. [1]Baseline dose = 0 mg/day. Source Modified from table 7 submitted July 23, 2007 in response to June 14, 2007 FDA request, and Listing 1.2 of Appendix 4 of the CR.

Of note, four of the 8 patients with parkinsonism in study 004 also had the following adverse events: sedation (1), akathisia (1), depression (1) and dysphagia/fatigue (1).

Not included in Table 3, are three cases that presented balance difficulties that could have been symptoms of parkinsonism, however, they could also be symptoms of worsening chorea. Without other AE terms that suggest parkinsonism or response to dose reduction, I am not including these patients in my analyses:

- Patient 447-223 developed "balance unsteady" and "gait unsteady" on day 38 of TBZ treatment, at the 75 mg dose. The gait/balance unsteady is listed as lasting one and a half months and resolving without dose reduction. These terms are consistent with but not specific of parkinsonism. This patient showed improvement in chorea scores at the end of the study, therefore the balance difficulty was unlikely to be due to worsening chorea. He had been recently started on carbamazepine for "agitation/anger." Unsteadiness is listed under the ADVERSE REACTIONS section of the carbamazepine labeling. Since the events resolved without dose reduction it may be incorrect to attribute to TBZ.

- Patient 447-237 presented "unsteady feet/balance difficulty" (listed as "ataxia" in the study dataset), on day # 45 of TBZ treatment, along with impaired concentration, insomnia, fatigue and "eyes burn". It is unclear if the AE resolved. This patient showed improvement in chorea scores at the end of the study (day #80), therefore the balance difficulty on day #45 is unlikely to be due to worsening chorea.

- Patient 447-313 reported prominent incoordination and balance loss while on TBZ on 1/8/04 (as per UHDRS file submitted September 2005). This AE is not listed in the Adverse Event listing. Listed AEs include akathisia, paranoid reaction and suicidal ideation.

Additionally, as per the UHDRS file, patient 447-314 on placebo had poorer balance but also worsening chorea; therefore the worsening in balance is unlikely to be parkinsonism.

Table 18. Patients who developed parkinsonism in study 007 (n=2)

ID	AE Onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])				
	Rel. Day	Dose (mg/d)		Base line[1]	Week			
					7	12	24	48
747-211	34	75	Dose reduced / None / Recovered on Relative Day 231 but parkinsonism reappeared at 25mg/d dose.	16		18 (50)	1 (37.5)	4 (25)
	345	25	Drug d/c on Day 350[2] / None / Unknown	16			?	
747-281	155	200	Dose reduced / None / Intensity decreased to mild on Day 169	11		7 (175)	2 (150)	6 (100)

Rel. Day = Day relative to dosing; d/c: discontinuation. Week 12: Rel. day 84; Week 24: rel. day 168; week 48: rel. day 336) [1]Baseline for studies 007 is 0 mg/day as patients were evaluated after washout prior to drug administration. Both patients were on placebo during study 004. [2] Patient's family member discontinued study drug. This patient had parkinsonism at the 75 mg dose that resolved 6 months later but reappeared with the 25 mg dose; as per the AE dataset, patient died of metastatic breast cancer and aspiration pneumonia. Source: Modified from table 9 submitted July 23, 2007 in response to June 14, 2007 FDA informational request.

Not included in Table 18 is patient ID#747-229, who had mask like facies and myoclonus, considered by the investigator to be probably related to study drug while on TBZ at the 175 mg/day dose, that resolved with dose reduction to 50 mg/day. This case may or may not be parkinsonism but it is consistent with drug induced extrapyramidal symptoms.

Of note, patient ID# 747-211 developed parkinsonism on Day 35, at the 87.5 mg/day dose. She recovered from parkinsonism after dose reduction on Day 231 (approximately 6 months later); however, symptoms reappeared soon at the 25 mg dose and she later died of metastatic breast cancer and aspiration pneumonia. The other patient developed parkinsonism on Day 155 (747-281) at the 200 mg dose. Symptoms of parkinsonism improved but did not resolve with dose reduction.

Adverse events of Parkinsonism in study 006 are presented in Table 19.

Table 19. Patients who developed parkinsonism in study 006

ID	AE onset Rel. Day	Dose	Study drug action/medical Rx/AE outcome	Total Chorea Score (dose [mg/day])				
				Baseline		At Week		
				005[1]	006[2]	12	24	48
647-402	375	150	None / None / Ongoing at study end, but UHDRS Parkinsonism score[3] at study end was 13 at study end vs. 21 at baseline.	25	27 Off TBZ 2.5 days	25 (75)	8 (125)	2 (150)
647-418	169	87.5	None / None/ Ongoing at study end, but UHDRS Parkinsonism score at study end was 8 at study end vs. 15 at baseline.	10	13[3] Off TBZ 4 days	16 (87.5)	16 (87.5)	15 (87.5)
647-419	-24	150[4]	Dose reduced[4] / None / Recovered on Relative Day 90.	5	12 Off TBZ 4 days	11 (100)	6 (100)	8 (100)

Rel. day: relative day of onset. Week 12: Rel. day 84; Week 24: rel. day 168; week 48: rel. day 336.
[1] Baseline Chorea scores from Study 005 are on tetrabenazine
[2] The baseline Chorea score for Study 006 was the Day 5 Chorea score from Study 005. As this was a staggered withdrawal study, patients were off TBZ from 1 to 4 days.
[3] UHDRS Parkinsonism score: Sum of UHDRS Items 6, 7, 9, 10 and 13-15.Patient 647-418: Day 5 Chorea score recorded as 15; Study 006 Baseline Chorea score recorded as 13
[4] AE began before study participation at dose of 150 mg/day and dose reduced to 100 mg/day upon entry into Study 006.Source: Table 8, July 23, 2007 response to FDA informational request of June 14, 2007.

Two patients (647-418 and 647-402) developed parkinsonism at doses of 87.5 and 150 mg/day, approximately 6 months and one year into the study. Although the parkinsonism did not resolve, the sponsor reports that both patients showed improvement in the Parkinson subscale of the UHDRS with dose reduction.

> *Comments: These two patients had high parkinsonism scores at entry to study 006 (15 and 21, respectively) however, adverse events of parkinsonism were noted only five months and one year into the study, respectively. There seems to be a disconnect between parkinsonism scores and adverse events of parkinsonism.*

Patient ID# 647-419, actually developed parkinsonism 24 days before participation in Study 006, while the patient was receiving tetrabenazine 150 mg per day through an investigator IND at Baylor before entering Study 005. The patient was off tetrabenazine for 4 days, due to the withdrawal procedures of Study 005, before entering Study 006. On study entry, the tetrabenazine dose was reduced to 100 mg per day and the parkinsonism resolved on Study Day 90.

- Response of parkinsonism to dose reduction

The course of parkinsonism in response to dose reduction is presented in Table 20.

Table 20. Course of cases of parkinsonism in studies 004, 007 and 006 (n=13)

Dose reduction[1] (3 for either sedation, depression or dysphagia)	**9/13**	Patient ID
Resolved (1 day to 3 months after dose reduction)	**4**	*447*-207, 263, 240, & *647*-419
Did not resolve with dose reduction	**4**	
1 resolved but reappeared at a lower dose; family stopped TBZ. Patient died from an unrelated condition (breast cancer)	1	*747*-211
1 decreased in intensity but did not disappear	1	*747*-281
1 case was ongoing at the time of enrollment into 007 but outcome unknown. Lost to fu. when admitted to a nursing home facility.	1	*447*-224
1 decreased in intensity but only resolved after stopping TBZ during washout.	1	*447*-203
Unknown response to dose reduction.[2]	**1**	*447*-231
No dose reduction	**4/13**	
1 resolved without dose reduction (after 4 weeks)	**1**	*447*-236
2 had decreased intensity of the event	**2**	*647*-402, 418
1 resolved after stopping TBZ during washout	**1**	*447*-233

[1] Three had dose reduction because of sedation, depression or dysphagia. [2]"Bradykinesia worse" is listed in the UHDRS file submitted September 2005, but it is not listed in AE dataset. Dose was reduced because of depression but there is no mention of the course of bradykinesia.

Conclusions about parkinsonism:

- **Was parkinsonism recognized as a TBZ-related AE?**

In general, investigators considered parkinsonism-related events as probably or possibly related to study drug, however, they often chose not to reduce dosing in order to decrease chorea scores. Dose was reduced in 9 out of 13 cases, however, in three of the cases dose reduction was made not because of parkinsonism, but because of other AEs. In other cases, despite the lack of resolution of the AE with dose reduction, some investigators preferred not to reduce the dose further (ID# 447-203).

- **Was parkinsonism dose-related?**

The mean and median time to onset of the first event in study 004 was 29 days (range 17 to 50 days). Mean and median dose at the onset of the first event in study 004 was 66 and 62.5 mg/day, respectively. All cases occurred at doses of 50 mg/day or above (except for

a couple of patients who had recurrence of the event at doses of 25 and 37.5 mg/day). Parkinsonism also occurred in the long term open label studies, at doses of 25 to 200 mg daily.

Four cases resolved with dose reduction (1 day to 3 months later) and one without dose reduction (within 4 weeks) and four cases did not. Two cases resolved after stopping TBZ during washout. The outcome of the patient who did not enter 007 and the one who was lost to FU in 007 is unknown.

The final dose among patients who had presented parkinsonism in study 004 was 25-50 mg daily.

- **What happened to the Total Chorea Score?**

  It varied. Some patients maintained a response, some got worse and some improved the chorea score despite decreasing the dose of TBZ. In general, chorea scores after the AE event were still improved as compared to baseline. Patients who had not responded at a higher dose did not respond when the dose was tapered down. In study 004 five out of 8 patients with parkinsonism underwent dose reduction. Of these, four had a drop in TCS ≥3 by the end of the study and one did not.

2.1.5 Analysis of Extrapyramidal Symptoms (EPS)

Akathisia and parkinsonism are part of a larger category of adverse events: the extrapyramidal symptoms (EPS), which also include tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, abnormal gait, involuntary muscle contractions, hyporeflexia, and extrapyramidal disorders. Notwithstanding the fact that some of these abnormal movements may also be manifestations of worsening chorea, an analysis of all potential extrapyramidal symptoms in study 004 is presented in Table 21.

Table 21. Potential extrapyramidal symptoms (EPS) in study 004

	TBZ (25-100 mg/day) N=54 n (%)	Placebo N=30 n (%)
Akathisia/restlessness[1]	11	-
Akathisia	7	
Restlessness	4	
Bradykinesia[2]	4	-
Clumsiness/balance difficulty[3]	1	-
Dystonia[4]	1	1 (3.3)
Gait unsteady/balance difficulty[5]	2	-
Parkinsonism	1	-
Stiffness when walking[6]	1	-
Unsteady feet/Balance difficulty[7]	1	-
Incoordination/balance loss[8]	1	-
All	22 (40)	1 (3.3)

n= number of patients with events [1] Given the inability to separate pure motor restlessness from akathisia in patients with HD, these terms are analyzed together as akathisia/restlessness (for listing see Table 4 of this review). [2] Three of these cases were identified as parkinsonism by the sponsor (ID# 203, 236 [also akathisia] and 263), and one was not, but was listed as "bradykinesia worsen" in UH file (ID# 231). [3] This case was not identified as parkinsonism by the sponsor (ID# 240). [4] Patient ID# 249 on TBZ and ID# 250 on placebo. Both were coded as "increased dystonia." [5] One case was identified by the sponsor as parkinsonism (ID# 224) and one was not (ID# 223). [6] This case was identified by the FDA reviewer as parkinsonism (ID# 233). [7] ID# 447-237 had other symptoms of TBZ toxicity. [8]I D#447-313. Source: Listing 1.16. Appendix 4, Complete Response and study 004 UH file submitted September 2005.

All four cases of balance difficulty occurred in the TBZ-treated group. If we do not take into account the cases of "balance difficulty", we still have 16 cases (29.6 %) of potential EPS in study 004.

> *Comment: EPS is a common adverse reaction observed with dopamine antagonist therapy, and therefore, not unexpected to occur with TBZ. Approximately one third of patients developed abnormal movements consistent with EPS in the TBZ group, as compared to 3% on placebo. EPS appeared to be dose-related (most cases occurred at doses >50 mg) and to respond (partially or completely) to dose reduction or discontinuation (although it might have taken several months).*
>
> *HD patients have an impaired subjective experience of chorea.[7] I share the concerns of one expert who states "It would seem inappropriate to treat an aspect of motor disorder of which the patient is unaware with agents that may worsen those aspects of motor dysfunction for which the patient does have awareness and are associated with greater functional disability [bradykinesia]".[8]*

[7] Cudkowicz, Martin and Koroshetz. Chapter 23. The neurololgy of Huntington's Disease. Movement Disorders in Neurology and Neuropsychiatry. Second Edition. Blackwell Science, Inc., 1999.
[8] Snowden et al, Arch. Neurol. Awareness of involuntary movements in Huntington's Disease. 1998; 55:801-805.

2.1.6 Other safety issues

Other safety issues associated with TBZ therapy are mentioned as follows. All these issues could be addressed in labeling.

2.1.6.1 Sedation

In study 004, 17 patients (32%) had an AE of sedation (including the term sedation, somnolence, sleepiness, drowsiness, lethargy) in the TBZ group as compared to 1 in the placebo group (data not shown, source: listing 1.26, Appendix 4, CR). Sedation was the most common adverse event that led to dose reduction; 12 patients had their dose reduced because of "sedation" (Table 31 of study 004 CSR -Total chorea scores as function of TBZ dose in participants in whom study drug was reduced due to sedation).

Sedation was clearly dose-related and resolved in all cases with dose reduction. Most of these patients maintained a drop in TCS of ≥3 despite dose reduction to doses ≤50 mg/day.

2.1.6.2 Falls/traumatic injury

Chorea of the trunk and legs along with poor postural control cause gait instability and increases the risk of falls and serious injury; however, many patients with HD may have a gait abnormality that is separate from chorea. Unexplained falling is common even early in the illness[9] By controlling chorea, TBZ could potentially reduce the incidence of falls and serious injuries. On the other hand, since TBZ is associated with sedation, parkinsonism and akathisia, it could potentially increase the risk of falls and injury by these mechanisms. Evaluation of Gait Scores in study 004 (which was one of the secondary efficacy endpoints) showed no benefit on gait for TBZ as compared to placebo.

Evaluation of the adverse event listing in study 004 shows that the total number of traumatic injuries in the TBZ group is 10 (18.5 %) as compared to 4 (13%) in the placebo group. (This analysis includes two patients in the TBZ group who had adverse events consistent with traumatic injuries, without a reported fall.) Moreover, three patients in the TBZ group reported several separate fall episodes throughout the study (up to five separate falls in one of these patients). No patients on placebo reported multiple falls. Falls and traumatic injuries did not appear to be dose-related (see Table 22).

[9] Cudkowicz M. et al. Chapter 23, The Neurology of Huntington's Disease. Movement Disorders in Neurology and Psychiatry. Second Edition. Blackwell Science Inc., 1999.

Table 22. Patients with adverse events suggestive of traumatic injury in study 004[1]

Tetrabenazine (N=54) n=10 (18.5 %)[1]			Placebo (N=30) n= 4 (13%)[2]	
ID# (day #)	Adverse event	Onset	TBZ dose (mg/day)	ID# (day#)	Adverse event	Onset
206-	Fall & subarachnoid hemorrhage	13	25	209-	Fall & wrist sprain	15
224-	Fall & head & face injury[3]	38 & 85	50	241-	Fall & chipped bone left ankle	42
228-	Fall & knee & arm bruises[4]	8 & 29	25-37.5	273-	Fall	17
229-	Fall[5]	13	37.5	298-	Fall & facial bruise	30
238-	Fall & scalp laceration	82	75			
251-	Fall & black eye	17	50			
258 -	Fall & eye ecchymosis	8	37.5			
274-	Fall & sacral pain[6]	6 & 96	25-87.5			
207-	Laceration of head[7]	35	25			
264-	Ankle fracture	81	50			

[1]In addition one patient who had a traumatic injury because he was assaulted is not included in this table. [2]In addition one patient on placebo who fell off his bike is not included in this table. [3]Reported three different fall episodes at this dose. Dose had been reduced from 62.5 for parkinsonism. [4]Reported two different fall episodes. [5] Increased chorea and truncal dystonia. [6]Reported five different fall episodes throughout study 004. He had depression and apathy. [7] Dose had been recently reduced from 62.5 mg/day for parkinsonism.

Therefore, in the small placebo-controlled study, TBZ did not reduce the risk of traumatic injuries as compared to placebo. They did not seem to be dose related, as several events occurred at the 25 mg/day dose. In study 007, 22 out of the 75 subjects had one or more falls. Most of these falls occurred in patients with reported AE of sedation, akathisia or depression and two were associated with worsening chorea.

2.1.6.3 Tardive dyskinesia (TD)

TD is characterized by involuntary movements of the tongue, jaw, trunk, or extremities in association with the use of neuroleptic medications. No cases of TD were reported in studies 004, 006 and 007, however, one patient was reported to have "uncontrollable movements of the mouth and tongue" in study 011 (103-011-529).

2.1.6.4 Hyperprolactinemia

TBZ is associated with increased prolactin levels as compared to placebo. This issue was raised in Dr. McNeil's first cycle review. She was concerned about the risk of osteoporosis. Hyperprolactinemia is known to occur with most antipsychotics (dopamine antagonists) and not unexpected to occur with a dopamine depleting agent.

2.1.6.5 Neuroleptic Malignant Syndrome (NMS)

NMS in association with TBZ has been reported in the literature[10] and as postmarketing reports to non-US regulatory agencies.

[10] Ossemann et al. tetrabenazine as a cause of neuroleptic malignant syndrome Mov Disord 1996;11(1).

2.1.6.6 Lack of data on concomitant use of antipsychotic medications

HD is known to be associated with behavioral and psychiatric disorders. None of the Prestwick sponsored studies allowed use of antipsychotic medications.

2.1.6.7 QTc prolongation

Mild prolongation of the QTc interval was identified in study 015 (a Thorough QTc study) in a prior review by the Clinical Pharmacology reviewer (Sally Yasuda, Ph.D.). These findings are summarized as follows:

"The maximum time-matched placebo-adjusted change from baseline in the QTcI was 3.6 and 7.7 msec with an upper confidence interval of 6.2 and 10.4 msec for TBZ 25 mg and TBZ 50 mg, respectively."

The reviewer felt that the study had not reached the maximum possible exposure to TBZ. At the time of this review, the issue of QTc prolongation with TBZ is still being evaluated.

2.1.6.8 Drug Interaction issue

Study 107,018 evaluated the effect of CYP2D6 inhibition in the presence of paroxetine, a strong CYP2D6 inhibitor. For α-HTBZ there was an approximate 1.3x increase in Cmax and an approximate 3.2x increase in AUCinf after administration of repeated doses of paroxetine. In addition, there was an approximate 2x increase in the elimination half-life (from approximately 7 to approximately 14 hours) in the presence of a strong CYP2D6 inhibitor. For β-HTBZ the Cmax was approximately 2.4x greater and the AUCinf 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 (approximately 4.5 vs. approximately 13.5 hrs). In addition, 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 observations raise concerns as patients taking strong CYP2D6 inhibitors or patients who are CYP2D6 poor metabolizers will have substantially increased exposure to α- and β-HTBZ. At the time of this review, this issue is still being evaluated by the Office of Clinical Pharmacology.

2.1.7 2005 Periodic Safety Update Report (PSUR) to non-US regulatory authorities

The latest PSUR submitted to non-US regulatory authorities on December 19, 2005, covers the period form June 2000 to October 2005. The adverse event profile of TBZ in this PSUR is consistent to what have been observed in the clinical studies reviewed as part of this NDA application.

2.2 Evaluation of dose-response relationship and benefit/risk assessment

An extensive review of the efficacy and safety of TBZ was conducted by Drs. Carole Davis and Elizabeth McNeil during the first review cycle. As mentioned in previous reviews, evaluation of the safety of TBZ is hampered by the following factors:

1. There is only one placebo-controlled study of 12 weeks duration (study 004)
2. Some of the adverse reactions associated with TBZ are also symptoms of or difficult to distinguish from the underlying disease (e.g. depression, dysphagia)

The sponsor recommends starting TBZ at the 12.5 mg twice a day dose with slow titration up over 12 weeks, to a maximum effect or to a maximum dose of 100 mg day.

Published literature over the past 40 years of TBZ use reports wide inter individual differences in the doses that cause dose-limiting side effects, as well as the "best dose", with a narrow difference between the dose that is effective and the dose associated with intolerable toxicity. Prior to study initiation, the sponsor had determined from a review of the literature that the common AEs related to monoamine depletion were thought to be dose-related and could be remedied by judicious dose titration. Events which were thought to fall in this category were sedation, depression, parkinsonism, akathisia, anxiety, nervousness, insomnia, irritability, confusion, increased salivation, nausea, vomiting, dizziness an diaphoresis. As per the sponsor's assessment, the risk for dysphagia was increased with doses greater than 100 mg/day. [11]

The studies in this application used a flexible dose design with dose titration to maximum drug effect or presence of adverse events (to a maximum dose of 100 mg/day in study 004, and 200 mg/day in 006 and 007). The flexible study design and the lack of a systematic approach in the presence of AEs makes very difficult to interpret the dose-response relationship, particularly in terms of toxicity in this NDA. Despite these difficulties, there seems to be evidence for a dose-response in terms of both, efficacy and toxicity (see sections 2.1.1 to 2.1.3).

2.2.1 Exploratory analyses of efficacy

An analysis by the FDA Office of Biometrics indicates a significant dose-response relationship in terms of efficacy. For details about the methodology of this analysis the reader is referred to Dr. Gubburu's review of March 20, 2006.

Additional analyses suggest that patients with the highest TCS at entry were the ones to benefit the most from TBZ (Table 23).

[11] Dr. Elizabeth McNeil's first cycle review of NDA 21-894, March 3, 2006.

Table 23. Adjusted mean (±SD) in Change from baseline in Total Chorea Scores (TCS) by baseline TCS.[1]

Total Chorea Score at baseline	TBZ (N=54)		Placebo (N=30)	
	N (%)	Adjusted mean change	N (%)	Adjusted mean change
>14	22 (41)	-7.35 ±0.98	13 (43)	-2.99 ± 1.25
≤ 14	32 (59)	-2.98 ± 0.67	17 (57)	-0.73 ± 0.86

[1]Nominal p value <0.05 for both analyses. Source: Table 19, study 004, Sponsor's Complete Study Report.

On the other hand, patients with the lowest functional impairment appeared to have less deleterious effects on the Functional Assessment score (See Table 23, also provided by the sponsor, but with a different format/analysis).

Table 24. Mean Change in Functional Assessment Score from baseline to week 12, by baseline FA severity.[1]

Baseline FA	TBZ (N=54)		Placebo (N=30)		Unadjusted effect size
	N	Mean change	N	Mean change	
Tertile 1 (≤17)	19	-0.26	7	1	-1.26
Tertile 2 (18-21)	15	-0.47	11	0.27	-0.74
Tertile 3 (≥ 22)	13	-0.54	11	0	-0.54

Note: higher scores on FA are associated with better function. Source: Table 35., Vol 48, Complete Response (February 9, 2007). Overall baseline score for FA was 18.8 ± 4.4 for TBZ and 19.6 ± 3.8 for placebo (Source Table 12, study 004 Complete Study Report).

TBZ treated patients who experienced an AE of sedation (including the terms sedation, drowsiness, sleepiness and lethargy) had a greater decline in Functional Assessment (-0.82 points) as compared to those who did not experience sedation-related events (-0.17), and compared to patients on placebo (0 to +0.36). The data suggest that sedation may be contributing to the small decline in Functional Assessment.

Table 25. Changes in Functional Assessment scores by presence of sedation[1]

	TBZ (N=54)		Placebo (N=30)	
Patients with	Sedation N=17	No sedation N=37	Sedation N=1	No sedation N=29
Mean (SD) change in FA	-0.82 (2.3)	-0.17 (2.04)	0 (0)	0.36 (1.13)

Source: July 18, 2007 response to June 14, 2007 FDA informational request. [1] Includes sedation, somnolence, sleepiness, drowsiness, lethargy, for patients with baseline and Week 12 data. FA: Functional Assessment (Domain 4 of the UHDRS, includes 25 questions)

A similar exploratory analysis of changes in Total Chorea Scores by the presence of sedation showed a greater reduction in chorea score (by approximately 2.1 points) among TBZ-treated patients with sedation related AEs (See Table below).

Table 26. Changes in Total Chorea Scores by presence of sedation[1]

	TBZ (N=54)		Placebo (N=30)	
Patients with	Sedation N=17	No sedation N=37	Sedation N=1	No sedation N=29
Mean (SD) change in Total chorea score	-6.65 (5.20)	-4.55 (4.11)	-3.00 (0)	-1.00 (3.8)

Source: July 18, 2007 response to June 14, 2007 FDA informational request. [1] Includes sedation, somnolence, sleepiness, drowsiness, lethargy, for patients with baseline and Week 12 data. FA: Functional Assessment (Domain 4 of the UHDRS, includes 25 questions)

2.2.2 Exploration of dose response in terms of toxicity

Dose toxicity response for akathisia, depression, dysphagia and parkinsonism have been discussed in detail under sections 2.1.1 to 2.1.4 of this review. Sedation is briefly discussed under section 2.1.6.1. These analyses are very suggestive of a dose response relationship in terms of toxicity. In study 004 the median dose at onset of the first event of akathisia, depression and parkinsonism was > 50 mg/day (75 mg/day for akathisia and 62.5 mg/day for parkinsonism and depression [although some cases of depression occurred at doses <50 mg/day]). No cases of dysphagia were reported at doses <50 mg/day. Sedation appeared at doses <50 mg doses but it clearly responded to dose reduction.

A formal assessment of the dose-response relationship is confounded by time (because of the flexible dose design) and hampered by the fact that not all patients with an AE underwent dose reduction. Modeling analyses of dose response conducted by the FDA Office of Pharmacometrics showed a trend for a greater decrease in Functional Assessment scores with higher doses of TBZ, but there did not seem to be evidence of a dose response for parkinsonism scores, sedation scores and cognitive scores. For details the reader is referred to Dr. Bhattaram's review.

2.2.3 Exploratory analyses of dose response relationship in terms of both, efficacy and safety

An exploratory analysis of the dose achieved at week 12 in study 004 indicates that 21 of 54 patients (39%) were on 100 mg/day and 11 (20%) were on 50 mg/day. Fifteen percent were on doses <50 mg/day and another 15% were at doses in between 50 and 100 mg/day. (Source: Listing 1.2, Appendix 4, February 9, 2007 CR).

Evaluation of the number of patients who achieved a drop in TCS ≥3, at week 12 shows that **10 out of 11 patients (91%)** who ended up at the 50 mg/day dose achieved a drop in TCS ≥3, as compared to **17 out of 29 patients (59 %)** who reached doses of 62.5 to 100 mg/day. Patients with a drop in TCS ≥3 are referred to as "responders" because this change was pre-defined as a clinically meaningful effect in chorea by HD experts in the study Steering Committee.

Table 27 lists subjects who reached the 100 mg dose and were responders at the end of the study (11 out of 21= 52%).

Further post-hoc evaluation of these patients shows that **7 of those 11 patients already had improved ≥3 points at the 50 mg dose** at week 3. The increase to 100 mg/day dose in these patients was associated with a further improvement in chorea score for eight patients, a worse chorea score for two patients and AEs that were likely drug-related (balance difficulty, sedation, concentration impaired difficulty and sedation/fatigue) for four patients.

Table 27. Chorea scores in patients who reached the 100 mg/day dose and achieved a change in chorea score of ≥3 points at week 12

Pt ID	Chorea baseline	Dose Wk 03	Delta Wk 03	Dose Wk 07	Delta Wk 07	Dose Wk 12	Delta Wk 12	AE (dose, mg/day)
447-210	15	50	-7	100	-9	100	-11	Somnolence (50)
447-223	16	50	-6	100	-2	100	-5	Balance difficulty (75)
447-227	15	50	-4	87.5	-8	100	-6	Sedation (75) Obsessive reaction (100)
447-237	13	50	-4	87.5	-5	100	-7	Concentration impaired, balance difficulty, insomnia (100)
447-242	17	50	-3	100	-4	100	-5	-
447-243	14	50	-5	100	-8	100	-9	-
447-249	11	62.5	-1	100	-1	100	-3	-
447-265	21	50	-10	87.5	-17	100	-16	-
447-268	20	62.5	-7	100	-4	100	-4	Upper respiratory infection (75)
447-275	15	50	-5	100	-10	100	-9	Sedation, fatigue (75)
445-297	14	62.5	-4	100	-6	100	-7	Anger outburst (25)

Source: Listing 1.2, April 2007 CR.

Table 28 lists subjects who reached the 50 mg dose and were responders at the end of the study (10 out of 11= 91%). **Six of these 10 patients had shown a drop in TCS score ≥ 3 points** at week 3 at doses up to 50 mg/day and could not proceed with titration up because of dose related adverse events. However, they still achieved a reasonable improvement at the 50 mg dose.

Table 28. Chorea scores in patients who reached the 50 mg/day dose and achieved a change in chorea score of ≥3 points at week 12 (n=10 out of 11 patients on 50 mg/day)

Pt ID	Chorea baseline	Dose Wk 03	Delta Wk 03	Dose Wk 07	Delta Wk 07	Dose Wk 12	Delta Wk 12	AE at ≤50 mg/day *(AE at other doses)*
447-214	20	37.5	-9	50	-11	50	-10	Drowsiness
447-224	10	50	-4	50	-3	50	-3	Fall *(Parkinsonism at 62.5)*
447-228	11	37.5	0	50	-3	50	-3	Dizziness, fall, depression
447-231	19	50	-6	50	-10	50	-7	- *(Depression at 62.5)*
447-251	10	50	-2	75	-8	50	-8	Fall, depression
447-257	22	62.5	-11	50	-8	50	-12	- *(Drowsiness at 75)*
447-263	10	50	-3	100	-10	50	-6	- *(Parkinsonism at 87.5)*
447-264	11	50	-8	75	-11	50	-8	Fatigue, insomnia, fall
447-267	19	62.5	-10	62.50	-5	50	-11	Sedation *(Depression at 62.5)*
445-316	10	50	-3	50	-8	50	-8	Fatigue, nausea

2.2.4 Discussion of benefits and risks

Efficacy analyses demonstrate a strong dose-response in terms of Total Chorea Scores (See analysis by Pharmacometrics' team). However, based on the percentage of patients who achieved improvements in chorea scores among patients who were on the 100 and 50 mg/day dose at the end of 12 weeks (52 vs. 91% respectively) and the observation that most cases of parkinsonism, akathisia, balance difficulty, depression and dysphagia were observed at doses >50 mg/day, the 50 mg dose appears to have a more favorable benefit/risk profile than the 100 mg dose.

TBZ is clearly effective to treat the chorea component of Huntington's Disease, but because of the way the drug is prescribed (to maximum effect on chorea unless AEs develop), most patients will present adverse events at some point. Some of the AEs associated with TBZ are easily recognizable and manageable by dose reduction (sedation, parkinsonism) but others are not (akathisia) or may be difficult to separate from the underlying disease (depression, dysphagia). Sedation responded rapidly to dose reduction, however, for some the other adverse events, resolution took days to months after dose reduction and data on resolution after withdrawal are missing for most patients.

The question remains whether TBZ's benefit of decreasing chorea scores by 50% in 38% of patients outweighs the risk evident in the placebo-controlled study of developing akathisia (13%), parkinsonism (11%) and depression (19%), as compared to 0% on placebo - particularly in patients who may not appreciate the extent of their abnormal movements-, and whether it is worth pushing the dose up to improve TCS further when some of the AEs will be difficult to manage or difficult to distinguish from the underlying disease.

When evaluating benefits and risks, one takes into consideration the effect size of the efficacy outcomes as well as the frequency, severity, reversibility and time to resolution of the AEs, among other factors. One very important factor that is missing in this application is the patients' perspective. As per Carole Davis' review, patients' perception/ appreciation of TBZ effects were not adequately evaluated in this study. A patient's global assessment was collected but it was done at the end of week 13 (after the washout) and was not consistently done by the patient (sometimes it was done by the caregiver).

In my opinion, notwithstanding the limitations of the available database, the data suggest that the sponsor may not have found the optimal dose or patient population for which the improvement in chorea outweighs the rate/severity of adverse events. I believe that a study comparing the efficacy and safety of the 50 mg dose vs. the 100 mg dose with an adequate assessment of the patient's global impression would be helpful in establishing the optimal dosing for this drug. This could be done as a Phase 4 commitment.

The use of a RiskMAP offers a potential approach reducing some of the safety concerns associated with TBZ. At the time of this review, the Office of Surveillance and Epidemiology (OSE) is conducting a detailed review of the proposed RiskMAP.

Appendix 1. Study 007. Patients in 007 who had been on placebo during study 004.

Study ID: 447202, 447209, 447211, 447215, 447220, 447222, 447226, 447230, 447232 447239, 447241, 447245, 447247, 447250, 447253, 447256, 447259, 447262, 447266 447272, 447273, 447281, 447287, 447291, 447298, 447307, 447314

Appendix 2. Sponsor's analysis of BARNES scores in patients with AE potentially related to akathisia.

Table 61. Highest BARNES Global Clinical Score in Patients With Akathisia, Anxiety, or Restlessness/Agitation Events in Studies 004, 007 and 006

Study AE	Cases	Highest BARNES Global Clinical Score 0	1	2	3	4	5
Study 004							
Akathisia	5	0	2	2	0	1	0
Anxiety	4[1]	4	0	0	0	0	0
Restlessness/Agitation	13[2]	8	3	1	0	1	0
Study 007							
Akathisia	15	6[5]	1	4	3	1	0
Anxiety	14[3]	10	3[6]	1[7]	0	0	0
Restlessness/Agitation	5[4]	2	1	2[8,9]	0	0	0
Study 006							
Akathisia	0	0	0	0	0	0	0
Anxiety	6	6	0	0	0	0	0
Restlessness/Agitation	4[10]	4	0	0	0	0	0

Source: CSR TBZ 103,004: 16.2.7.1, 16.4.14; Amended CSR TBZ 103,006: 16.2.7.1, 16.4.14; Amended CSR TBZ 103,007: 16.2.7.1, 16.4.1.4

Note: Patients who had an AE of akathisia are counted as akathisia only; patients who had an AE of restlessness or agitation are counted in that category even if they also had an AE of anxiety.

1. Patients 238 (maximum score of 0), 251 (maximum score of 0), and 313 (maximum score of 0) had anxiety-like events as an AE and were excluded from anxiety. In addition, Patient 299 (maximum score of 1) had restlessness, irritability and anxiety as an AE and was counted only in anxiety-like events.
2. One patient (ID 299) had AE of restlessness and irritability (maximum score of 1) and was only counted once in anxiety-like events. Patient 279 (maximum score of 1) had AE of akathisia and was excluded from anxiety-like events.
3. Patient 207 (maximum score of 2) and Patient 245 (maximum score of 0) also had akathisia as AE and were excluded from anxiety. Patient 202 (maximum score of 0) had akathisia, anxiety and anxiety-like event as an AE and is counted only in akathisia.
4. Patients 250 (maximum score of 2), 263 (maximum score of 2) and 266 (maximum score of 0) had anxiety-like events as an AE and were excluded from anxiety. Patient 223 (maximum score of 0) had AE of akathisia and was excluded from anxiety-like events. In addition, Patients 202 (maximum score of 0) and 245 (maximum score of 0) had an anxiety-like event, anxiety and akathisia as AEs and was counted only in akathisia.
5. Two (ID 202 and ID 219) of six patients had mild akathisia.
6. Baseline score of 2 for one patient (ID 279), therefore this is a decrease.
7. One patient (ID 262) was direct rollover from Study 004 and akathisia was a pre-existing condition.
8. Baseline score of 1 for one patient (ID 263), therefore a 1 point increase.
9. AE of restlessness (moderate) began after discontinuation from tetrabenazine.
10. One patient (ID 424) had AE of anxiety, agitation and restlessness (maximum score of 0) and was counted in anxiety-like events.

Appendix 3. Cases of depression in study 007 (n=27)

Pat ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])				
	Rel. Day	Dose		Base line[1]	At week 12	At week 24	At week 48	At week 80
747-203	220	25	None/Started Fluoxetine 20 mg on D 232, ↑to 30 mg on D 243/ Ongoing at study end. Final HAM-D was 4. D/c due to need for exclusionary med and AE of chorea	15	9 (25)	17 (25)	4 (25)	N/A
747-207	172	25	None/Continued Amitriptyline 50-150 mg from study entry; ↑Paxil from 20 mg to 40 mg on D 172/Ongoing at W80. Total HAM-D of 13 at W80, down from 20 at W48.	16	12 (12.5)	12 (25)	5 (12.5)	7 (12.5)[2]
747-208	253	137.5	None/ Continued Imipramine 150 mg from study entry; Zoloft dose ↓ to 100 mg on Day 6 and Neurontin stopped on D 253; Mirtazapine on Day 547-564/ Ongoing. HAM-D score at W80 was 6, down from 11 when AE reported.	23	19 (112.5)	15 (112.)	24 (137.5)	12 (112.5)
747-209	145	62.5	Dose ↓on Day 166 to 37.5 mg and to 25 mg on D 170 when depression called severe / Switched Effexor 75mg to Paxil 12.5 mg on D 263, switch back to Effexor 75 mg D 266, Effexor increased to 150 mg one day after severe depression stopped (D 360) /Recovered on rel D 359.	11	7 (62.5)	9 (62.5)	5 (50)	9 (37.5)[3]
	535	25	None/Continued Amitriptyline 50-150 mg from study entry; Increased Paxil from 20 mg to 40 mg on Day 172/Ongoing at W80. HAM-D of 13 at W80, down from 20 at W24.	11				
747-210	80	87.5	None/ ↑ Prozac from 40 to 120 mg on D81, added Trazodone 100 mg D 160-220; Switched Prozac to Celexa 40 mg on D 448 /Ongoing at W80 but HAM-D score of 5 to 6 during last 28 weeks of study	17	3 (87.5)	2 (87.5)	5 (87.5)	10 (87.5)
747-217	157	87.5	None/Switched from Citalopram to Zoloft 50 mg on Day 261 /Recovered Day 267	15	6 (87.5)	8 (87.5)	7 (87.5)[4]	NA

Appendix 3. (cont) Cases of depression in study 007 (n=27)

ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])				
	Rel day	Dose		Baseline	At week 12	24	48	80
747-223	89	100	None indicated for depression, but pt had numerous dose ↓ for sedation or akathisia / Increased Citalopram to 30 mg on Day 55, then ↓ to 20 on Day 174; added Buspar Day 55-62. Did not complete study due to caregiver preference/ Ongoing at end of study, but HAM-D was 9 (down from max of 18)	15	11 (62.5)	11 (75)	15[5] (50)	
747-230	428	50	None/↑ Effexor from 75 mg to 150 mg on Day 428 & later↓to 75 mg (Day 460) /Recovered on Relative Day 460	17	10 (75)	10 (50)	10 (50)	13 (25)
747-231	24	62.5	Dose reduced/Continued Prozac 20 mg from study entry /Recovered on Day 32	15	10 (50 mg)	12 (50 mg)	7 (50 mg)	10 (50 mg)
747-237	31	75	Dose reduced/ None/ Recov D 37. Patient d/c due to abnormal LFT's on Day 87	15	10 (50)[6]	NA	NA	NA
747-239	76	75	Dose reduced/Continued Paroxetine 40 mg from study entry/Recovered on Day 89	20	9 (62.5)	13 (62.5)	13 (50)	11 (62.5)
747-243	31	50	Dose reduced/Started Paxil 20 mg D 31, ↑ to 30 mg on D 44/ Recovered D 83. D/C due to request of caregiver on D 176	14	4 (62.5	8 (50)	NA	NA
747-245	142	75	Dose reduced, then stopped D 153 /Zoloft 25 mg started Day 149-153/ Ongoing at study end, final HAM-D score= 12 with 'Depressed Mood' =0 (range 0-4). D/C TBZ on Day 149[7], restarted x 3 days, but then withdrew consent D 153	17	14 (62.5)	NA	NA	NA
747-247	57	62.5	Dose reduced/Started Citalopram 10 mg on Day 85, ↑ to 20 mg on Day 107/ Ongoing at study end. D/C on Day 113 due to depression and akathisia. Patient had HAM-D of 16 (down from max of 23), but HAM-D 'Depressed Mood' score was 1 (range 0-4)	14	7 62.5)	10 (37.5)	NA	NA

Appendix 3. (cont.) Cases of depression in study 007 (n=27)

ID	AE onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])				
	Rel day	Dose		Baseline	At week 12	24	48	80
747-252	2	12.5	None/Started Zoloft 25 mg on Day 16, to 50 mg on Day 23/Recovered on Day 44	11	9 (25)	6 (25)	9 (37.5)	8 (12.5)
	183	25	None/increased Zoloft to 75 mg, D 213, Recovered D 237.	11				
747-262	69	75	Dose reduced 5x / ↑Zoloft to 100 mg on Day 86, further to 150 mg on Day 117/ D/C Day 145 for suicidal ideation. Depression ongoing at study end (Week 25), but 1 week later mood improved with no suicidal thoughts.	10	7 (50)	15 (12.5)	NA	NA
747-266	56	75	Dose reduced/Continued Citalopram 20 mg from study entry /Recovered on Day 169	9	3 (50 mg)	0 (50 mg)	6 (50 mg)	1 (37.5 mg)
	337	50	None/Switched Citalopram to Wellbutrin 150 mg on Day 357 /Ongoing at Week 80, but HAM-D of 1 at study end	9				
747-267	125	62.5	Dose reduced/Increased Paxil to 50 mg on Day 162/ Intensity reduced from mod to mild on Day 233 but increased to mod on Day 438. TBZ d/c Day 463. Psychosis with depressive features began Day 466, Recovered on Day 473.	21	13 (62.5)	7 (50)	12 (50)	NA
747-272	46	100	None/None/ Intensity increased to mod on Day 86	16	10 (125)	18 (125)	11 (137.5)	NA
	87	125	None/None/ Intensity reduced to mild on Day 174	16			(Day 280) [8]	
	175	125	None / Zoloft 50 mg started (Day 189-194) and Celexa 10 mg for insomnia (Day 255-267) / Recovered on Day 266. D/C moved out of state D 280.	16				
747-279	~225[9]	50	None/Continued Mirtazapine; Paxil increased to 40 mg ~Day 225[9]/Ongoing at study end, but last HAM-D was 6		9 (50)	7 (50)	5 (50)	NA
747-288	50	50	Dose reduced / Continued Zoloft 150 mg. Amitriptyline 20 mg started D 43, to 50 mg Day 77 / Recovered D 182	13	5 (50)	7 (50)	7 (50)	2 (50)

Appendix 3. (cont) Cases of depression in study 007 (n=27)

ID	AE onset		**Study Drug Action/ Medical Rx/AE Outcome**	Total Chorea Score (dose [mg/day])				
	Rel day	Dose		Baseline	At week 12	24	48	80
Same Pt. (288)	355	50	None / Continued Zoloft to D9 358, Wellbutrin 100-200 mg (Day 344-study end) and Amitriptyline / Recov D 580	13				
747-291	42	87.5	Dose reduced/ None/ Recovered on Relative Day 71	11	4 (75)	4 (75)	8 (75)	6 (75)
	210	75	None/None/Recovered on Day 596. HAM-D scores from Day 176 to 596 ranged from 0 to 5	11				
747-313	145	200	Dose reduced /Started Citalopram 10 mg on D 247, increase to 20 mg Day 473, Started prn Xanax / Intensity ↑ to severe on Day 479	13	7 (200)	9 (150)	5 (150) 11 (Wk 64)	
	480	150	None / Added Amitriptyline 100 mg on Day 547 / Ongoing at study end, with final HAM-D score of 23.	13				
747-316	19	37.5	None / Continued Zoloft 200 mg, Wellbutrin 150 mg Day 16-27; Started Pamelor 50 mg on Day 31 and prn Klonopin on Day 33 / Recovered on Day 171. HAM-D scores ranged from 7-10 during depression and were 5-8 thereafter	16	7 (37.5)	4 (37.5)	1 (37.5)	0 (37.5)
747-225	*586*	*?*	*Not listed as AE. Zoloft increased from 100 to 220 for indication of depression.*	*?*	*?*	*?*	*?*	*?*
747-279	*225*	*?*	*Not listed as AE. Paxil dose increased from 30 to 40 for indication of depression.*	*?*	*?*	*?*	*?*	*?*
747-314	*399*	*?*	*Not listed as AE. Trazodone added on day 399 and amitriptyline dose increased on day 455 for indication of OCD/depression.*	*?*	*?*	*?*	*?*	*?*

[1]Baseline = 0 mg. [2] Patient 747-207 stopped taking study drug one day before the Week 80 visit. [3] Patient 747-209 stopped taking study drug one day before the Week 80 visit. [4] Patient 747-217 withdrew 11 days before the Week 80 visit. Had TCS=6 at Week 64 visit. [5] Patient had a TCS score =9 at Week 64 visit. [6] Patient 747-237 had last dose on Day 87 (withdrawn for abnormal labs).[7] Patient 747-245 stopped taking study medication 16 days before the Week 24 visit and was withdrawn from the study, with akathisia, agitation, anxiety and ongoing depression. [8] Patient 747-272 withdrew between the Week 36 and Week 48 visit due to a move out of state and inability to continue participation in the study.[9] Patient 747-279: Month and year but specific start date for adverse event not specified. Source: July 18 and 31, 2007 response to June 14, 2007 informational request. *Cases found by FDA from review of concomitant medications listings are in Italics.* No data was available on chorea scores for these patients.

Appendix 4. Cases of depression in study 006 (N=10)

Patient ID	AE onset Rel. Day	Dose	Study drug action/medical Rx/AE outcome	Total Chorea Score (dose [mg/day])				
				Baseline		At Week		
				005[1]	006[2]	12	24	48
647-401	270	87.5	None/ None / Recovered on Relative Day 361. HAM-D ranged between 5 and 8 during study.	13	13 Off TBZ 16 hr	15 (75 mg)	3 (87.5 mg)	6 (87.5 mg)
647-402	11	100	Dose reduced / Continued Zoloft 100 from entry. Started mirtazapine 7.5 mg QD on Day 14 / Intensity decreased to Moderate on Day 182	25	27 Off TBZ 2.5 days	25 (75 mg)	8 (125 mg)	2 (150 mg)
	182	125	None / None / Intensity increased to severe on Day 252					
	252	150	None / Change from Sertraline 100 mg QHS to Paxil 20 mg QD on Day 321 /Ongoing; HAM-D scores improving from W12 visit, and final HAM-D was 7.					
647-411	105	50	None / Zoloft increased from 100 mg to 150 mg on Day 106/ Recovered on Day 112	10	12 Off TBZ 2.5 days	7 (62.5)	11 (62.5)	9 (62.5)
647-414[3]	236	50	None / Continued Prozac 20 mg from entry/ Ongoing. HAM-D scores were 3 from Wk 12 to Study end.	8	9 Off TBZ 4 days	14 (37.5)	5 (50)	5 (50)
647-418	169	87.5	None / None / Recovered on Day 340. HAM-D scores ranged from 3-6 between Wk 12 and Study end.	10	154 Off TBZ 4 days	16 (87.5)	16 (87.5	15 (87.5)
647-419	158	100	None / None / Recovered on Relative Day 330.	5	12 Off TBZ 4 days	11 (100)	6 (100)	8 (100)
647-426	95	37.5	None / Paxil 12.5 mg started Day 95; increased to 25 mg Day 110, then switched to Paxil CR 20 mg on Day 201 / Ongoing. Final HAM-D score 16.	7	125 Off TBZ 4 days	6 (37.5)	5 (37.5)	4 (62.5)
647-428	282	75	None / Continued Lexapro 30 mg from entry; Added Wellbutrin 150 mg on Day 41 for smoking cessation / Ongoing. Final HAM-D 13.	3	126 Off TBZ 2.5 days	6 (75 mg)	6 (75 mg)	3 (75 mg)
647-430	1	37.5	None/Paxil 12.5 started and later switched to Paxil CR. Had 2 day suspension of TBZ for delutional suicidal ideation on day 75.	5	15 Off TBZ 4 days	3 (37.5)	15 (0)	NA

Appendix 4. (cont) Cases of depression in study 006 (n=10)

Patient ID	AE onset Rel. Day	Dose	Study drug action/medical Rx/AE outcome	Total Chorea Score (dose [mg/day])				
				Baseline		At Week		
				005[1]	006[2]	12	24	48
647-403	*2*	*?*	*None/ amitriptyline dose increased for depression.*	*?*	*?*	*?*	*?*	*?*

Rel. Day = Day relative to dosing d/c: discontinuation [1] Baseline Chorea scores from Study 005 are on Tetrabenazine [2] The baseline Chorea score for Study 006 was the Day 5 Chorea score from Study 005. As this was a staggered withdrawal study, patients were off TBZ from 1 to 4 days. [3] Patient 647-414 experienced depression and anxiety on same start date and remained ongoing at study end. Both AEs were attributed to legal issues. [4] Patient 647-418: The listing for the Baseline UHDRS chorea score for TBZ 103,006 states '13,' but it should state '15', as per protocol, the measurements made during the end-of study visit of TBZ 103,005 will serve as Screening/Enrollment/Baseline values for TBZ 103,006. [5] Patient 647-426 experienced anxiety approximately 1 month prior to start of depression– [6] Patient 647-428: The listing for the Baseline UHDRS chorea score for TBZ 103,006 states '14,' but it should state '12', as per protocol, the measurements made during the end-of study visit of TBZ 103,005 will serve as Screening/Enrollment/Baseline values for TBZ 103,006. Source: July 18 and July 31, 2007 response to FDA informational request of June 14, 2007. *Cases found by FDA from review of concomitant medications listings are in Italics.* No data was available on chorea scores for these patients.

Appendix 5. Antidepressant and benzodiazepine medications prior to and on study entry in study 004

Medications at entry	TBZ (N=54)	Placebo (N=30)
Antidepressants	30 (56%)*	20 (67%)*
Amitriptyline	3	2
Bupropion	1	0
Citalopram	7	2
Fluoxetine	3	2
Imipramine	1	0
Mirtazapine	2	1
Nefazodone	1	0
Nortriptyline	0	1
Paroxetine	6	5
Sertraline	10	3
Trazodone	3	1
Venlafaxine	0	4
Benzodiazepines	9 (17%)*	5 (17%)*
Aprazolam	1	2
Clonazepam	5	2
Diazepam	2	1
Temazepam	1	0

*Patients taking more than one medication are counted only once in the table. Source Table 13, 004 CSR

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

/s/

Maria Villalba
11/9/2007 11:21:12 AM
MEDICAL OFFICER

Alice T. Hughes
11/9/2007 11:30:48 AM
MEDICAL OFFICER

Reference:

Walker, F.O., (2007). Huntington’s disease. *Seminars in Neurology 27*(2), 143-150.