

pedigree in Venezuela. The affected gene contains an expanded section with a pattern of trinucleotide (CAG) repeats. Affected patients have ≥ 37 repeats and the number of repeats may predict the age of onset.

Typically, a patient with HD would develop their first symptoms around the age of 40 years. The disease would then steadily progress over the course of about 20 years resulting in death. The presentation is quite variable and this is believed to be characteristic of the CAG repeat disorders as a whole. Initial symptoms might include behavioral changes, mild chorea, rigidity, or cognitive changes. Even within the same pedigree, there is often marked phenotypic variability with any one of the above symptoms predominating.

Shoulson and Fahn developed the Total Functional Capacity (TFC) scale to measure clinical status of patients over time. The scale includes 5 items, graded from 0 to 2 or 3, with 0 representing the poorest function. The 5 items are occupation, finances, domestic responsibilities, capacity to perform ADLs, and level of care. The total score ranges from 0 to 13. Progression over time was delineated by 5 stages: 13-11, 10-7, 6-3, 2-1, and 0. These stages have been correlated with clinical worsening of signs and symptoms and with radiographic changes (typically measures of caudate nucleus size). On average, patients progress by 1 point on the TFC per year.

There have been numerous studies investigating the correlation between movement through the 5 grades of the TFC and either increasing chorea or cognitive decline. In general, chorea increases during the early grades of HD. There is some evidence that it either plateaus or diminishes in the later stages.

The TFC has been incorporated into the Unified Huntington's Disease Rating Scale (as Part VI), the rating scale used in the 2 TBZ controlled trials submitted with the current NDA.

The Unified Huntington's Disease Rating Scale (UHDRS)

This scale was developed by the Huntington Study Group as a clinical rating scale to assess motor, cognitive, behavioral, and functional status of patients with Huntington's disease.¹ There are 6 relevant subparts:

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

¹ Huntington Study Group. Unified Huntington's Disease Rating Scale: Reliability and Consistency. *Movement Disorders* 11: 136-142, 1996.

Part 1 consists of 15 items, graded from 0-4 with 0 representing normal status. Because the ocular items are graded in both the horizontal and vertical directions and some of the motor items are graded for different body regions, the total motor score can vary from 0 to >100.

Part 2 consists of 5 timed items, the verbal fluency test, the symbol digit substitution test, the Stroop color naming test, the Stroop word reading test, and the Stroop interference test. All 5 are thought to reflect attention and executive function, the loss of which is typical of the so-called subcortical dementias like HD. In the verbal fluency test, patients are asked to name as many words beginning with a certain letter within a certain time. In the symbol digit test, patients must substitute a digit for symbols, following presentation of the code. In the Stroop color test, patients must name the colors seen. In the Stroop word test, patients must read a number of words in a given time. In the Stroop interference test, words are presented in colored text. Patients are asked to identify the colors, but the task requires that they ignore the actual spelled color. The total score on the cognitive test is the total number of correct responses within the specified times. The range can be from 0-several hundred for the whole test. Each of the 5 items is timed over roughly a minute.

Part 3 consists of 11 behavioral items rated from 0 to 4 for frequency and from 0 to 4 for severity. The total score ranges from 0 (no problems) to 88. There are several additional questions asking the examiner about the presence or absence of confusion, depression, and dementia.

Part 4 consists of a list of 25 activities. The examiner is asked to decide if the patient is capable of performing the activities (0=no; 1=yes). Both the patient and family/companions can be interviewed and the examiner must base their answer on capacity to do the activity, even if the patient does not normally do the activity. The total score can range from 0 to 25.

In Part 5, the examiner is asked to rate the patient's level of independence, in increments of 5, on a scale from 10 (tube feeding, total bed care) to 100 (no special care needed).

Part 6 was originally developed by Drs. Shoulson and Fahn as the Total Functional Capacity (TFC) scale. It consists of 5 items (occupation, finances, domestic chores, ADL, and care level) rated from 0 to 2 or from 0 to 3. A zero represents the lowest level of function. The total score ranges from 0 to 13.

Study 004

Study 004 was a multicenter, randomized, double-blind, placebo-controlled trial comparing TBZ to placebo. Patients were titrated to an "optimal dose" based on tolerability and effect, to be no more than 100mg/day. The study consisted of a 7-week titration phase, followed by a 5 week maintenance phase.

Patients were started on 12.5mg qd and titrated at weekly intervals. Drug was administered qd and bid at dosages of 12.5 and 25mg/day, and tid for all other doses.

Patients with a clinical diagnosis of HD (supported by a family history) and who were greater than 18 years of age were enrolled. Patients were required to have a Total Chorea Score of 10 or greater. The Total Chorea Score, taken from Part I of the UHDRS, is rated from 0 to 28 (0 to 4 in seven parts of the body, with 0 representing no chorea). A score of about 10 is roughly equivalent to slight, intermittent chorea in 4/7 areas and mild, common chorea in 3/7 areas.

Patients had to be ambulatory and had to have a TFC score > 5.

There was no minimum score on a formal cognitive assessment required. Patients were required to be free of serious psychiatric illness. Patients who were diagnosed with depression, based on a HAM-D score of 15 or less, were excluded.

There were 84 patients enrolled at 16 study sites:

005	Rush Presbyterian	4
007	Baylor	5
018	Pennsylvania Hospital	4
019	University of South Florida	6
020	Ohio State	6
032	Emory	6
037	Albany Medical College	7
045	Indiana University	8
051	UC San Diego	9
055	North Shore University Hospital	6
071	Park Nicollet Clinic	6
073	UC San Francisco	5
104	Medical College of Wisconsin	3
123	University of Maryland	2
145	University of Texas	6
151	JFK Medical Center	1

The primary outcome variable was the Total Chorea Score, taken from Part I of the UHDRS. This is rated from 0 to 28 (0 to 4 in seven parts of the body, with 0 representing no chorea).

The primary analysis was a comparison of change from baseline in chorea score (average score of weeks 9 and 12, minus baseline) between TBZ and placebo.

There were numerous other assessments made throughout the study:

UHDRS, parts I-VIII
CGI, part 2
Barnes Akathisia Scale
HAM-D Depression Scale
Functional Impact Scale (FIS)
Epworth Sleepiness Scale
UPDRS Dysphagia Scale
UPDRS Dysarthria Scale

Four of the above outcome measures were specified in hierarchical order as secondary outcomes of interest. In order, they were: 1) CGI, part 2; 2) UHDRS Part I, the motor subscale; 3) UHDRS Part IV, the functional assessment checklist; and 4) the Gait Score (from UHDRS Part I, the motor subscale).

Patients were required to return to clinic for evaluations at the end of weeks 1, 3, 5, 7, 9, and 12. Patients also returned to clinic for a follow-up visit at the end of week 13 after being off treatment for 1 week.

Results

A review of baseline test scores reveals a profile of the patients enrolled in Study 004. About 10% were thought to have some degree of dementia. Roughly 20% walked with difficulty, but no one's gait was considered worse than that. The average chorea score was 14. The mean and median TFC scores were about 8 and only 1/84 had a TFC score of 2 or less.

In Study 004, 40% of patients achieved a dose of 100mg/day at week 12, 20% achieved a dose of 50mg/day at week 12, with the rest roughly equally distributed between 37.5 and 100mg/day.

The table below shows the adverse events that led to discontinuation of upward dose titration and/or reduction in daily dose of TBZ during Study 004.

Adverse Event	TBZ (n=54)	Placebo (n=30)
Sedation	15 (28%)	0
Akathisia	5 (9%)	0
Depression	3 (6%)	0
Parkinsonism	3 (6%)	0

For each of the AEs in the above table, females outnumbered males by at least a 2:1 margin.

The mean change from baseline on the chorea score was -5 for the TBZ group and -1.5 for the placebo group, a difference of 3.5 points in favor of TBZ ($p < 0.0001$). These

results reflect the protocol-specified maneuver of adding the week 9 and week 12 scores together to represent the on-study score. Dr. Massie notes that, ignoring the week 9 score, the between-group difference was even larger, 4.4 points. (The corresponding median difference was 4.5 points.)

Categorical results for change from baseline (using week 12, alone, compared to baseline) are shown below:

Reduction of Chorea Score	TBZ (n=54)	Placebo (n=30)
≥ 10	10 (19%)	1 (3%)
6-9 points	17 (31%)	1 (3%)
3-5 points	10 (19%)	5 (17%)
0-2 points	11 (20%)	15 (50%)
Worsening Chorea	6 (11%)	8 (27%)

By the hierarchical analysis plan, the first secondary outcome analyzed was the CGI, part 2, a physician global. The results showed a clear shift in favor of TBZ. Almost half of TBZ-treated patients were rated much improved or better as compared to 7% of placebo-treated patients ($p=0.006$). Note that the CGI was performed by the patients' physicians. Investigators were instructed that the CGI should reflect overall clinical status and not just chorea.

The next secondary outcome in the hierarchical analysis was the UHDRS, Part I, the total motor score. The between-group difference on this not statistically significant by the protocol analysis which required averaging the week 9 and week 12 scores, $p=0.075$. If only the week 12 scores are used, the result would have been significant, $p=0.012$. Either way, the between-group difference was driven almost entirely by the score on the chorea item.

The third secondary outcome in the hierarchical analysis was the UHDRS, Part IV, the functional assessment checklist. By protocol, the hierarchical analyses would not have proceeded this far because of the insignificant p-value, $p=0.075$, above. The average change from baseline on this scale was -0.8 for TBZ and 0.4 for placebo, a difference of 1.2 points favoring placebo, nominal p-value=0.018. Dr. Massie looked at each of the 25 items at week 12 for the TBZ and placebo groups. The absolute difference in percent with "yes" responses was 15% or greater for 6 items, including doing laundry, shop for groceries, supervise children, do housework, use public transportation, and take meds without help. Only 1/25 items had more "yes" answers for placebo. The overall pattern of results does suggest that the ability to do more complex tasks might be somewhat impaired by TBZ.

The fourth and last secondary outcome in the hierarchical analysis was the gait item from the UHDRS, Part I. There was no apparent difference between groups for gait. Recall that the inclusion/exclusion criteria required that all patients be ambulatory to enter the trial.

Videotapes were done at week 12 and week 13 for a subgroup of patients (n=23) in the trial. These results were consistent with the results of the on-site evaluations.

Other Outcome Assessments

UHDRS, Part II, Cognitive

The cognitive assessment consists of 5 items. Overall, movement on this scale favored placebo over TBZ, $p=0.025$. Baseline mean scores were 172 and 156 for placebo and TBZ, respectively. The mean change from baseline was 5 for placebo and -7 for TBZ.

The first 2 items on the cognitive assessment are a test of verbal fluency and the symbol digit modalities test. There was no between-group difference on these tests. The next 3 items are the Stroop Test (color naming), Stroop Test (word reading), and the Stroop Test (interference). There was no between-group difference on the color test, but the between-group differences on the word reading and interference tests were nominally significant, $p=0.012$ and $p=0.053$ respectively. The between-group difference on the word reading test was 7 words. The between-group difference on the interference test was 3. The clinical significance of these changes is debatable.

UHDRS, Part III, Behavioral

Overall, there was no difference between TBZ and placebo on this outcome measure. Both groups showed almost no change from baseline. Dr. Massie identified one item in the scale that was nominally significant in favor of placebo, the anxiety item. Roughly 30% of TBZ patients vs. 10% of placebo patients had some evidence of anxiety by this measure. This was also reflected in the adverse event data.

UHDRS, Part V, Independence Scale

On a 100-point scale, the TBZ group had a mean change of -2 vs. a mean change of 0.6 for the placebo group, $p=0.134$. This trend seems clinically insignificant.

UHDRS, Part VI, Functional Capacity (TFC)

The mean change from baseline for the TBZ group was -0.4 vs. -0.06 for placebo, $p=0.3$.

Functional Impact Scale in HD (FIS)

The mean change from baseline for the TBZ group was 0.11 and the mean change for the placebo group was 0.13, $p=0.97$.

Hamilton Depression scale (HAM-D)

The sponsor reported no difference between groups on the change-from-baseline HAM-D scores. Dr. Massie found a very small between group difference favoring placebo that was nevertheless statistically significant, $p=0.009$.

The sponsor notes that the lack of effect on the functional scales was surprising given the effect noted on chorea. They hypothesize that, because patients enrolled were independently ambulatory and did not have major functional impairment, there was little room for improvement on the functional scales.

There were 16 sites. Across the 13 sites with 4 or more patients enrolled, the results for only 1 site trended in favor of placebo. (That site enrolled only 4 patients.) When the results for the remaining 3 smaller sites are pooled, they also trended in favor of TBZ.

At the end of the maintenance period, patients were withdrawn from study drug, returning for a follow-up evaluation about 1 week later. The group mean chorea score results from week 12 to week 13 are shown in the following table. The means for the TBZ group and the placebo group were the same at week 13.

	Baseline	Week 12	Week 13
TBZ	14.7	9.4	15.1
Placebo	15.2	14.1	14.9

Dose-Response Analysis

According to the sponsor's review of the published literature, there are wide inter-individual differences in the doses that cause dose-limiting toxicity, with a range from 25mg/day to 200mg/day. This would suggest wide inter-individual differences in optimal dose. At the same time, the sponsor maintains that there is little intra-individual variability so that the optimal dose for a patient tends to remain the same over time.

For these reasons, the sponsor incorporated a flexible dose design into Study 004 as opposed to a randomized fixed dose design. Absent dose response information from Study 004, I asked Dr. Joga Gobburu from FDA's clinical pharmacology group to explore dose-response information by modeling the data collected on individual patients throughout the 7-week dose titration phase of Study 004. A strong dose response relationship might provide additional evidence bearing on the efficacy of TBZ for chorea.

The results of these analyses do show a dose-response and are discussed in his separate review.

Study 005

Study 005 was a randomized, withdrawal study performed at Baylor University. Thirty patients were randomized to 3 different treatment sequences in a 2:2:1 ratio. Patients in Group 1 received placebo (had TBZ withdrawn) after the baseline assessment and remained on placebo for the duration of the trial. Patients in Group 2 were to continue to receive TBZ until after the outcome assessments on day 3; then they were to receive placebo. Patients in Group 3 were to stay on TBZ throughout the trial.

The primary outcome was a comparison of change-from-baseline on chorea score between the 12 patients in Group 1 (placebo) and the 18 patients in Groups 2/3 (TBZ), combined. The time of the primary outcome was day 3.

Additionally, the complete UHDRS was to be performed on day 3 of the study. Due to an administrative error, only Part VI (TFC) was performed. Therefore, other secondary analyses could not be done.

Results

A review of baseline test scores reveals a profile of the patients enrolled in Study 005. About 20% were thought to have some degree of dementia. Roughly 35% walked with difficulty, and for 15% of patients enrolled, gait was worse than that. The average chorea score was 9 (on TBZ). The mean and median TFC scores were about 6 and 3/30 had a TFC score of 2 or less.

To be included in the study, patients were required to have been on a stable dose of TBZ for at least 2 months. The actual duration of treatment for the enrolled patients is shown below:

Duration	Group 1	Group 2	Group 3
> 5 years	3	0	1
< 2 years, ≤ 5 yrs	2	5	1
≥ 1 year, < 2 yrs	2	1	2
< 1 year	5	6	2

Roughly 1/3 of patients enrolled had taken TBZ for between 2 and 4 months.

The following table shows the mean and median doses of TBZ at baseline for the 3 randomized groups:

	Mean Dose	Median Dose
Group 1	59mg/day	50mg/day
Group 2	46mg/day	37mg/day
Group 3	54mg/day	62mg/day

The following table outlines the results for the protocol-specified primary analysis:

Treatment Group	Baseline Chorea Score	Day 3 Chorea Score Change
Group 1 Placebo, n=12	9.4	5.3
Groups 2 and 3 TBZ, n=18	9.8	2.9

The between-group difference was 2.4 points and was not statistically significant, $p=0.078$.

One of the many possible categorical breakdowns for the primary outcome data is shown below:

Increase in Chorea Score (Worsening Chorea)	Group 1 Placebo	Groups 2 and 3 TBZ
> 10	2 (17%)	0
6-9	4 (33%)	3 (17%)
3-5	4 (33%)	8 (44%)
0-2	2 (17%)	4 (22%)
< 0 (Improving Chorea)	0	3 (17%)

Exploring the reasons for the small between-group difference which was not statistically significant, the sponsor discovered that the study was not conducted as per protocol. On the morning of day 3, before the primary outcome data was collected, patients in group 1 were to receive their placebo tablets and patients in groups 2 and 3 were to receive their TBZ tablets. Contrary to this, patients in Group 2 received placebo on the morning of day 3. [On the morning of day 5, test medication was withheld from all patients by mistake; an analysis on day 5 was not planned as a primary analysis.]

The following table shows the results for the TFC at day 3:

Treatment Group	Baseline TFC	Day 3 TFC Change
Group 1 Placebo, n=12	x	0
Group 2 TBZ, n=12	x	-0.17
Group 3 TBZ, n=6	x	-0.83

The largest decrement in TFC occurred in Group 3, the group that received TBZ. This would not have been expected. However, note that the items on the TFC include gross measures such as occupation, finances, and care level, items that would not be

expected to show any movement in the context of a small, 5-day withdrawal study. The significance of this finding is debatable.

The following table outlines the pattern of chorea score results for the entire trial.

Treatment Group	Baseline Chorea Score	Day 3 Chorea Score Change	Day 5 Chorea Score Change
Group 1 Placebo/Placebo	9.4	5.3	5.3
Group 2 TBZ/Placebo, n=12	9.1	3.6	5.5
Group 3 TBZ/TBZ, n=6	11.2	1.7	4.0

The sponsor performed a post hoc trend analysis on the above data, yielding a p-value of 0.0486. This was one of many post hoc analyses performed by the sponsor.

Safety

There are 3 main sources of safety data in the NDA for patients with HD:

- Study 004 (and the corresponding open-label extension study), n=84
- Dr. Jankovic's data from patients with HD, n=98
- Nitoman data, n=66

There is additional safety information provided in the NDA taken from the experience in non-HD chorea as well as in movement disorders other than chorea.

From the Baylor site, data were presented for 47 non-HD chorea patients. Baylor data were also presented for 280 patients with hyperkinetic movement disorders other than chorea, such as Tourette's syndrome.

Dr. Jankovic's data were compiled by a retrospective record review. Data from clinical records were entered into case report forms (CRFs) in 2003-4 to support the current NDA. As discussed below, details were often lacking about critical events; the narratives for many deaths were fairly scanty. SAEs were not prospectively reported, so they were retrospectively defined for purposes of the NDA. Note that 162 patients had been treated for chorea, but records were only available for 145 of these. CRFs were not created for the Baylor non-chorea database. Because of this SAEs are not reported for the non-chorea database.

The Nitoman data was purchased by the sponsor from Roche; it would generally be considered inadequate. The records were very old, they did not include the level of detail normally expected in a current NDA, and many records were missing. This data is

taken from an open-label protocol conducted by Roche Canada from 1989 to 1995. A total of 757 patients with various hyperkinetic movement disorders were treated under that protocol; the current sponsor was provided with paper records and CRFs for 541 of the 757 patients. It is unknown what happened to the missing 216 records. Of the 541 patients, 66 had HD and 475 had other disorders.

Dr. McNeil mentions another Roche database in her safety review. TBZ was marketed in foreign countries many years ago for the treatment of schizophrenia, at doses up to 600mg/day. Ultimately, it was withdrawn from the market for that indication when the newer anti-psychotics became available; the efficacy of the newer drugs was superior. Roche apparently developed a 1200 patient safety database to support the schizophrenia indication, but none of that data is presented in the current NDA.

In summary, prospectively-collected, systematic data on a cohort of patients with HD really only exists for the patients enrolled in Study 004 (and its extension), n=84.

Deaths

Study 004

There was 1 death due to suicide in Study 004 in a patient randomized to TBZ. This was a 40 y.o. man who had been taking TBZ for 2 months. He had decided to stop working due to disease-related disability. On the day that he stopped, he was found drowned.

Baylor Chorea Database

There were 14 deaths reported from the roughly 100 patients with HD treated at Baylor. Four additional deaths were reported from the roughly 50 additional patients treated at Baylor with non-HD chorea. Note that records were missing for 17 additional patients treated at Baylor.

Two of the non-HD deaths appeared to have end-stage diseases (1 had Creutzfeldt-Jakob disease and 1 had SLE). Both were treated for only 1 month. The 2 other non-HD deaths occurred in elderly patients with tardive chorea; both had been treated with TBZ for years.

One of the HD deaths was attributed to metastatic lung cancer and 2 deaths were attributed to myocardial infarction. The cause for 1 death was listed as dysphagia with aspiration pneumonia. The cause for 1 death was listed as unknown. The 9 remaining HD deaths were all attributed to end-stage HD. The majority of patients with end-stage HD had been treated with TBZ for several years or longer.

Dr. McNeil reviewed the narratives for the deaths from Baylor. In general, they do not provide much detail beyond what is described above (and in Table 1 on page 9 of Dr. McNeil's review).

Baylor Non-Chorea Database

There was 1 suicide reported in a patient with Tourette's syndrome. He had stopped TBZ one month earlier. While still taking TBZ, he made a suicidal gesture by taking an overdose of TBZ.

Nitoman Database

There were 45 deaths reported from the Nitoman database. Ten suffered with HD. The remaining 35 had various other hyperkinetic movement disorders.

The causes of death that were listed for the 10 HD patients were end-stage disease (n=3), dysphagia with aspiration pneumonia (n=6), and subarachnoid hemorrhage (n=1).

The causes of death listed for the other 35 patients included unknown (n=11), dysphagia with aspiration pneumonia (n=10), stroke (n=4), MI (n=4), and various unrelated disorders to include cancer.

The narratives for the deaths that occurred in the Nitoman database are generally very non-specific. A number of patients were reported to have Parkinsonism, possibly drug-related, and then died of pneumonia.

One concerning report is a death in a 13 y.o. with Tourette's syndrome. The cause of death was not provided in the narrative.

Serious Adverse Events

In Study 004, there were 4 serious AEs (all in the TBZ group), including the suicide described above. In addition to the suicide, a 62 y.o. man developed restlessness and later suicidal ideation, psychosis, and paranoia. TBZ was discontinued after 68 days. Another patient had a fall with subarachnoid hemorrhage and another patient had recurrence of cancer.

In the open-label continuation studies of Study 004 and Study 005, there were 14 additional serious AEs. Notable among these were several more cases of depression, at least 1 with suicidal ideation.

At the time that Baylor began treating patients, there were no guidelines in place for SAE reporting. Therefore, when data was entered into CRFs for purposes of the current NDA, SAEs were captured retrospectively applying current definitions. In the Baylor database, there were 21 serious AEs identified in this manner. Notable among the 21 SAEs were 2 cases of suicidal ideation and 1 case of a suicidal gesture.

Because CRFs were not created for the Baylor non-chorea database, no SAEs were identified or presented in the NDA.

In the Nitoman database, there were only 8 serious AEs reported. This seems unbelievable since there were 45 deaths in this same database. This low number of serious AEs speaks to the weakness of the Nitoman data in general. One of the 8 serious AEs reported was a case of renal and hepatic failure with associated pancreatitis; no further details are provided. One was a suicide attempt.

Dropouts for Adverse Events

In the Baylor chorea database (n=145), roughly 10% of patients discontinued because of either depression or Parkinsonism/akathisia.

In the Baylor non-chorea database (n=280), again roughly 10% of patients discontinued because of either depression or Parkinsonism/akathisia.

Common Adverse Events

The following table shows AEs that were particularly common:

Adverse Event	Study 004 (n=54)	Study 007 (n=75) Open-label, continuation of 004	Baylor Chorea Database (n=145)
Somnolence	28%	47%	45%
Insomnia	22%	21%	28%
Parkinsonism	2%	3%	14%
Depression	15%	24%	30%
Akathisia	9%	15%	12%
Dysphagia	2%	7%	15%

One of the concerns for TBZ is the potential to cause or worsen dysphagia in a HD population already at risk for this problem. This could lead to aspiration and pneumonia. Perhaps reflecting this, in Study 004, the incidence of upper respiratory track infection was 13% for TBZ and 7% for placebo.

Dose-Response Information for AEs

Because Study 004 had a flexible-dose design, there is no information on dose-response for AEs.

Laboratory Data

Labs were systematically collected in Study 004. Of note, compared to placebo, TBZ was associated with a mean increase in ALT of about 10.

Labs were not systematically collected in the Baylor database.

The sponsor also performed a small study in 6 male subjects measuring prolactin levels after TBZ 25mg bid. Prolactin levels rose as much as 3-fold. Prolactin levels were collected in a small subset of patients enrolled in the controlled trial. Dr.McNeil believes those results are unreliable as described in her review.

Vital Signs

Dr.McNeil reviewed the vital sign data, to include data bearing on orthostatic hypotension. There were no obvious effects of TBZ on vital signs.

EKGs

The sponsor did perform a formal EKG study, with special attention to the QT interval. Dr.Yasuda reviewed that study. In that study, single doses of 25mg and 50mg were investigated. TBZ caused a 7msec increase in QTc and a 10msec increase could not be excluded. Two subjects characterized as 2D6 poor metabolizers were not outliers on QT. Dr.Yasuda notes that greater effects at higher doses cannot be excluded.

The metabolism of TBZ is not fully characterized at this point. Therefore, we do not have confidence that we know which metabolic inhibitors would be important to study further. We do know that exposures to parent TBZ are extremely elevated in patients with hepatic impairment. Therefore, Dr.Yasuda is recommending that TBZ be contraindicated patients with hepatic impairment.

EKGs were collected in Study 004 at baseline and week 12. There was a small increase from baseline in QT interval noted in the TBZ group.

Neuroleptic Malignant Syndrome

Dr.McNeil describes a number of cases of NMS in the setting of overdose. There is a single case of NMS not associated with overdose. This patient had stopped TBZ and, upon re-starting at a dose of about 100mg/day, developed NMS.

Tardive dyskinesia has not been reported to date with TBZ.

Post-Marketing Experience

The sponsor submitted several PSURs for TBZ which describe the foreign marketing experience. They do not add to the safety profile already described above.

Literature

The sponsor has performed a literature review that covers experience in roughly 2000 patients with various disorders. Dr. McNeil has included pertinent results of this search in her review.

There is an old, troubling report in the **Lancet**, dated March 9, 1974.² It is a very brief report, noting the authors' belief that TBZ had contributed to dysphagia in several patients with HD, leading to aspiration pneumonia and death in 3 out of 5 patients treated with TBZ. The authors describe coincident improvement in chorea with worsening dysphagia. They conclude, "It seems from our experience that dysphagia may be a grave side-effect of tetrabenazine, and we have reported our experience to the Committee on Safety of Medicines. It seems to us that 2 weeks is too short a trial period to elicit the full effects of these long-term drugs, and it seems dangerous to suggest that tetrabenazine is the drug of first choice in patients with Huntington's chorea." [The **Inspections** section below suggests that dysphagia as an adverse event may have been systematically under-reported at Dr. Jankovic's site, the primary source of safety data in the current NDA.]

Inspections

Four clinical sites were inspected. The data from all 4 were deemed acceptable. Three of the sites contributed efficacy data. The fourth was the Baylor safety database. It should be noted that in 3 records at Baylor, the site inspection noted that the adverse event of dysphagia was not reported because the investigator attributed it to the underlying disease process.

Division of Medication Errors and Technical Support (DMETS)

In a consult dated February 28, 2006, DMETS reviewed the proprietary name, Xenazine, and found it acceptable. However, another proposed name, _____ for an _____ drug product had some potential for confusion; DMETS had previously found that the name _____ was unacceptable and that product received _____

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² Snaith RP and Warren H. Treatment of Huntington's Chorea with Tetrabenazine. *Lancet* 1(7854): 413-4, 1974.

Discussion

Has the Short-Term Efficacy of TBZ for the Treatment of Chorea Been Established?

The usual standard for approval for a drug that does not have an effect on mortality or irreversible morbidity is demonstration of efficacy in 2 independent clinical trials. TBZ provides only symptomatic benefit. By the usual standard then, efficacy has not been established. An effect was shown in Study 004, $p < 0.001$. The effect size was smaller in Study 005 and the p-value was greater than 0.05 ($p = 0.08$).

Within Study 004, there is additional supportive evidence bearing on the efficacy of TBZ for the management of chorea.

First, the results are internally consistent. Across the 13 sites with 4 or more patients enrolled, the results for only 1 site trended in favor of placebo. (That site enrolled only 4 patients.) When the results for the remaining 3 sites are pooled, they also trended in favor of TBZ. That none of the sites enrolled more than 9 patients makes this consistency even more impressive.

Second, the pattern of chorea scores for the 2 randomized groups when the drug is withdrawn (week 13 scores compared to week 12 scores) is consistent with loss of effect for patients originally randomized to TBZ.

Third, Dr. Joga Gobburu's modeling of dose-response data throughout the 7-week titration period reveals evidence of a dose-response for TBZ. Given the marked variability in the pharmacokinetics of TBZ, a dose-response relationship would seem especially hard to demonstrate.

At the same time, the failure of Study 005 to show an effect at the 0.05 level does not necessarily argue against an effect. The pattern of the chorea scores in that study trends in favor of TBZ and the problems with the conduct of the study (failure to follow protocol-specified dosing guidelines) cloud the overall interpretation of the study.

The strength of evidence provided by Study 004, alone, seems to establish the efficacy of TBZ after 3 months of treatment (maximum of 5 weeks at maintenance dose). To require a second study of similar design and duration would seem unnecessary. The one added value to such a study would be the incorporation of some type of global assessment performed by the patient. Such an evaluation might bring into perspective the value of the chorea change *to the patients themselves*.

Has the Long-Term Efficacy of TBZ for the Treatment of Chorea Been Established?

Study 005 was designed to show a maintained effect in patients treated at a stable TBZ dose for 2 months or longer. The between group difference in Study 005 was 2.4 on the chorea score, a difference that was not statistically significant, $p = 0.078$. Therefore, long-term efficacy has not been established.

The sponsor believes this result reflects the improper conduct of the study; patients in Group 2 accidentally did not receive TBZ the morning of day 3, the day for collection of the primary efficacy data. As a result, patients in Group 2 received their last dose of TBZ 12-18 hours before assessment.

Pertinent to the time off drug for patients in Group 2, the sponsor would like to distinguish TBZ from another similar drug, reserpine. Both are monoamine depleting agents. The sponsor maintains that the effect of TBZ is rapidly reversible, different from the irreversible, long-lasting monoamine depletion seen with reserpine. The sponsor maintains that the duration of action for TBZ in humans is short (approximately 12 hours) as compared to days for reserpine.

There is another plausible explanation for the smaller between group difference seen in Study 005. The average TBZ doses across the 3 groups in Study 005 were 60mg/day, 45mg/day, and 54mg/day. In Study 004, 40% of patients achieved a dose of 100mg/day at week 12, 20% achieved a dose of 50mg/day at week 12, with the rest roughly equally distributed between 37.5 and 100mg/day. The lower doses, on average, in Study 005 could have resulted in the smaller between-group difference.

Has the Sponsor Presented Adequate Information to Support the Approval of TBZ for the Treatment of Chorea in Huntington's Disease?

The effect size from Study 004 appears modest, a mean between-group difference of 3.5 points on the chorea scale, but the categorical results appear more impressive. No benefit on any of the numerous functional outcome scales was demonstrated to reflect this change on the chorea scale and the functional checklist and cognitive scale move in the wrong direction. The CGI nominally suggests "much improvement" for almost half of the TBZ-treated patients, but the CGI was completed by the treating physician. As such, it might mirror the results on the chorea scale and it probably does not reflect the clinical relevance from the patients' perspectives. At the same time, the adverse events of depression and Parkinsonism could easily alter functionality and quality of life for patients with Huntington's disease.

Therefore, at best, we have evidence of an effect on the chorea and only maintained for a period of 5 weeks. At the same time, I am not aware of any evaluations performed in Study 004 that were performed specifically by the patients that might establish the value of the change in chorea to the patients themselves.

One expert in the movement disorder field wrote, "In general, mild chorea should not require any treatment, as the consequences of therapy may be worse than any short-term relief."³ Another wrote, "In general, the fewer medications the better because the side effects are often more deleterious than the medicines are beneficial...In the early stages of HD, the chorea and rigidity can be alleviated somewhat by dopamine

³ O'Brien CF. "Chorea." Chapter in: Jankovic and Tolosa (eds), Parkinson's Disease and Movement Disorders, Williams and Wilkins (1998).

antagonists and agonists, respectively, but these substances become less helpful later in the illness.”⁴

The clinical presentation of Huntington’s disease is variable. Indeed, this phenotypic variability is believed to be characteristic of the CAG repeat hereditary disorders. Even within the same pedigree, any number of problems can be the presenting symptom and predominate over time, to include chorea, rigidity, cognitive decline, and behavioral disorders. Given that the disease is multifaceted and progresses over time, it seems critical to establish the efficacy of TBZ beyond a few months. In doing so, it seems important to better understand the effect of TBZ not only on the chorea, but also on the other dimensions of the disease, to include the rigidity, the cognitive decline, and the functional status of the patient.

The approval of TBZ with the accrued data would require suspension of the usual requirements for 2 independent controlled trials. There is a guidance document (Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products) that allows for approval with a single study plus confirmatory evidence, but this is generally intended for cases where there is an effect on mortality or irreversible morbidity. That is not the case here.

Absent that, the question is whether TBZ is a case where we would want to suspend the usual requirement for 2 independent studies. HD is a tragic disease. There are no drugs that carry an approved indication for the treatment of HD. I think if the sponsor could present evidence that the change in chorea seen in Study 004 resulted in some measurable benefit to patients (patient global or functional scale improvement), then I would argue to suspend the usual requirements and approve TBZ with the one study plus confirmatory evidence standard.

But that is not the case. Consider that: 1) there is no patient measure of satisfaction in Study 004; 2) there is no evidence of a functional correlate with the decreased chorea in Study 004; 3) there is some evidence of a cognitive decrement; 4) there is some evidence of functional decrement based on the functional checklist; 5) the safety profile of TBZ prominently includes depression, suicidality, and Parkinsonism; and 6) there is a concern raised in the literature of worsened dysphagia due to TBZ predisposing to aspiration pneumonia.

Given these points, this does not seem to me to be the place to abandon the usual 2-study standard. Further, I think there is something valuable that can be gained by further study. And, pending further study of TBZ, neuroleptics are available for the off-label treatment of chorea.⁵

⁴ Young A. “Huntington’s Disease and Other Trinucleotide Repeat Disorders.” Chapter in: Martin (ed), Molecular Neurology, Scientific American, Inc. (1998).

⁵ A further note about neuroleptics: in contrast to TBZ, the metabolism of many neuroleptics is well-described allowing for labeling for drug-drug interactions. Such information is currently lacking for TBZ and this fact alone raises questions whether TBZ can be safely marketed for the HD population.

One possible option would be to repeat a randomized-withdrawal study. The study should ideally include all relevant assessments for HD, not just the chorea score and TFC scale. The period of withdrawal should also be longer than 5 days, perhaps 2 weeks, to allow for washout of drug effects.

There are 2 questions that a new randomized-withdrawal study could address:

- 1) Is the efficacy of TBZ maintained over time in patients with Huntington's disease?
- 2) If the efficacy is maintained, at what cost to the steadily declining cognitive, behavioral, and functional status of patients with Huntington's disease?

Even if Study 005 had been conducted per protocol, it might not have fully addressed the first question. The inclusion criteria only required that patients be treated for a minimum of 2 months with TBZ prior to randomization. As such, many patients were enrolled who had only taken TBZ for 2-3 months. To fully answer the first question, a new study might only enroll patients treated for a minimum of 18 or 24 months.

Even a new randomized-withdrawal study will not fully address the second question. Patients who develop the most marked declines in cognitive, behavioral, or functional status on TBZ might be expected to stop TBZ, so that the patients enrolled in the new study might represent an enriched population of patients who tolerated the drug over time. Nevertheless, even with that limitation, such a study in patients treated with TBZ long-term would be the best way to characterize the long-term effects of TBZ on cognitive, behavioral, and functional status in patients with HD.

Another option would be to perform a 3-6 month study, but including patients with greater functional impairment than were enrolled in Study 004. The sponsor has argued that the failure to show functional improvement in Study 004 resulted from the fact that patients did not have significant functional impairment at baseline. In a new study, patients could be enrolled with impaired ambulation and the effect of TBZ on chorea could be correlated with improvement in gait.

Recommendations

I recommend a Not Approvable action at this time. I believe an additional study should be performed. The randomized-withdrawal study described above has the potential to characterize the long-term efficacy and safety of TBZ.

There are a number of issues that should be included in the Not Approvable letter. Several are listed here.

Obviously, the results of Study 004 were driven largely by a subset of patients with marked improvement in chorea scores. I am concerned that there may be a direct correlation between improvement on chorea and worsening in other domains, to include cognitive, behavioral (especially depression), and functional (resulting from Parkinsonism and worsening dysphagia). The sponsor should investigate the effects of TBZ on these other domains (by reviewing the different outcome scales) for the subset of patients with the greatest improvement in chorea in Study 004.

The sponsor should also directly address the possible under-reporting of dysphagia in their database, suggested by the clinical site inspection at Baylor.

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/s/

John Feeney
3/21/2006 02:03:36 PM
MEDICAL OFFICER

Carole L. Davis
NDA 21,894
Tetrabenazine (TBZ)

CLINICAL REVIEW

Application Type NDA
Submission Number 21,894
Submission Code RS

Letter Date September 23, 2005
Stamp Date September 23, 2005
PDUFA Goal Date March 26, 2006

Reviewer Name Carole L. Davis, DNDP
Review Completion Date March 23, 2006

Established Name Tetrabenazine (TBZ)
(Proposed) Trade Name Xenazine
Applicant Prestwick Pharmaceuticals, Inc.

Priority Designation Priority

Formulation Tablets
Dosing Regimen 12.5 to 100 mg/day
Indication Chorea of Huntington's disease
Intended Population Adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

For the efficacy review, I would consider the application of tetrabenazine, for the indication of management of the chorea associated with Huntington's disease, as NOT APPROVABLE. Prestwick Pharmaceuticals has presented the FDA with one well-designed, multi-center clinical study that demonstrated the effectiveness of tetrabenazine in decreasing the chorea of Huntington's disease. The second pivotal trial, the withdrawal study, showed a trend suggestive of effectiveness, but was not statistically significant. It experienced major implementation flaws, and other problems, that limit, or eliminate, its usefulness in support of the application. The FDA had recommended repeat of a second confirmatory trial, but had not required it in order to go forward with the review process of the NDA, and a repeat or additional study was not done.

Based on the strong clinical findings of the pivotal multi-center study, an approvable action would be recommended based on the efficacy review if supportive data suggested by the failed second study, and the uncontrolled open-label studies, were allowed to contribute to the decision. This evidence to date suggests that if a second controlled clinical trial were done, it would show a level of effectiveness similar to that documented in the multi-center trial. However, the 1962 Drug Amendments Act establishes requirements on the establishment of a drug's effectiveness. "With regard to quantity, it has been the FDA's position that Congress generally intended to require at least two well-controlled studies, each convincing on its own, to establish effectiveness" (Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May, 1998). With a well-designed multi-center single study, flexibility has been allowed under certain special circumstances that allow acceptance in situations where the strong evidence for the drug has important clinical benefits, such as effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

Some of the factors considered for exemption of the two-confirmatory studies rule include, in addition to very convincing statistical results, evaluation for internal consistency across subgroups, centers, and multiple endpoints. While this application does provide such evidence for both of the first two factors, the only endpoint on which it was able to demonstrate effectiveness was on chorea scores. It had been given a priority review status primarily based on the assumption that improvement of chorea control would result in improvements in gait safety and functional activities (activities of daily living). The study was not able to show significant treatment benefit in these areas, and results generally trended toward the placebo group. On cognitive assessment, the placebo group was favored at a statistically significant level. The only ratings done by HD patients and/or caregivers were on the functional assessments. Lack of expected other effects accompanying a critical outcome can weaken the persuasiveness of a single trial. Tetrabenazine is presented for review for the management of a symptom (chorea), not for affecting the course of the underlying disease. At present, there is no accompanying indication from the subjects involved in the studies that the drug improved their functioning or

made them feel better. In view of the agency regulations, an additional confirmatory study is probably necessary before the drug could be marketed, and the population of HD patients is large enough that enrollment for an additional study should not pose a serious obstacle for the Sponsor.

Based on the efficacy review, I consider the tetrabenazine application as having established most of the criteria for effectiveness in managing the chorea of Huntington's disease, but failed in its obligations to meet the established parameters for drug approvals. Prior to full approval, the following should be done:

- Completion and review of an additional placebo-controlled, double-blind study that confirms effectiveness of tetrabenazine for the management of chorea associated with Huntington's disease. If the study design is for a withdrawal trial, it should be lengthened to ~ 2 weeks. The extra time would allow a longer follow-up for assurance that the chorea scores evidenced in the first few days after drug withdrawal are not including a rebound effect. The study could be simplified to a two group trial.
- An assessment of the effect of tetrabenazine on cognitive functioning.

Safety Summary – Dr. D. Elizabeth McNeil conducted the review, and has requested:

A confirmatory placebo-controlled, double-blind 12-week study showing that the incidence of parkinsonism was reduced with a slower rate of titration;

A drug-drug interaction study evaluating the potential interaction with oral contraceptives since many women with this hereditary neurodegenerative disease choose not to reproduce;

A drug-drug interaction study to evaluate the potential interaction between tetrabenazine and common antidepressants since depression has a high prevalence in Huntington's disease patients;

An endocrine study of at least 12 weeks to evaluate the effect of tetrabenazine on the endocrine function in women. Hyperprolactinemia may be associated with osteoporosis in addition to decreased fertility. Osteoporosis may be an additional risk factor for broken bones in patients who are prone to falls due to their chorea.

CMC Summary – Dr. Tele and Dr. Soldatova conducted the review and state that NDA 21-894 for Xenazine (tetrabenazine) Tablets is recommended APPROVABLE from the CMC standpoint. The approval from CMC standpoint is contingent on the overall recommendation on establishment from the Office of Compliance and satisfactory resolution of the DMF deficiencies. Based on the stability data, 36 month expiry could be granted for Xenazine Tablets.

Biopharm. Summary - The clinical pharmacology and biopharmaceutics information submitted to NDA 210894 is acceptable provided that the following are addressed prior to approval:

1) The Sponsor has been asked to clarify the rotation speed at which the dissolution method as generated (request was sent on 1/2/06 and as of 2/14/06 there has been no response).

If the Sponsor has data to support the proposed rotation speed and agreement is reached between the Sponsor and the Agency 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, the Sponsor 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) Adequately performed *in vitro* metabolism studies be submitted to address the potential for inhibition or induction of P450s by TBZ and its metabolites. The Sponsor should also characterize the *in vitro* metabolism of TBZ and its metabolites as well as the role for Pgp in TBZ disposition. Finally, the Sponsor 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.

5) Tetrabenazine should be contraindicated in patients with hepatic impairment since the exposure to TBZ in hepatic impairment is > 70-fold greater than the exposure in healthy subjects. Without information on changes in efficacy and safety, it is not possible to recommend a dosage adjustment.

6) Agreement is reached between the Sponsor and the Agency regarding labeling

1.2 Recommendation on Post-marketing Actions

No recommendations are included at this time.

1.2.1 Risk Management Activity

The risk management plan submitted by Prestwick Pharmaceuticals, Inc. states that "Overall, risk management in patients with chorea associated with HD treated with tetrabenazine is primarily associated with the intrinsic problems of HD rather than the unique features of the drug". The only AE mentioned that was considered to require monitoring was depression. The strategy and tools to be used were not yet finalized, but plan to rely on proposed labeling that contains warning information on depression and educational tools to communicate information about depression risk to various audiences.

The Sponsor should be encouraged to expand monitoring to include surveillance on drug-drug interactions since the intended population will frequently be on multiple medications. In addition to depression, the efficacy studies to date have also indicated the potential for AEs related to parkinsonism, akathisia, falls and injuries (sometimes associated with "blacking out" according to accompanying reports) possibly due to orthostatic changes, increased confusion, and aspiration pneumonia secondary to increased dysphagia. Sedation and drowsiness are common AEs for tetrabenazine, so safety issues will need consideration. The effect of tetrabenazine on cognitive functioning is not yet clarified, and may need monitoring.

1.2.2 Required Phase 4 Commitments

Biopharmacology recommends the following Phase 4 commitments:

The Sponsor should address the following issues as Phase IV commitments:

- 1) *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.

See the Safety Review and the Pharm/Tox Review for additional recommendations.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests at this time, but Pharm/Tox review is pending.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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 has been 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.

Prestwick Pharmaceuticals, Inc. has 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.

1.3.2 Efficacy

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)

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, the Functional Assessment Checklist, and Gait on the UHDRS, and change in the Clinical Global Impression, Part II.

(b) Prestwick Tetra Withdrawal Study (TBZ 103,005)

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 score of the UHDRS from Day 1 to Day 3 comparing Group 1 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 (contained in Appendix C). 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 Clinical Global Impression Scale (CGI). The CGI is an evaluation (3 items) by the investigator of

whether the change in a subject's condition was due to the drug treatment. 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).

Protocol TBZ 103,004

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 an assessment after a 1-week drug withdrawal at the end of the study.

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 (± 3.84) UHDRS points at baseline and 9.41 (± 4.45) points at the End of Week 12. This gave them a change in score of -5.04 (± 0.49) points. This was compared to the placebo group's mean TCS decrease of 1.52 UHDRS points (15.20 ± 4.41 at baseline, and 14.07 ± 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 (± 4.21) UHDRS points, only slightly higher than their baseline score of 14.69 (± 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 (± 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 (± 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. There was in the scores of the groups (only a fraction of a point) making statistical 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, but have been included in this review. The study included 10 exploratory endpoints, and the Functional Impact Scale which apparently was added later.

- 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).

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 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 (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 part 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 Stroop Interference – Words reached statistical significance (p-value = 0.0123), and Stroop Interference – Interference nearly did (p-value = 0.0532). The sum of the Cognitive Assessment showed TBZ group worsened by 7.7 (± 3.3) points from its mean baseline of 156 (± 56) points, while the placebo group improved by 5.1 (± 4.5) points from a baseline of 172 (± 55) points. The estimated difference of 12.8 (± 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 (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 and daily functional activities of HD patients. The secondary endpoints failed to show any connection with that 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 ≥ 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.

Withdrawal Protocol TBZ 103,005

The other efficacy study submitted, the Prestwick Withdrawal Study Protocol TBZ 103,005, was designed to show that chorea returned/increased if tetrabenazine was discontinued. It was a staggered 5 day withdrawal study using 30 subjects at one site. For evaluation of the primary efficacy endpoint, the first group was to be withdrawn from the drug, switched to a placebo, and the return of their chorea was contrasted to the two groups still receiving the TBZ.

Evaluation of Withdrawal Protocol TBZ 103,005 was problematic due to a "flawed execution" of the study design. The designated primary endpoint for demonstration of efficacy was change on Day 3 in the TCS of Group 1 (withdrawn from TBZ on Day1) compared to the mean combined scores of Group 2 and Group 3 (still on "best dose" TBZ). On Day 3, due apparently to a misinterpretation of the protocol, the Group 2 had been prematurely taken off the TBZ for 12 to 18 hours prior to the assessments. The resulting analysis did not show statistical significance (p-value = 0.0779).

A comparison close to the original endpoint could have been the same analysis with the Group 2 excluded (i.e., comparison on Day 3 of Group 1 to Group 3). This comparison still did not show statistical significance (p-value = 0.111) because of an underlying problem with the small numbers and the randomization. The baseline TCS was closely matched for Group 1 and Group 2 (9.4 \pm 4.9 points and 9.1 \pm 6.2 points respectively) and each had 12 subjects. Group 3, on the other hand had only 6 subjects, and their baseline TCS was 11.2 (\pm) points, which could introduce some error into group comparisons.

In finding other ways to evaluate the data, the Sponsor suggested that a trend was evidenced if Group 2 was used as a “middle group” of the withdrawal continuum. Using that, the Sponsor did a retrospective, ad hoc trend analysis which gave an unadjusted p-value = 0.0486. However, using a trend analysis would require shifting the level for significance to $p = 0.025$ after adjusting for the other tests conducted, and the analysis would not reach statistical significance. They also looked at combining Group 2 with Group 1 (since both were off TBZ) for comparison to their baseline scores, which did indicate more statistical significance ($p < 0.001$).

Again on Day 5 there was apparently miscommunication about the protocol. The subjects were to have taken their assigned Bottle 2 tablets prior to evaluation (placebo for Groups 1 and 2, and TBZ for Group 3). However, none of the subjects received their assigned tablets prior to testing, so Group 3 had been off TBZ for 12 to 18 hours. As a result, Group 3 could no longer serve as a control group for the study. It is also necessary to note that four of the subjects were taking prohibited neuroleptics throughout the study which was a protocol deviation.

Despite the fact that the study did not achieve statistical significance, or even protocol adherence, it is note-worthy for the change in chorea scores within each group and the time-response curve that it suggests. Group 1 (off TBZ since Day 1) had a mean increase in the Maximal Choreia Score of 5.4 points on Day 3, and 5.4 points on Day 5. The change of 5.4 points on the chorea scale was achieved by Day 3 and stable on the follow-up evaluation (Day 5) which argues against a rebound effect occurring. Likewise, Group 2 (off TBZ for 12 to 18 hours on Day 3) had an increase in the mean TCS of 3.6 points on Day 3, and 5.5 points on Day 5. The finding suggest that there is a rapid change in chorea scores after discontinuation of TBZ, and it stabilized at nearly the same level of change as that seen in Group 1.

Additional Comments on the Efficacy Trials:

The 12 week study showed strong statistical significance in the change from baseline to maintenance phase (Weeks 9 + 12), the pre-specified endpoint, with the 3.5 point decrease in chorea attributed to tetrabenazine effect ($p\text{-value} = < 0.0001$). If only the baseline to end of study (Week 12) TCS score is used, the treatment effect difference was even larger at -4.4 points ($p\text{-value} = < 0.0001$). Data analysis evaluating for the possible effect of missing data, dropouts and protocol deviations indicated that the primary results would not have been significantly altered by any of these factors. The study strongly provides evidence of efficacy that supports the indication for chorea in Huntington’s disease.

Tetrabenazine is treating a symptom (chorea) during a period of the illness, but not affecting the course of the underlying disease, so it must have independent substantiation. It could be argued that the need for independent substantiation of a single study could be met in the case of this application by consideration of the consistency of the findings at the multiple study sites, and/or the comparison of the study findings to the published literature of uncontrolled studies. Overall, the 30+ years of clinical experience with the drug both overseas and in the US could be argued to strongly reinforce the claims for efficacy. However, under FDA guidelines, the burden of prove still lies with well-designed, well-controlled studies.

The pivotal study also had a withdrawal study component in its Week 13 evaluation which could have been viewed as a stand-alone study for internal reinforcement. Its usefulness is compromised by the loss of randomization inherent in the loss of subjects during course of the study. The other measures of internal reinforcement that could be applied to the efficacy claims of the study are problematic. When checking for internal reinforcement of results by looking at the non-chorea endpoints, they did not translate into any improvement in the gait or functional scores, nominally but rather consistently trending toward placebo, and the cognitive assessments statistically favored placebo, which is very troubling, especially when considering bringing a drug onto the market that could be used continuously by any patient for several years.

The Baylor Chorea Database and review of the literature is all suggestive of improvement of chorea with the use of tetrabenazine. The open-label studies and published literature lack recent controlled studies, but generally place the response rate at 60 to 90% of the patients showing at least minimal improvement in their chorea with TBZ use. The findings of the Sponsor's pivotal study, with 69% rated as "responders", falls within the same range.

Adequacy of blinding is rather problematic in trials of a condition such as chorea, especially when there is a very high association of side-effects such as sedation in the groups receiving the drug, and with flexi-dosing titration, subjects receiving placebo should have progressed steadily to the maximum of allowed tablets. For this reason, the FDA had recommended to the Sponsor that videotaping of subjects be done and reviewed by an independent expert, but as noted above, there were some implementation problems with it that might have affected randomization.

Only the first study could give a real indication of how the drug would work on the intended population in terms of estimating the number of non-responders, serious adverse events, and all the other exploratory information that application trials should elicit. The design of the withdrawal study adds no additional information on the possible responses of patients that might be started on the drug in the future, since the subjects were previously on "best dose" of the drug, but is quite useful as an evaluation of the maintenance of effectiveness of the drug treatment over time. In the Withdrawal Study, information on the amount of time that each subject had been receiving tetrabenazine prior to enrollment was not recorded on the CRFs, but when contacted, the Sponsor obtained the information from patient records. The mean duration of prior TBZ treatment was 2.5 years with a range of 0.21 to 7.07 years. The largest group had been on the drug for < 1 year, 13 of the 30 subjects (43.3%). Overall, 60% had been on TBZ for ≤ 2 years, and 40% for > 2 years (including the 13.3% who had used it for > 5 years) prior to the withdrawal. The findings suggest that the chorea returns to previous level shortly after discontinuation of the drug. A longer follow-up after the withdrawal would be useful to determine that the post-withdrawal scores do not include a temporary rebound effect. In the multi-center trial, the TCS assessment scheduled for Week 13 (one week after study drug withdrawal) was not done for several of the subjects until a few weeks later, so any possible score elevation due to a rebound effect would have been eliminated.

1.3.3 Safety

This addressed in the safety review done by Dr. D. Elizabeth McNeil, DNP

1.3.4 Dosing Regimen and Administration

Tetrabenazine is administered orally in 12.5mg or 25 mg. tablets. BID and TID dosing has been used with higher doses. The drug has a rapid onset (C_{max} within 1 to 1½ hours), and a relatively short half-life (from 3 to 5 hours) for its active metabolite, so split-dosing is considered more likely to provide control of the symptoms. The adequacy of dose finding has been best addressed historically by the number of patients and the total patient-years on the drug. Since tetrabenazine is used clinically on a flexi-dose pattern of titration to efficacy balanced against tolerability, there is a great deal of accumulated information on individual “best dose” dynamics.

The study investigators argued against the use of fixed dose use in the studies stating that a fixed dose pattern was not in keeping with the clinical practice for chorea management, and that flexi-dosing had been used in the previous published studies. The FDA concurred with the use of flexi-dosing for the current studies.

The window between decreased chorea symptoms and intolerability due to side-effects has been noted to be quite narrow in previous studies, and the same findings emerged in the current trials. “Best dose” attainment seems to be quite varied between patients, but generally remains relatively stable, once established, for each patient. The single most common “best dose” in the Baylor Database was 75 mg/day. The mean “best dose” was 65.3 (± 35.4) mg/day. The mean duration of treatment was 2.6 (± 2.5) years, and 32 patients had been treated for ≥ 4 years. Change in the required dosage has generally been attributed to the progressive course of the Huntington’s disease rather than decreased responsiveness to the tetrabenazine.

In the 12 week study submitted. The most frequently ascertained “best doses” were 50 mg/day and 100 mg/day. Nearly all of the subjects taking 50 mg/day (10 of the 11, 91%) had a decrease in chorea score of > 3 points. Only 13 of the 22 (59%) receiving 100 mg/day had the same decrease in chorea, probably because the group included non-responders. Nearly all (93%) of the placebo group were taking the maximum of 8 tablets/day by the end of the titration phase.

1.3.5 Drug-Drug Interactions

Prestwick Pharmaceuticals, Inc. did not formally evaluate this product for potential drug-drug interactions.

1.3.6 Special Populations

There were no significant differences in response to tetrabenazine based upon gender or age. in The mean age in the 12 week study was 49 years, and only 7 (9%) of the subjects were age 65 or older (5 on TBZ and 2 on placebo) which is too small a number for meaningful analysis. Similarly, this product was not adequately assessed in non-Caucasians (only 5 subjects, 6%), so it is not possible to comment on potential racial or ethnic differences.

2 INTRODUCTION AND BACKGROUND

Huntington's disease is a neurological disorder associated with the progressive degeneration of nerve cells in the basal ganglia structures of the brain. It primarily targets the caudate nuclei and the pallidum of the striatum affecting movement and coordination, but also affects the cortex which controls thought, perception and memory. It is an autosomal dominant disorder with a 50% chance of inheritance from an affected parent; it does not skip generations. Research has shown that it is inherited as a single faulty gene on chromosome 4, with abnormal repeats in a part of the gene which result in gene folding. The gene contains a specific section of expansion with a pattern of "trinucleotide repeats" of CAG occurring >40 times (in most people such repeats occur = ≤ 30 times). The symptoms usually appear in adulthood, with onset typically between ages 35 to 50 years, but it can present much earlier. About ~ 10% of the cases affect children or adolescents (Westphal variant). The HD gene was found in 1993, and a test developed to determine the possible gene-carrying status. Diagnosis is determined by the number of CAG repeats. The prevalence rate of HD in the U.S. and Europe has been reported to be in the range of 4-5 to 8-10 per 100,000. Clinically manifest HD occurs in approximately 1 in 10,000 people in the U.S.; currently about 30,000 people in the U.S. have HD.

Huntington's disease is inexorably progressive, and most patients require institutionalization in the end-stages of the disease. Among the characteristic symptoms of the disease is a variety of movement disorders. Huntington's disease is usually characterized by a symptomatic triad of chorea, progressive dementia, and personality disorder. Progressive abnormal facial and body movements develop, including unsteady gait and choreiform movements. Not all of the HD patients have symptoms of chorea, and ~ 6 – 10% have muscular hypertonicity and bradykinesia. There is no cure or halting of the progression of HD. It is usually fatal within 15 to 20 years (often due to infections such as aspiration pneumonia, or suicide due to depression). Treatment has been symptomatic to manage the depression, abnormal behaviors and movements. Some of the commonly used drugs have been haloperidol, phenothiazine, Resperine, Tetrabenazine, Amantadine and Co-Enzyme Q10, as well as the antidepressants.

Tetrabenazine (TBZ) is proposed as an original NDA by Prestwick Pharmaceuticals, Inc. for the treatment of the chorea associated with Huntington's disease (HD). It is a catecholamine depletory used for the treatment of a variety of movement disorders. TBZ has been granted "orphan" designation and "fast track" designation for the specific indication of chorea associated with HD. It is available in the US under several investigator INDs and has been used on hundreds of patients with hyperkinetic movement disorders over the past 25+ years.

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 that indication because of the entry of more efficacious psychiatric drugs.

Tetrabenazine is a selective, centrally-acting monoamine depletory. Monoamine depletion is caused by the selective binding and inhibiting of the synaptic vesicular monoamine transporter type 2 (VMAT2) expressed nearly exclusively in the brain. The result is preferential depletion of dopamine (DA) from nerve terminals located primarily in the caudate (Pearson, et al., 1988).

Reserpine, another dopamine-depleting drug, has binding-affinity to both VMAT2, and to VMAT1 which is expressed in the peripheral tissues. It is inferred that the selectivity of TBZ for central rather central & peripheral binding may give it an advantage in symptomatic management of HD by being less likely to cause problems such as orthostatic hypotension.

2.1 Product Information

2.1.1 Product Name and Description

Tetrabenazine, the proposed marketed name is Xenazine

2.1.2 Chemical Class

Tetrabenazine is a hexahydro-dimethoxy-benzoquinolizine derivative

2.1.3 Pharmacological Class

Tetrabenazine is a monoamine depletor

2.1.4 Proposed Indication, Dosing Regimen, Age Groups

The proposed indication for tetrabenazine is the management of the chorea associated with Huntington's disease. Chorea is one of the symptoms of HD and the pattern and severity varies from person to person. During the early stage of the disease, the movement changes are usually subtle changes in coordination and perhaps some involuntary movements. Abnormal movements tend to be increased by volitional effort, stress and excitement. Chorea becomes more prominent in the middle stages of the disease, often accompanied by a staggering gait due to difficulties with balance and coordination, and also speech and/or swallowing problems. In the late stages of the disease, chorea may become more severe, but more often problems develop instead with rigidity.

and some subjects in the controlled clinical trials were on one tablet of the lowest strength as their "best dose". The recommendation is for titration of the drug to the "best dose" level which is individualized for each patient as the level where efficacy and tolerability is achieved with minimal side effects. During the controlled clinical study Protocol TBZ 103,004, the drug was started at 12.5 mg/day and titrated upward weekly by 12.5 mg increments until "best dose" was achieved. The study rationale for the timing of the adjustments was that tetrabenazine achieves maximal effectiveness in 5 days, and the development of parkinsonism as a drug-related side-effect takes 3-4 days. Most patients achieve their "best dose" level at < 100 mg/day.

Tetrabenazine 12.5 mg. strength is a white unscored tablet. The 25 mg. strength is a scored, yellowish-buff tablet. Both are taken orally. These are the strengths that have been marketed overseas, and the same dosages are proposed for manufacturing in the US market.

Controlled testing on tetrabenazine has only been done using adult subjects.

2.2 Currently Available Treatment for Indications

There currently is no FDA-approved treatment for the chorea symptoms of HD, and no treatment to prevent the progression of neurodegeneration in the disease. Chorea is the movement disorder most commonly associated with HD. It is brief, purposeless involuntary movements primarily of the distal extremities and face. These may merge imperceptively into purposeful or semi-purposeful acts that mask the involuntary motion.

The choreic movements and agitated behaviors may be suppressed, usually only partially, by antipsychotics (eg, chlorpromazine 100 to 900 mg/day po, or haloperidol 10 to 90 mg/day po) or Reserpine begun with 0.1 mg/day po and increased until adverse effects of lethargy, hypotension, or parkinsonism occur. Therapeutic strategies to replace brain GABA stores have been ineffective. Experimental therapies aim to reduce glutamatergic neurotransmission via the N-methyl-D-aspartate receptor and bolster mitochondrial energy production.

Patients in the US have been receiving TBZ for the treatment of chorea since the early 1980s under physician Investigational New Drug Applications (INDs) for studies, and for compassionate use. The first study was conducted at the Parkinson's Disease Center and Movement Disorder Clinic at Baylor College of Medicine in 1982 with 19 patients. Between 1980 and 1995, 526 patients have been treated with TBZ in the open-label studies done at that center by Dr. J. Jankovic, and other movement disorder centers around the US have made the drug available to individual patients.

2.3 Availability of Proposed Active Ingredient in the United States

Tetrabenazine is not licensed for sale in the US. It is currently available to HD patients enrolled in studies under physician INDs, but obtained from overseas manufacturing plants.

2.4 Important Issues with Pharmacologically Related Products

Reserpine, a rauwolfia alkaloid, is the only other drug known to inhibit vesicular monoamine transporter-2 (VMAT2). The central effects of TBZ closely resemble those of Reserpine. Tetrabenazine primarily depletes dopamine in the CNS (VMAT1-selective). Reserpine has binding-affinity for VMAT2 and VMAT1. In addition to dopamine, it also depletes 5-hydroxytryptamine (5-HT) and norepinephrine (NE) which gives it more peripheral involvement. Reserpine has been tried for the management of hyperkinetic movement disorders, but is licensed only as an anti-hypertensive medication, and would require close monitoring for orthostatic hypotension if used for other patients. Depression has been reported in the literature as a side-effect of both TBZ and Reserpine treatment.

Dopamine receptor blocking agents have generally been considered the first line treatment for chorea. Neuroleptics such as haloperidol and perphenazine have been used for the management of various movement disorders. They are usually started at a low dose and titrated to effectiveness. They appear to have at least a modest suppressive effect on chorea because of their ability to block dopamine receptors, and their antipsychotic properties may also be of some

short 2-day withdrawal study, to provide a second confirmatory study. Error was noted in the method used to adjust for baseline differences in chorea scores, and the Sponsor agreed to correct its analysis.

06/13/05 Prestwick Pharmaceuticals submitted a voluntary withdrawal of NDA 21,894.

6/30/04 Meeting Minutes FDA and Sponsor

- FDA discussed weaknesses in the TetraHD study that mitigate its use alone as a single study – sponsor required to submit 2 pivotal studies.
- FDA noted that between-group difference on the primary endpoint is rather modest even though the p value is substantial; the between-group difference on the secondary global endpoint is also modest; and some functional scales showed no benefit.
- Problems = (a) some degree of unblinding may occur since study calls for titration to a max. tolerated dose. Recommendation was for chorea analysis to be done by video record by blinded investigator (being done, but not as an end-point)
- For the second study (proposed) concern that a 3 day primary endpoint measure may be a little short because of the issue of potential rebound. (Sponsor noted no rebound on day 5 of withdrawal) – needs analyzed
- Lit review of risk of effects on other transporters or drug-drug interactions via transporters
- FDA questioned why TBZ was given IV in some of the pre-clinical studies, and stated that a mass balance study was needed since only 55% of dose recovered after 48 hours.
- FDA inquired as to whether hepatic impairment studies had been done.

9/12/05 FDA acknowledging withdrawal without prejudice & discussed filing issues (deficiencies in ISS module) & suicide signals guide NDA letter – drafted 06/14/05

09/23/05 Prestwick resubmitted NDA 21,894 (paper form, 80 volumes) with an Integrated Summary of Safety (ISS), which the FDA had required prior to review.

10/18/05 Prestwick submitted eCTD Reviewer's Tool.

2.6 Other Relevant Background Information

Tetrabenazine has been registered in several countries (including Australia, Canada, Denmark, Hong Kong, Ireland, Israel, New Zealand, Norway, Portugal and the United Kingdom) between 1971-present. It is currently in use in these countries for the treatment of a variety of hyperkinetic movement disorders, including Huntington's disease and tardive dyskinesia.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

Tetrabenazine is not a biological agent. The full chemistry review has been filed separately.

3.2 Animal Pharmacology/Toxicology

The Pharmacology and Toxicology review was conducted by Dr. Andrea Powell, DNDP. Review currently pending.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the studies conducted for Prestwick Pharmaceuticals, Inc. and included in this application. Additional information was obtained from the company in response to requests for information.

(a.) Trials conducted by the Sponsor:

Phase I studies (six in healthy volunteers, and one in liver-impaired subjects)

Bioavailability Studies PK - Prestwick Food Effects, Phase 1 Study (TBZ 103,003)

Bioequivalence, Phase 1 Study (104,012)

Healthy Subject PK and Initial Tolerability Studies

PK - Cambridge Laboratories Study 1700114

Extrinsic Factor PK Studies - Digoxin

PK - Prestwick TetraDig Study (TBZ 203,009)

Intrinsic Factor PK Studies

PK - Prestwick Comparison of TBZ in Liver-impaired and Healthy Subjects (TBZ 203,010)

Healthy Subject PD and PK/PD Studies - Hormones

PK/PD - Prestwick Prolactin Study (TBZ 202,001)

PK/PD - Prestwick Tetra-Hormones Study (TBZ 203,008)

Phase II/III Studies

Efficacy and Safety – Double-blind, Randomized, Placebo-controlled Clinical Studies Pertinent to the Claimed Indication of Chorea:

Prestwick TetraHD Study (TBZ 103,004)

Prestwick Tetra Withdrawal Study (TBZ 103,005)

Safety & Tolerability - Open-label Follow-on Studies (interim reports only - with cut-off date of 10/31/04 received and SAE/deaths information through 02/28/05):

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Tetra Withdrawal FU (TBZ 103,006)
Tetra HD FU (TBZ 103,007)

(b.) Submitted studies not conducted by the sponsor:

Baylor Chorea Database - (Project TBZ 103,011)
Baylor Non-Chorea Database

(c.) Published Reports in the Literature

4.2 Tables of Clinical Studies

The following pages contain the lists of the studies submitted by the Sponsor for the use of tetrabenazine for the management of chorea. The studies are grouped by research Phase and type.

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Table 1. Description of Clinical Efficacy and Safety Studies

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/ discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
PK	Prestwick Food Effects Phase 1 Study [Study No. TBZ 103,003]	<ul style="list-style-type: none"> Determine effect of a high fat, high calorie meal on bioavailability of tetrabenazine 25-mg tablet. Compare the pharmacokinetics of HTBZ in men and women. 	Open-label, single-dose, randomized two-period, two-sequence, two-treatment crossover study.	Healthy volunteers; 28/25/3; Age range: 19-44 years; Mean age: 28.5 years; Gender: 14/14.	Oral dose of 25-mg tablet.	Two treatment periods of single dose each.
Bioequivalence	Prestwick Bioequivalence Phase 1 Study [Study No. 104,012]	<ul style="list-style-type: none"> Examine the bioequivalence of 2 x 12.5-mg and 1 x 25-mg tablets. 	Open-label, single-dose, randomized, two-period, two-sequence, two-treatment crossover study.	Healthy volunteers; 28/23/5; Age range: 18-44 years; Mean age: 26.9 years; Gender: 14/14.	Oral dose of 2 x 12.5-mg tablets or 1 x 25-mg tablet.	Two treatment periods of single dose each.

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Table 1. Description of Clinical Efficacy and Safety Studies (continued)

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/completed/discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
PK	Cambridge Laboratories Study 1700114	<ul style="list-style-type: none"> Evaluate tolerability and safety of single and repeat doses. Determine dose-proportionality of 12.5-mg and 50-mg single doses. Determine steady state of PK of 25-mg/day. 	<p>Regimen A: Two-way crossover study. Regimen B: Repeated-dose once daily for 5 days.</p>	<p>Healthy volunteers; Regimen A: 12/12/0 Age range: 22-45 years; Mean age: 33.25 years; Gender: 3/9.</p> <p>Regimen B: 25/25/0 Age range: 20-45 years; Mean age: 33.32 years; Gender: 10/15.</p>	<p>Regimen A: Oral dose of 0.5 or 2 x tetrabenazine 25-mg tablets. Regimen B: Repeated oral dose study of 25-mg tetrabenazine tablet.</p>	<p>Regimen A: 12.5 mg or 50 mg of oral tetrabenazine in a two-way crossover segment (1 day each segment).</p> <p>Regimen B: In the second segment, 25 additional healthy volunteers received 25 mg of tetrabenazine once daily for 5 days.</p>

Table 1. Description of Clinical Efficacy and Safety Studies (continued)

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/ completed/ discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
PK	Prestwick TetraDig Study [Study No. TBZ 203,009]	<ul style="list-style-type: none"> Assess effect of repeated doses of tetrabenazine (25-mg b.i.d.) on P-glycoprotein based on the bioavailability of digoxin. Examine the PK profile of tetrabenazine and its metabolites (α- and β-HTBZ) when co-administered with digoxin. 	Open-label, single treatment period study.	Healthy volunteers; 16/12/4; Age range: 20-42 years; Mean age: 27.9 years; Gender: 6/10.	Oral doses of 0.5-mg digoxin tablet Day 1 then 0.25-mg digoxin tablet daily on Days 2-6; oral doses of 25-mg tetrabenazine tablets b.i.d. Days 7-10 co-administered with digoxin 0.25-mg daily.	3 days
PK	Prestwick Comparison of Tetrabenazine in Liver Impaired and Healthy Subjects [Study No. TBZ 203,010]	<ul style="list-style-type: none"> Compare PK in subjects with mild- moderate liver impairment to those of age-matched healthy subjects. 	Open-label, single-dose study.	Healthy volunteers; 6/6/0 to date; Liver impaired subjects; 6/6/0 to date; Age range: 18-65 years; Mean age: NA years; Gender: 12/0.	Oral dose of 25-mg tetrabenazine administered as two 12.5 mg tablets; single dose.	6 days

Table 1. Description of Clinical Efficacy and Safety Studies (continued)

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/completed/discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
PK/PD	Prestwick Prolactin Study [Study No. TBZ 202,001]	<ul style="list-style-type: none"> Determine the effect of a single 12.5-mg oral dose of tetrabenazine on prolactin plasma levels. Determine α- & β-HTBZ after single 12.5-mg dose. 	Double-blind, randomized, placebo-controlled crossover study.	Healthy volunteers; 6/6/0; Age range: 22-41 years; Mean age: 31.2 years; Gender: 6/0.	Oral dose of 12.5-mg tetrabenazine tablet or placebo; single dose crossover.	1 day
PK/PD	Prestwick Tetra-Hormones Study [Study No. TBZ 203,008]	<ul style="list-style-type: none"> Establish effects of single (Day 1) and multiple (Day 2 to Day 4) doses of tetrabenazine on serum and plasma concentrations of prolactin, growth hormone, adrenocorticotrophic hormone, arginine vasopressin, cortisol, thyroid stimulating hormone and testosterone. 	Randomized, double-blind, placebo-controlled crossover study.	Healthy volunteers; 13/12/1; Age range: 18-35 years; Mean age: 27.7 years; Gender: 13/0.	Oral doses of 25-mg tetrabenazine tablets once daily (Days 1 and 4) or twice daily (Day 2 and Day 3) during 1 of 2 treatment periods.	4 days

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Table 1. Description of Clinical Efficacy and Safety Studies (continued)

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/ discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
Efficacy	Prestwick TetraHD Study [Study No. TBZ 103,004]	<p>Establish the efficacy and safety of tetrabenazine titrated to "best dose"</p> <ul style="list-style-type: none"> • 	Randomized, double-blind, placebo-controlled study in two parallel unbalanced (2:1) groups (tetrabenazine titrated to best dose: placebo)	Patients with Huntington's Disease; 84/78/6; Age range: 25-77 years; Mean age: 49 years; Gender: 32/52	Oral dose of 12.5mg Tetrabenazine tablets; titrated to optimal dose based on efficacy and tolerability from 12.5mg/day to maximum of 100 mg/day during the first 7 weeks, stable dose final 5 weeks	12 weeks; (includes 7 weeks titration, 5 weeks maintenance, followed by a 1 week washout)
Efficacy	Prestwick Tetra Withdrawal Study [Study No. TBZ 103,005]	<ul style="list-style-type: none"> • Examine the efficacy of tetrabenazine for the treatment of Huntington's chorea. • Assess the difference in the severity of emerging chorea 5 days vs. 3 days after tetrabenazine treatment discontinuation. 	Randomized, double-blind, placebo-controlled, staggered withdrawal study in three parallel, unbalanced groups of participants.	Patients with Huntington's Disease on stable doses of tetrabenazine; 30/30/0; Age range: 39-75 years; Mean age: 52.3 years; Gender: 12/18	Oral doses of 12.5-mg tetrabenazine tablets; participants randomly allocated to staggered withdrawal. 40% of participants switched to placebo on Day 1, 40% switched to placebo on Day 3, and 20% remain on study drug at original dose.	5 days

Table 1. Description of Clinical Safety and Efficacy Studies (continued)

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/completed/discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
Safety	Prestwick Open-Label Extension for Withdrawal HD study [Study No. TBZ 103,006]	<ul style="list-style-type: none"> Document the long-term safety of tetrabenazine for the treatment of chorea. Document the maintenance of efficacy in long-term treatment 	Open-label follow-up on study (48 weeks)	Patients with Huntington's Disease from TBZ 103,005; 29/29/0 at time of interim report; Age range: 39-75 years; Mean age: 57.28 years; Gender: 12/18	Oral doses of 12.5 mg or 25-mg tetrabenazine tablets; titrated to "best dose"; 12.5-200-mg/day.	Various as of interim report; planned 48 weeks
Safety	Prestwick Open-Label Extension for TetraHD study [Study No. TBZ 103,007]	<ul style="list-style-type: none"> Document the long-term safety of tetrabenazine for the treatment Document the maintenance of efficacy in long-term treatment 	Open-label follow-up on study (48 weeks)	Patients with Huntington's Disease from TBZ 103,004; 49/49/0 at time of interim report; Age range: 29-77 years; Mean age: 50.6 years; Gender: 26/49.	Oral doses of 12.5 mg or 25-mg tetrabenazine tablets; titrated to "best dose" 12.5 to 200mg/day	Various as of interim report; planned 48 weeks. planned 48 weeks

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Table 1. Description of Clinical Efficacy and Safety Studies (continued)

Type of Study	Study Identifier	Objectives of the Study	Study Design / Type of Control	Study Population; Total no. enrolled/completed/ discontinued; Age range; Mean age; No. per Sex (M/F)	Route of Administration and Test Product(s); Dose Regimen	Duration of Treatment
Safety	Baylor Chorea Database [Project No. TBZ 103,011]	<ul style="list-style-type: none"> Evaluate tolerability and safety of tetrabenazine for chorea in dose-titration study. 	Prospective, open-label, individualized dose study.	Patients with chorea due to Huntington's Disease and other causes; 145 evaluated, no formal assessment of "completion"; Age range: 3-80 years; Mean age: 51.4 years; Gender: 58/87	Oral doses of 25-mg tetrabenazine tablets; titration to tolerability or efficacy; 25-300-mg/day.	1 week to 13 years (mean duration 2.6 years)
Safety	Baylor-Cambridge Review 1997-2002	Assess the safety of tetrabenazine in patient with hyperkinetic movement disorders of various etiologies.	Review and summary of an earlier Cambridge Laboratories project done with Baylor using retrospective information from medical records.	Patients with hyperkinetic movement disorders treated with tetrabenazine at Baylor 1997-2002; 309 of 357 patients "evaluable"; Age range: 4.8-89.7 years; Mean age: 52.8 years; Gender: 127/182	Oral doses of 25-mg tetrabenazine tablets; titration to tolerability or efficacy; 25-300-mg/day.	1 week-21 years

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4.3 Review Strategy

The emphasis of the efficacy review was on the two controlled Phase III trials. All the submitted material was reviewed for the claims of effectiveness, but data from the open-label studies were not a primary focus since there was no comparison group. Information provided by the previous controlled studies cited in the literature was very incomplete since only very short summaries of the research were presented in each, and the very small number of patients (HD or other chorea) involved in the studies makes statistical analysis problematic. Also, there have been considerable changes in the research standards and techniques in the intervening two to three decades since they were done, which might affect how the studies were designed or evaluated if they were more recent.

The efficacy review and study coordination were done by Carole Davis, DNP. The safety review was done by D. Elizabeth McNeil, DNP. The clinical pharmacology review was done by Sally Yasada. The chemistry review was done by Chhagan G. Tele and Lyudmila Soldatova, DNDP. The statistical analysis was done by Tristan Massie, DND. The pharm.tox. review is being done by Andrea Powell, DPN.

The final study reports, except for Protocols TBZ 103,007 and TBZ 103,006 (only interim reports submitted), were used as the starting point and basis for the reviews. Each report was checked against the study protocol, statistical and analytical plan to assure that any changes from the original design were reported and explained.

Tables, charts and graphs are adapted from the original study reports of the two efficacy trials submitted by the Sponsor, Tetra HD Protocol TBZ 103,004 and Tetra Withdrawal Protocol TBZ 103,005.

4.4 Data Quality and Integrity

An audit by the Division of Scientific Investigations was requested for this NDA on October 18, 2005. The clinical sites recommended for audit were selected based on size of the enrollments in the pivotal TBZ 103,004 study. The largest single site was at the University of California – San Diego School of Medicine (n = 17). The next larger single sites were at the _____) and Indiana Univ. School of Medicine, Outpatient Clinical Research Facility (n=14). _____ n Texas were included, _____ the Department of Neurology, Baylor College of Medicine (n=10). The latter site was also included because of the TBZ 103,005 study (n=30). / _____

The site evaluation was completed too late for this review. Only an interim report is available at this time, and it has been placed in Appendix B. It includes a list of previously unreported adverse events from the CRFs of Dr. J. Jankovic at Baylor College of Medicine, but subsequent communication from the investigator. _____ suggests that the list is incomplete for

several reports of increasing dysphagia as well since Dr. Jankovic attributed dysphagia to the HD process and did not consider it reportable.

4.5 Compliance with Good Clinical Practices

Submitted reports of each of the Sponsor's trials include assurances that the studies were each conducted in accordance with the International Conference on Harmonization (ICH) Guidance E6 on Good Clinical Practice (GCP), with FDA regulations for investigational new drugs as outlined in Parts 50, 54, 56, and 312 of Title 21 of the CFR, and with the Declaration of Helsinki.

The studies were managed by the Huntington Study Group (HSG) Clinical Trials Coordination Center at the University of Rochester. Prior to initiation of each of the studies, the protocols and Informed Consent Forms were reviewed and approved in writing by the University of Rochester Institutional Review Board (IRB). Following approval, the protocol and ICF were submitted to the local IRBs at each of the study sites where they were reviewed and approved. IRB procedures were performed in accordance with the FDA regulations outlined in Part 56 of Title 21 of the Code of Federal Regulations (CFR). Any amendments to the protocol during the study were reviewed by the University of Rochester IRB and the local IRBs.

4.6 Financial Disclosures

Prestwick Pharmaceuticals, Inc. has provided financial disclosure statements from the investigators at all the study sites stating that they had no financial connections with the Sponsor.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology review was done by Chhagan G. Tele, DNDP, and Lyudmila N. Soldatova, DNDP. See Clinical Pharmacology report filed separately.

5.1 Pharmacokinetics

Tetrabenazine is a hexahydroxy-dimethoxy-benzoquinolizine. TBZ claims two modes of action: depletion of pre-synaptic stores of monoamines, and a post-synaptic receptor blocking action. TBZ selectively and reversibly binds to the principal brain synaptic vesicular monoamine transporter type 2 (VMAT2). It inhibits the translocation of monoamines from the cytoplasm to the storage vesicles, thus allowing their rapid degradation. The effects of TBZ are largely restricted to the CNS where it preferentially blocks dopamine from nerve terminals. This action affects the transmission of electrical signals in the brain involved in the control of motor activity. TBZ has been used for the control of involuntary movements in movement disorders associated with diseases of the brain and nervous system such as dystonia (generalized and focal: axial, Meige syndrome, torticollis, blephrospasm, bruxism), Huntington's disease, senile chorea, hemiballismus and tardive dyskinesia.

5.2 Pharmacodynamics

Not included in the efficacy review.

5.3 Exposure-Response Relationships

Dosage is variable. A flexible-dose design was used in the studies, see Section 1.3.4.

6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION: CHOREA

The approval of TBZ for movement disorders in other countries does not appear to have been based on any single large controlled study.

The Prestwick clinical program was designed to demonstrate and assess efficacy of orally administered TBZ in the symptomatic management of the chorea associated with of Huntington's disease. It includes the following studies:

The two randomized, double-blind, prospective, placebo-controlled studies in HD patients that were used in support of efficacy in the NDA included:

- Prestwick Tetra HD Protocol TBZ 103,004
- Prestwick TBZ Withdrawal Study - Protocol TBZ 103,005

The primary objective of the two open-label extension studies was to document the long-term safety and tolerability of tetrazenazine for the treatment of chorea, but they did include some data analysis on efficacy (only interim results reported). The studies included:

- Prestwick Protocol TBZ 103,007 (follow-on of TBZ 103,004) – up to 48 weeks
- Prestwick Protocol TBZ 103,006 (follow-on of TBZ 103,005) – up to 80 weeks

Also included with the application was a review of an on-going study on the use of tetrabenazine for management of chorea done at the Baylor College of Medicine. This was an analysis of previously collected data on the open-label treatment of chorea patients (HD and other chorea) treated by Dr. Jankovic under investigator IND 16,161 since 1979 (Project TBZ 103,011). A summary of tetrabenazine use for non-chorea patients done by Dr. Jankovic was also submitted, but was not a part of the efficacy review for this application since it was outside the indication.

The review of published literature on trials of tetrabenazine for the treatment of chorea showed only 3 accessible studies. As noted above, these were incomplete, under enrolled for statistical analysis, not specific for HD patients, and the research is dated. However, they were reviewed, and the information obtained in them is noted in the sections to which it is relevant.

6.1.1 Methods

The efficacy review looked at the data collected on all four of the Prestwick sponsored studies. The Baylor Database analysis and the literature review were evaluated, but their findings were considered in the context of various specific comparisons to the current studies. Of the four Prestwick studies that did data analysis of efficacy, only two were designed for support of the efficacy claims (Tetra HD Protocol TBZ 103,004, and Tetra Withdrawal Protocol TBZ 103,005). The other two (Protocol TBZ 103,007 and Protocol TBZ 103,006) were the follow-on studies designed to test safety and tolerability, and had evaluation of efficacy only as a secondary or exploratory endpoint.

Both of the two efficacy studies were randomized, double-blind, placebo-controlled studies. However, the main emphasis in this review was placed on Protocol TBZ 103,004. It was designed as the main study and used an enrollment of new subjects in a multi-site 12 week treatment, all of which makes the findings more easily generalized to an intended population. The Tetra Withdrawal Protocol TBZ 103,005 apparently had a “flawed” implementation that precluded any accurate analysis of their designated primary endpoint. It also used a pre-selected base of TBZ responders in a small, short, 1 site trial. As a result, its usefulness in supporting the efficacy results of the main study is severely restricted. The detailed reviews for both studies are located in Appendix A, Section 10.1.

Demonstration of efficacy for the indication of chorea has to rest primarily with the main study (Tetra HD Protocol TBZ 103,004), but the claim could be made that there is supportive evidence offered in the combination of findings in the other studies. As a result, every effort has been made to weigh in the analysis of efficacy provided by these, while still recognizing their limitations in claiming agency-recognized support for the indication.

6.1.2 General Discussion of Endpoints

The primary endpoints in the Prestwick TBZ protocols all used the UHDRS (United Huntington’s Disease Rating Scale) Part I (Motor Assessment), Item 12 (questions 12 a to 12 g) for the Maximal Chorea score. The investigators gave a chorea rating of 0=absent to 4=marked/prolonged to each of 7 body regions (face, bucco-oral-lingual, trunk, and each extremity) of a subject. The scores, if not limited by the inclusion/exclusion study parameters, could range from 0 to 28 points. Change in the maximal chorea score from the baseline score to an assigned point in the study timeline was the primary endpoint. The rating scales were administered at each clinic visit (end of Weeks 1, 3, 5, 7, 9 and 12).

The secondary and exploratory efficacy endpoints in Prestwick TBZ protocols used:

- the UHDRS Part I (Motor Assessment), Part II (Cognitive Assessment), Part III (Behavioral Assessment), Part IV (Functional Assessment), Part V (Independence Scale), and Part VII (Clinical Summary). The TBZ 103,005 protocol also used a Part VI subscale (Total Functional Capacity Score) as a secondary efficacy parameter.

- the Clinical Global Impression (CGI) ratings - Part 1 (Severity of Illness), Part 2 (Global Improvement) and Part 3 (Efficacy Index), were used as secondary and/or exploratory parameters in Protocol TBZ 103,004.

In Protocol TBZ 103,004, the primary outcome measure was the change in the UHDRS Part I, Item 12a-g, called the Total Chorea Score (TCS) in this study, from Baseline Visit to the average of the scores at Week 9 and Week 12. The four secondary efficacy parameters were the Clinical Global Impression (CGI) Part 2; the UHDRS Part I (Total Motor Score), Part IV (Functional Assessment), and the Gait score (subset of Part I). There were 10 exploratory parameters using the UHDRS and CGI.

In Protocol TBZ 103,005 the primary outcome measure was also the change in the UHDRS Part I, Item 12a-g (the Total Maximal Chorea Score), from the Baseline Visit to Day 3 for Group 1 compared to the scores of Groups 2 and 3 combined, done by ANOVA analysis.

The Total Functional Capacity Score (TFC) UHDRS – Part VI was used as a secondary parameter in Protocol TBZ 103,005. There is a consistent 0.5 to 1.0 unit decrease per year in this 13 point scale in longitudinally followed populations. (Evans, 2000). It evaluates occupation, ability to handle finances and domestic chores, and ADL (activities of daily life) level all on a 4 point scale between normal = 3 and unable = 0, also care level on a 3-point scale (0=full skilled nursing, 1=home or chronic care, 2=home). The change in the TFC from the Baseline Visit to Day 3 in Group 1, compared to the scores of Groups 2 and 3 combined, was the primary of the secondary efficacy measures. The secondary outcome measure was the difference of the change scores in TFC from the Baseline Visit to Day 3 and from Day 3 to Day 5 for each of the three treatment groups. The categories may have been too broad to show significant differences in such a short study. Most of the categories, such as occupation and care level would not change; and since TBZ withdrawal should not be affecting cognitive status, ability to handle finances is unlikely to change.

In the two open-label follow-on studies, Protocol 103,007 and Protocol 103,006, evaluation of the safety and tolerability of tetrabenazine was the primary objective. Protocol TBZ 103,007 had an analysis of efficacy as a secondary objective for evaluating the maintenance of efficacy during long-term treatment. Protocol TBZ 103,006 evaluated efficacy data, but not as a primary or secondary objective. Both studies have supplied only interim analyses based on baseline to Week 24 data. Both used the Total Maximal Chorea Score (UHDRS Part I, item 12a-g) as the efficacy parameter. Change in the TCS was the only efficacy analysis information submitted, although protocols state that other parameters will be evaluated at the conclusions of the studies.

6.1.3 Study Design

Prestwick Tetra HD Protocol TBZ 103,004

Objective – Establish the efficacy & safety of oral tetrabenazine titrated to “best dose” in HD subjects who had not previously been medicated with tetrabenazine.

Endpoint -

Study Design – Randomized, double-blind, multi-center (16 Huntington Study Group sites in the US), placebo-controlled study in two parallel, unbalanced (2:1, drug: placebo) groups. The study

recruited 84 HD patients (78 white, 6 non-white), age range 25-77 years (mean 49 years), gender 32 males/52 females.

The dose of TBZ was started at 12.5 mg/day and titrated upward by one tablet at weekly intervals for the first 7 weeks of the study until efficacy was achieved, dose-limiting side-effects occurred, or a maximum dose of 100 mg/day was reached.

Duration = 12 weeks of active treatment (7 weeks titration, and 5 weeks maintenance), followed by a 1 week wash-out.

Treatment Suspension – for up to 7 days for any reason; only one treatment suspension allowed during the trial

The Steering Committee for the study defined a 3-point decrease in Total Chorea Score as clinically relevant.

Prestwick Withdrawal Study Protocol TBZ 103,005

Objective – Examine the efficacy of oral tetrabenazine for the treatment of HD

Endpoint - Assess the difference in the severity of emerging chorea 5 days vs. 3 days after TBZ withdrawal (using Maximal Chorea Score – UHDRS Item 12a-g)

Study Design – 30 HD subjects stabilized on “best dose” of TBZ Randomized, double-blind, placebo-controlled (“placebo” = tetrabenazine withdrawn), staggered withdrawal study in 3 parallel, unbalanced groups of HD patients. Subjects were randomized to Group 1 (40%) – switched to placebo on Day 1, to Group 2 (40%) – last dose of TBZ on the evening of Day 2, or Group 3 (20%) – last dose of TBZ on the evening of Day 5. When TBZ was discontinued, subjects were switched to placebo of identical appearance. Subjects were evaluated for changes in chorea at Days 1, 3, and 5.

A more detailed review of each of the two pivotal efficacy studies is included in Appendix A, Section 10.1.

Prestwick Protocol TBZ 103,007 (48 week follow-on study of TBZ 103,004 – interim results at 24 weeks submitted)

Objective – Document long-term safety and tolerability of TBZ

Secondary objective – confirm efficacy of TBZ is maintained during long-term treatment

- test if doses > 100 mg/day would increase efficacy in subjects that were taking the 100 mg/day maximum allowed dose on Protocol TBZ 103,004

Study design – 75 of the eligible subjects that completed TBZ 103,004 enrolled at the 16 sites

Prestwick Protocol TBZ 103,006 (48 week follow-on study of Tetra Withdrawal Study Protocol TBZ 103,005 0 interim results at 24 weeks submitted)

Objective – confirm the tolerability and safety of TBZ for the treatment of Huntington’s chorea

Secondary objective – evaluation of change in the Total Maximal Chorea Score from baseline to End of Week 24 Visit and End of Week 48 Visit

Study design - enrolled 27 of the 30 subjects that completed the Withdrawal Protocol TBZ 103,005 (1 declined due to lack of efficacy, the other 2 enrolled after the deadline and were included only on the safety and AE data). Each subject resumed their previous “best dose” without titration for a 48 week follow-up study (plus ~ 1 week each for screening, and F/U visit after conclusion of the study).

Project TBZ 103,011 was an analysis of the chorea patients treated at Baylor College of Medicine under investigator IND 16,161 since 1979. It consisted of a data analysis (done 04/2004 – 12/2004) using information previously collected on 145 chorea patients, including 98 with Huntington's disease. Many of the patients had been receiving tetrabenazine for several years.

6.1.4 Efficacy Findings

Three Prestwick sponsored trials (TBZ 103,004, TBZ 103,007, and TBZ 103,006) had similar dosing protocols. All used a flexible dosing plan to achieve the "best dose" for each subject. The "best dose" in all cases showed considerable variability between subjects. Plasma concentrations showed a similar pattern of variability.

Study TBZ 103,004, enrolled subjects who had not previously used tetrabenazine, and randomized them to an experimental or a placebo group. Analysis of the primary objective, compared the maximal chorea score (UHDRS, Item 12) at baseline to the average score of Week 9 and Week 12. The enrollment criteria required a chorea score (TCS) of ≥ 10 UHDRS points, and the mean baseline score of the subjects was 14.7 (+0.52) for the TBZ group and 15.2 (+0.81) for the placebo group. Analysis showed that the maximal chorea score of the subjects receiving tetrabenazine decreased by 5.0 UHDRS points, compared to a reduction of 1.5 points in the placebo group. The mean treatment effect of -3.5 units was statistically significant at p-value = < 0.0001 , and since it was ≥ 3 points, it was considered by the Steering Committee of the study to be clinically significant.

Overall, 69% of the TBZ group vs. 20% of the placebo group had a decreased chorea score of ≥ 3 units, and 50% of the TBZ group (vs. 7% of placebo group) had a decrease of ≥ 6 units in the Total Chorea Score. By the end of the study, 61% of the TBZ group, vs. 14% of the placebo group, had a Total Chorea Score < 10 points. A score of ≥ 10 points had been part of the inclusion criteria for the study.

An ad hoc analysis was done to show that the treatment effect was greater for subjects that had higher baseline chorea scores (> 14.0 units). In that sub-group, 10 of the 22 subjects had a decrease in the chorea score of ≥ 10 units, compared to only 1 of 13 in the placebo group. However, the mean changed score attributable to TBZ treatment (change in placebo score subtracted) was a decrease of 4.36 UHDRS points for the TBZ group with the higher baseline TCS, compared to a decrease of 2.25 points in the TBZ group that had a baseline chorea score of ≤ 14 points.

Tetrabenazine showed significant superiority to placebo treatment in only one of the four secondary endpoints, the CGI Part 2. It used an investigator assessment of whether the subject had changed from baseline to Week 12 due to drug treatment (1 = very much improved to 7 = very much worse). The adjusted effect size showed change attributable to TBZ treatment of -0.7 CGI unit on the 7-point scale (p=0.0058) favoring TBZ treatment. Sixty-nine percent (69%) of the TBZ group showed at "least minimal global improvement", versus 24 % of the placebo group (p<0.0001). Forty-five percent (45%) of the TBZ group were rated "much" and "very much" improved, versus 7% of the placebo group (p<0.0001).

Tetrabenazine did not show statistical significance in the other 3 secondary efficacy parameters:

- There was a trend toward improvement in the 15-item (UHDRS Part 1) Total Motor Score which incorporated the ratings of chorea (item 12) and gait (item 13). The adjusted mean treatment effect was -3.3 UHDRS points ($p = 0.075$) favoring the treatment group.
- The Gait Score (UHDRS Part 1, item 13) was rated on a 5 point scale ranging from 0=normal to 4=cannot attempt. The mean change scores were slightly worse for both the placebo (0.11 ± 0.07) and TBZ (0.001 ± 0.05) groups, but the TBZ group showed less change.
- The change in the Functional Assessment Checklist (UHDRS Part IV) assessed a combination of complex and simple daily tasks (from employment to combing hair) with responses from the subject or subject and care-giver. Analysis of the change in scores from baseline showed that the placebo group improved (0.37 ± 0.40) while the TBZ group worsened (-0.81 ± 0.29). The difference was statistically significant (p -value = 0.0183) favoring the placebo group. The Sponsor attributed the result to the high functional level of the subjects at baseline which may have precluded significant improvement in scores.

Of the 10 exploratory efficacy parameters, only the CGI Part 3 (the Efficacy Index) showed superiority over placebo ($p=0.0008$). It is an investigator rating of therapeutic effect vs. side effects for each subject. A copy of the scale is located in Appendix B, Table 31 or Appendix C. By Week 12, 51% of the TBZ group; compared to 7% of the placebo group, was judged to be in a category of “therapeutic effects greater than side effects” for the assigned study drug.

Study TBZ 103,005 enrolled patients who were being treated open-label with TLBZ under Investigator IND 16,161 and stable on a “best dose”. It subjected them to a staggered 5 day withdrawal monitoring for the re-emergence of chorea. A multi-site study of 45 subjects had been planned, but the DAP was amended to 30 subjects at the Baylor College of Medicine. The reason noted was the difficulty of getting subjects to agree to a drug withdrawal. The primary efficacy analysis demonstrated a treatment effect of 2.39 units increase in the chorea scores ($p=0.0779$) when the withdrawn Group 1 was compared to average of the combined Group 2 and Group 3 scores on Day 3. The Sponsor states that there was a misunderstanding of the protocol at the site, and the tetrabenazine for the Group 2 subjects had been discontinued on the evening of Day 2, instead of discontinuation after the Day 3 assessments. They used a retrospective, ad hoc trend analysis with ANCOVA which gave a p -value of 0.0486.

Given the problems with timing, the only way to compare Group 1 (withdrawn) to a control group is by eliminating the Group 2 data from consideration. That leaves a comparison of Group 1 (withdrawn) to Group 3 (still on “best dose”) on Day3. However, this would still only give a p -value = 0.111.

The secondary efficacy endpoint was to have used the change in scores on the UHDRS sections for each group. However, the protocol didn’t have the tests indicated on Day 3 of the study schedule, and they were conducted. The TFC (UHDRS Part VI), originally designated as a safety evaluation, was substituted as the secondary efficacy assessment. The change in TFC from the Baseline Visit to Day3 was measured with Group 1 (TBZ withdrawn) compared to the

combined Groups 2 and 3. Analysis of the data shows virtually no change in either group from their baseline scores to the end of the study.

Prestwick Protocol TBZ 103,007 was the open-label 48 week extension study for Protocol TetraH D 103,004 using the same subjects and same 16 sites. Prestwick Protocol TBZ 103,006 was the 48 week open-label extension study for the TBZ Withdrawal Protocol TBZ 103,005 using the continuing HD patients at Baylor College of Medicine. Both were designed and submitted as safety studies, but did analysis of some of the data for efficacy.

TBZ 103,007 evaluated the maintenance of efficacy during long-term treatment. All the subjects enrolled had completed the Protocol TBZ 103,004 and had a 1 week drug withdrawal (TBZ or placebo) at the end of the study. At the enrollment onto the extension study, all were started on an escalating titration of TBZ. Clinical response was indicated by a decline in the Total Maximal Chorea Score, which was rapid, and was maintained for the duration of the study. The mean change in the chorea score was $-7.27 (\pm 4.51)$ points at Visit 7, Week 36.

TBZ 103,006 evaluated the resumption (after a short withdrawal at the end of the previous study) of each subject's previous "best dose" of TBZ without titration. 25 of the 27 subjects (92.6%) were able to resume their "best dose" without adjustments. The resumption was well-tolerated, and the reduction on the Total Maximal Chorea Score was rapid. The score change from baseline to Visit 1 (the 12 week visit) was $-3.70 (\pm 5.75)$ units, and baseline to Visit 2 (the 24 week visit) was $-5.94 (\pm 5.21)$ units. The Sponsor felt that the decreased later score represented sub-optimum dosing of some subjects earlier in the study rather than increasing efficacy since 9 of the 17 subjects had their daily TBZ dosage increased between Visit 1 and Visit 2. By week 24, 76.5% of the subjects experienced a decrease of ≥ 3 points units on the Maximal Chorea Score. Again, in both the extension studies, the subjects with higher baseline chorea scores (> 14) were noted to have greater decline in chorea.

In the Baylor Database (Project TBZ 103,011), patients started on tetrabenazine had been evaluated with a response grade of 1 (marked or complete relief of chorea) through 5 (worsening of chorea). Investigators assessed improvement in chorea to be "marked" or "very good" in 108 of 137 (79%) of the patients with valid response ratings during active treatment.

6.1.5 Clinical Microbiology

Not applicable; tetrabenazine is not a biological product.

6.1.6 Efficacy Conclusions

Study TBZ 103,004 showed that TBZ was more effective than placebo. It also indicated that when weekly upward titration done in subjects that had not previously used tetrabenazine, efficacy (by decreased maximal chorea score) showed a characteristic dose-response curve. There was a decrease attributable to drug treatment of 3.5 UHDRS points. The change was more significant for the HD subjects that had higher (> 14.0 points) baseline chorea scores. Their mean TCS decrease attributable to TBZ use was 4.36 points.

A primary difficulty in forming conclusions comes with trying to compare the decrease in the chorea scores to the lack of impact on the functional scores. Nearly all of the functional measurements showed at least nominal trending that favored placebo. The expectation is that as the chorea is decreased, there will automatically be measurable gains in gait patterns/safety and in the activities of daily living. The Sponsor suggests that this did not occur due to a rather high baseline level required for study enrollment. All of the subjects had to be independently ambulatory for inclusion. Still, with several rating scales measuring a wide variation in the level of functions (everything from “able to comb hair” to “able to continue or return to employment”), it would be expected that some of these would have shifted with a reduction of chorea. Each of the functional skills items was evaluated independently, in addition to being grouped together in scales, so even subtle differences should not have escaped notice. The functional scales were the only areas in which the subjects and/or caregivers furnished the evaluations. As a result, the pivotal study lacks any evidence that use of tetrabenazine improves the quality of life or functioning for the target consumers.

The data analysis of the cognitive assessment scores raises an area of concern. From a baseline score of 172 (+55) the placebo group improved by 5.1 (+4.5) points, while from an average baseline of 156 (+56), the TBZ group worsened by 7.7 (+3.3) points (p-value = 0.025). Since cognitive changes can be part of the course of HD, any changes due to drug use might not be detected. Dosage adjustment or drug discontinuation for changes in cognitive status may be less likely to occur than for more easily evidenced AEs. Additional studies that address this issue would be helpful to clarify the effect of TBZ on cognition.

7 INTEGRATED REVIEW OF SAFETY

The safety review was done by D. Elizabeth McNeil, DNDP. See Safety Review filed separately.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Administration of tetrabenazine is oral. The plasma half-life of tetrabenazine is 5.5 hours, and published reports indicate the return of chorea in less than 24 hours when the medication is discontinued. The studies also suggest that the responsiveness to tetrabenazine is stable over time, and the upward adjustments in dose, when they occur for some patients, are related to the progression of the disease rather than the development of drug tolerance.

In the Prestwick 12-week study, the titration rate was determined by the observations previously appearing in the literature that the maximum efficacy with a given dose of tetrabenazine takes approximately 5 days to achieve, while parkinsonism takes 3-4 days to occur.

In the Prestwick withdrawal trial with Huntington's patients, the subjects were already receiving TBZ for their chorea at their optimal dosage for at least 2 months prior to inclusion on the studies. The subjects had been receiving the drug for an average of 2.5 years prior to enrollment.

8.2 Drug-Drug Interactions

Prestwick did not formally evaluate this product for potential drug-drug interactions.

8.3 Special Populations

There were no apparent differences in response to tetrabenazine based on gender or age, although very few subjects in the age range > 65 years were evaluated in the 12 week study making statistical assurances difficult. The drug was not adequately assessed in non-Caucasians to allow for generalizations to be made.

Studies are still needed for review on the potential interaction with contraceptive medications, and with common antidepressants. In addition, an endocrine study to assess the effect of tetrabenazine on women of child-bearing age has been recommended.

8.4 Pediatrics

Pediatric studies have not been done for the use of tetrabenazine, exemption was claimed under the Pediatric Research Equity Act of 2003, Section 505B(g) Orphan Drugs.

8.5 Advisory Committee Meeting

No advisory committee meetings have been held for this application.

8.6 Literature Review

Adverse events were common in the review of published studies on TBZ (see Table). Approximately 50% of patients in controlled studies reported their occurrence. In the Baylor Chorea Database, a rather high drop-out rate was observed; approximately 20% withdrew from use of the drug due to side-effects. In general, a therapeutic effect was observed after 24 hours. Studies examined patients following weeks to months after treatment; some patients were examined after many years of exposure. While not a subject of careful examination, the data from Baylor analysis indicates that the optimal dose required may exhibit slight increase (approximately 40%) over many months of treatment. The Sponsor attributes this to disease progression and not to tachyphalaxis.

Table 2 is a list of trials and open-label study reviews on the efficacy of tetrabenazine in the management of chorea.

Table 2. Published Studies on the Efficacy of Tetrabenazine for the Treatment of Chorea

Author/Investigator	Year	No. of Patients With Chorea	Improvement of Chorea	Literature Reference
Double-Blind Placebo-Controlled Cross-Over Studies				
McLellan et al	1974	10	8/9 (89%) Patients Improved	(McLellan, et al., 1974)
Asher and Aminoff	1981	8	6/8 (75%) Patients Improved	(Asher, 1981)
Gilligan et al	1972	6	Not clearly reported	(Gilligan, et al., 1972)
Double-Blind Placebo-Controlled Cross-Over Added on to Neuroleptics Study				
Shoulson and Goldblatt	1981	12	Mean chorea intensity decrease Placebo: 14%; Tetrabenazine: 42%	(Shoulson, 1981)
Double-Blind Comparator Cross-Over Study (Tetrabenazine versus Amantadine)				
Swash et al*	1972	7	Tetrabenazine: 6/7 (86%) Patients Improved Amantadine: 0/7 (0%) Patients Improved	(Swash et al., 1972)
Single-Blind Comparator Study (Tetrabenazine versus Haloperidol)				
Gimenez-Roldan and Mateo	1989	11	Tetrabenazine superior to Haloperidol Mean Improvement Tetrabenazine: 46 points Mean Improvement Haloperidol: 29 points	(Gimenez-Roldan et al., 1989)
Open-Label Studies in 15 Patients or More				
Astin and Gumpert	1974	26	24/26 (92%) Patients Improved	(Astin et al., 1974)
McLellan et al	1972	24	14/24 (58%) Patients Improved	(McLellan, 1972)
Kingston	1979	31	30/31 (97%) Patients Improved	(Kingston, 1979)
Jankovic and Beach	1997	29	28/29 (97%) Patients Improved	(Jankovic, 1997)
Ondo et al	2002	19	15/19 (79%) Patients Improved	(Ondo et al., 2002)
Paleacu et al	2004	28	19/28 (68%) Patients Improved	(Paleacu et al., 2004)
Open-Label Studies in 14 Patients or Less				
Brandrup	1960	7	4/7 (57%) Patients Improved	(Brandrup, 1960)
Moller-Christensen and Videbech	1963	11	55% Patients Improved	(Møller-Christensen et al., 1963)
Pakkenberg	1968	11	6/11 (54%) Patients Improved	(Pakkenberg, 1968)
Sattes Hase	1964	14	14/14 (100%) Patients Improved	(Sattes et al., 1964)
Dalby	1969	8	8/8 (100%) Patients Improved	(Dalby, 1969)
Soutar	1970	2	2/2 (100%) Patients Improved	(Soutar, 1970)

Swash et al*	1972	2	2/2 (100%) Patients Improved	(Swash et al., 1972)
Fortemps and Laterre	1976	7	7/7 (100%) Patients Improved	(Fortemps et al., 1976)
Jancovic and Orman	1988	10	Mean CGI score: 2.6	(Jancovic, 1988b)
Shanahan et al	2001	1	1/1 (100%) Patients Improved	(Shanahan et al., 2001)
Linazasoro et al	2001	1	1/1 (100%) Patients Improved	(Linazasoro et al., 1993)
Author/Investigator	Year	No. of Patients With Chorea	Improvement of Chorea	Literature Reference
Open-Label Studies with High Doses Of Tetrabenazine				
Toglia et al	1978	7	5/7 (71%) Patients Improved	(Toglia et al., 1978)
Huang et al	1976	8	7/8 (88%) Patients Improved	(Huang et al., 1976)
Studies in Pediatric Chorea				
Hawkes and Nourse	1977	2	2/2 (100%) Patients Improved	(Hawkes et al., 1977)
Chatterjee and Frucht	2003	5	4 /5 (80%) Patients Improved	(Chatterjee et al., 2003)
Study During Pregnancy				
Lubbe and Walker	1983	1	1/1 (100%) Patients Improved	(Lubbe et al., 1983)
Studies of Tetrabenazine Combined with Other Psychotropic Drugs				
Fog and Pakkenberg TBZ + pimozide	1970	12	10/12 (83%) Patients Improved	(Fog et al., 1970)
Aminoff and Marshall	1974	4	Efficacy not clearly described	(Aminoff et al., 1974)
McArthur et al	1976	3	3/3 (100%) Patients Improved	(McArthur et al., 1976)
Lang and Marsden	1982	5	4/5 (80%) Patients Improved	(Lang et al., 1982)
TOTAL		331		

Five of the controlled trials examined Huntington's chorea. Of these, two studies are almost completely devoted to the examination of Huntington's and not other movement disorders. In total, approximately 37 patients with Huntington's disease were examined. Many of the studies appeared only to use descriptive statistics to describe outcome. The effects consistently favored tetrabenazine over placebo or comparison drug. The study design for all of the studies was cross-over. Most of the studies were of short duration (1 to 10 weeks), and it is not often clear if a washout period between treatments was used. One study, however, lasted 16 months.

In the study by McLellan, et al, 9 of the 10 patients had HD. The study was a 3-phase, randomized sequence, double-blind, cross-over study of tetrabenazine, thiopropazate (a neuroleptic), and placebo. The subjects were hospitalized for 6 consecutive weeks and in each of the 2 week phases, they received tetrabenazine 25 mg, thiopropazate 30 mg, or placebo. Dose titration was every 2 days by one tablet unless AEs occurred. Videotapes of admission and end of treatment were randomized and compared by a panel of 8 physicians that rated the chorea on a 0 to 4 scale. Chorea was rated as moderate to marked improvement for 70% on tetrabenazine ($p < 0.001$), 10% on thiopropazate ($p < 0.01$), and none of the placebo group. Reduction in chorea correlated with a 50% increase in speed of writing in manual dexterity testing. There was a statistically significant increase in CSF HVA during TBZ treatment, but not with thiopropazate. Two patients on TBZ and one on thiopropazate developed marked parkinsonism that reversed with drug withdrawal.

Asher et al compared tetrabenazine to placebo in a crossover study of 33 subjects with a variety of movement disorders. The tetrabenazine starting dose was 25 mg twice daily and increased by 25 mg every 3 days until therapeutic effect reached AEs occurred or 200 mg/day. CrossOver occurred after 3 weeks on optimal dose. Videotaping was done at the start, cross-over and end of study and tapes randomized for review. Improvement was rated as none, slight, moderate or marked. Seven subjects dropped out, all during the TBZ phase, reasons were not clearly specified. Of those completing the study, 6 of the 8 HD patients were rated moderately to markedly improved on TBZ. The average daily dose on TBZ was 125 mg for HD, and 175 mg for the other conditions. AEs were reported in 15 subjects, including drowsiness (10), drooling (4), parkinsonism (3), depression (2) and akathisia (1), myoclonus/ increased involuntary movements (2).

Gilligan et al conducted an 8-week, double-blind, placebo-controlled trial of 27 patients (6 with HD). Patients received 6 tablets/day of TBZ or placebo. Videotapes were made and reviewed by 3 reviewers. Reduction in involuntary movements was judged to be moderate improvement in 3 of the 18 completing the study while on TBZ, and 8 had slight improvement on the drug, the remainder had no clinical benefit from it. The HD patients were not analyzed separately.

The published study by Shoulson and Goldblatt consists of only a short abstract of a trial of 12 HD patients. Eight were already taking haloperidol (8 to 29=0 mg/day) and four were on perphenazine (16 to 32 mg/day). Tetrabenazine (50 to 200 mg/day) or placebo was added on, and the patients were followed for a 16-month period. The sequence of tetrabenazine and antipsychotic therapies was varied, and a placebo was given before or after TBZ. Blinded observations were made without videotapeing. Overall intensity of chorea during the placebo period was reduced 14% on antipsychotic therapies, and by 42% on TBZ ($p < 0.001$). During the placebo + haloperidol or + perphenazine phases, only mild parkinsonism was reported. There were also episodes of aspiration pneumonia in 2 patients.

The study by Swash et al conducted a double-blind crossover comparison of amantadine to tetrabenazine in 7 HD patients, with dementia to varying degrees, in a long-term care hospital. there was an initial 2-week washout of prior drugs, a 2-week treatment with TBZ or amantadine, a 1-week washout, then crossover to 2 weeks on the other drug. Drugs were increased gradually over the first 5 days of each treatment to a final dose of 50 mg t.i.d. for TBZ,

or 100 mg b.i.d. for amantadine. Videotapes done at the start of the study and the end of each treatment were randomized and reviewed. Six of the 7 patients showed improvement in chorea with TBZ. Five had nearly complete control of involuntary movements. One experienced exacerbation of confusion during the TBZ phase. Three other patients experienced drowsiness and confusion during the TBZ phase. There was no discernable change in chorea with use of amantadine.

The single-blind crossover study by Gimenez-RoldanMateo compared tetrabenazine to haloperidol for 11 HD patients. Improvement of chorea scores was greater with tetrabenazine than with haloperidol, but failed to reach statistical significance. Severe depression occurred in 3 patients (including a suicide attempt) while on TBZ. Tardive dyskinesia was occurred as an AE in the haloperidol group.

Overall, in the controlled studies, the response rate to tetrabenazine for chorea was 67 to 90%. The majority of the patients experiencing benefits were taking tetrabenazine in the 50 to 150 mg/day range.

8.7 Postmarketing Risk Management Plan

See Section 1.2.1.

8.8 Other Relevant Materials

Full reports for the safety review, chemistry review, Pharm/Tox review, statistical review, and biopharmacology review have been filed separately. A copy of the clinical inspection summary is located in Appendix B.

9 OVERALL ASSESSMENT

9.1 Conclusions

There is certainly a sizable amount of evidence that tetrabenazine does have effectiveness in managing the chorea of Huntington's disease. However, most of the evidence is obtained from open-label studies. The few controlled trials enrolled very small numbers making statistical conclusions unreliable, and they are out-dated and lack study details. The Sponsor had submitted one controlled clinical study showing statistically significant results for the indication. Using it as a stand-alone study is undercut by several factors including the fact that the secondary endpoints failed to show that reduction in chorea improved gait, functions abilities such as ADLs, or perceived quality of life for the patients.

9.2 Recommendation on Regulatory Action

Based on the efficacy review, the recommendation would be to delay full approval for tetrabenazine until an additional confirmatory controlled study on the drug has been completed and reviewed.

9.3 Recommendation on Postmarketing Actions

None at this time.

9.3.1 Risk Management Activity

See section 1.2.1

9.3.2 Required Phase 4 Commitments

Requirements have been listed by Clinical Pharmacology, pending for Pharm/Tox.

9.3.3 Other Phase 4 Requests

None at this time.

9.4 Labeling Review

9.5 Comments to Applicant

Biopharm. Comments to Sponsor:

The following additional comments should be sent to the Sponsor for guidance on performing the *in vitro* drug metabolism studies (and were generally communicated to the Sponsor in an email of 12/21/05):

1. The Sponsor has 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 the Sponsor has 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. The Sponsor should follow-up with 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. The Sponsor 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.

Also see the Safety review and Pharm/Tox reviews for additional comments.

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10 APPENDICES

10.1 Appendix A - Review of Individual Study Reports

10.1.1 Tetra HD Study 103,004 – Phase 3, Efficacy Study

Objective

The primary objective of the study - to establish the reduction in chorea in HD subjects treated with an “optimized dose” of TBZ.

The primary efficacy outcome measure was the change in Total Maximal Chorea Score (TCS) (UHDRS, subset of Part 1, questions 12 a-g) from baseline to the maintenance period (average of Week 9 and Week 12 scores). Secondary efficacy measures were the change in scores from baseline on the Total Motor Score (UHDRS Part 1, questions 1-15), the Functional Assessment Checklist (UHDRS IV, questions 43-67), Gait score (UHDRS subset Part 1, question 13), and change in Clinical Global Impression (CGI) Part 2.

Design & Sample Size

The study was designed as a randomized, double-blind, multi-center (16 sites in the US – see Table 30, Appendix B), placebo-controlled trial of subjects with Huntington’s disease who had not previously received treatment with tetrabenazine. The study design used two parallel, unbalanced (~2:1 TBZ:placebo) groups

The treatment duration was 12 weeks which included: 7 weeks titration (up or down) to optimal “best dose” by 12.5 mg increments until efficacy, intolerability, or 100 mg/day level was reached, a 5 week maintenance period (from week 7 to week 12), and 1 week wash-out from the TBZ or placebo. The subjects that completed the study were eligible for inclusion on the Prestwick open-label extension study (TBZ 103,007) if they experienced recurrence of chorea after the withdrawal of the drug.

Definitions

“Best dose” = (judged by the Investigator) the dose that provided moderate to marked improvement in the patient’s condition while causing either no side effects or side effects that do not significantly interfere with the patient’s functioning. A dose that gave a rating of 01, 02, 05 or 06 on Item 3 of the Clinical Global Impression

CAG score = Nucleotide repeat assessment of Huntington’s disease diagnosis obtained from genetics testing

CGI = Clinical Global Impression Scale – a three-part questionnaire rating: Severity of Illness – Part 1, Global Improvement – Part 2, and Efficacy Index – Part 3.

FIS = Functional Impact Scale, a new functional scale, first piloted in this study, consisting of 5 items scored by the caregiver assessing the HD impact on functional activities

Functional Assessment Checklist (UHDRS 43 – 67) = scores 25 to 0 in increasing dysfunction

Gait score = (subset of UHDRS Part I, item 13)

HAM-D = Hamilton Depression Rating Scale of 17 items

LOCF = last observation carried forward

TCS = Total Chorea score obtained from the Total Maximal Chorea Scale (subset of UHDRS Part I, item 12a - g)

TFC = Total Functional Capacity (UHDRS Part VI, items 70 - 74)

TMS = Total Motor Scale (UHDRS Part I, items 1 – 15)

UHDRS = Unified Huntington's Disease Rating Scale, includes:

Part I – Total Motor Scale (TMS), questions 1-18

Part II – Cognitive Assessment, questions 19-24

Part III – Behavioral Assessment, questions 25-42

Part IV – Functional Assessment Checklist, questions 43-68

Part V – Independence Assessment, question 69

Part VI – Total Functional Capacity (TFC), questions 70-76

Part VII – Clinical Summary, questions 77-82

Part VIII – Clinical Disposition, question 83

UPDRS = Unified Parkinson's Disease Rating Scale (used for dysphagia and dysarthria scores in this study)

Key Inclusion Criteria

- Male or female, ≥ 18 years of age.
- Diagnosis of HD confirmed by:
 - Characteristic chorea;
 - Positive family history of HD;
 - CAG repeat > 37
- Be independently ambulatory.
- Required grading of symptoms of Huntington's included the following:
 - Total Functional Capacity (TFC) > 5 (part VI of the UHDRS).
 - Have a Total Maximal Chorea Score ≥ 10 (item 12 of the UHDRS);
 - Have a total score ≤ 15 on the Hamilton Depression Scale (HAM-D);
 - UPDRS dysphagia score < 2 ;
 - UPDRS dysarthria score < 3 .
- Be capable of taking oral medication.
- Be on adequate contraception (for women of child-bearing potential).
- Signed informed consent.

Key Exclusion Criteria

- Significant unstable medical condition; life-threatening disease or neurologic
- Processes or therapies that may obscure the results of treatment.
- Abnormal lab values graded as 3, or according to the NCI classification of common toxicities.
- Change in dosage or regimen of any concomitant antidepressant baseline (randomization) visit.
- Treatment with a neuroleptic or experimental drug within 4 weeks.

- Concomitant treatment with dopamine depleting drugs, dopamine D2 receptor blockers, MAOIs, levodopa or dopamine agonists.
- Patients who previously received tetrabenazine.
- Lack of caregiver
- Patients who are deemed to be uncooperative or unreliable.
- Pregnant or lactating females.

Baseline Demographic Characteristics

The study screened 91 potential subjects, and enrolled 84. The age range was 25-77 years (mean age, 49 years), a gender distribution of 32 males, 52 females, and 79 white, 5 non-white subjects in the study population. Table 3 shows the demographic characteristics of the groups at enrollment.

Table 3. Demographic Characteristics by Group, TBZ 103,004 Subjects

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

The majority of the subjects were in the “moderately ill” category (59% of the TBZ group, and 53% of the placebo group) on the Clinical Global Impressions (CGI) Part 1 ratings at entry. There were no subjects in the “not ill”, “borderline ill” or “most extremely ill” categories. There was only 1 subject in the “severely ill” category in each group. (see Table 4). The number of subjects treated with antidepressants at study entry was nominally higher for the placebo group (67%), compared to the TBZ group (56%), but was not a statistically significant difference.

Table 4. Baseline Illness Characteristics by Group, TBZ 103,004 Subjects

Baseline Illness Characteristic	Tetrabenazine (N= 54)	Placebo (N=30)	P-Value
Disease Duration (yrs) mean / range	8.7 (1.6 – 25.6)	7.5 (2 – 18.5)	t-test 0.254
Total Chorea Score (UHDRS 12) mean “ “ “ “ range	14.7 + 0.52 10 - 23	15.2 +0.81 10 - 26	0.578 ANCOVA
CGI Part 1; Number of Patients:			
Not Ill	0	0	
Borderline Ill	0	0	
Mildly Ill	12 (22%)	10 (33%)	Cochran Armitage Trend 0.355
Moderately Ill	32 (59%)	16 (53%)	
Markedly Ill	9 (17%)	3 (10%)	
Severely Ill	1 (2%)	1 (3%)	
Among the most extremely ill patient	0	0	
CAG Repeat			
Mean	44.9	44.3	
Median	44	43	t-test
Standard Deviation	3.4	3.7	0.490
Range	41 – 54	39 -54	

Dosage

Dosage was administered in the form of 12.5 mg TBZ tablet or identical looking placebo. The daily dosage was initiated at 12.5 mg/day and adjusted to the “best dose”. This was accomplished by increasing the dose 12.5 mg each week for 7 weeks until the “maximum desired effect” was achieved, intolerable side effects occurred (prompting decrease of the dose), or 100 mg/day was reached. Dose regimen was QD or BID for the lower doses of 12.5 and 25 mg/day. Larger doses were divided on a TID schedule. By the end of the 7 weeks, subjects were to have achieved their “best dose,” and continue on it during the subsequent 5 weeks. Subjects were permitted 1 suspension of study drugs for ≤ 7 days.

Schedule

Initial screening of subjects was done within 2 weeks prior to the start of the study. Screening evaluation consisted of evaluation of medical history, physical and neurological exam, pertinent parts of the UHDRS and UPDRS, blood pressure and pulse, as well as blood for laboratory evaluation (CBC, complete SMA 20) and CAG evaluation. Also, lab work was done for pregnancy evaluation in women of childbearing potential. Complete blood work and chemistry profiles were also obtained at the end of Week 12. The patients were randomized on the Baseline Visit one day prior to drug initiation. Clinical follow-ups occurred every 1 to 3 weeks throughout the study, and 2 phone follow ups were interspersed between the clinic visits. (See Study Schedule for Protocol 103,004, Table 33, Appendix B)

Concomitant Medications

Except for the drugs noted in the exclusionary criteria, concomitant medications were permitted. An attempt was made to stabilize such drugs prior to the study, and to maintain the dose throughout the study. The most common concomitant medications at entry were antidepressants (60%) and benzodiazepines (17%). There were no statistically significant differences between the groups in the use of these medications. Overall, both treatment groups were comparable both for the use of concomitant medications and the types of medications used.

Analysis Plan

A copy of a sample CRF questionnaire containing the UHDRS, the Clinical Global Impression (CGI) scale, and the Functional Impact Scale (FIS) is located at the end of this review in Appendix C. Efficacy was evaluated primarily on the Total Maximal Chorea Score (the TCS - UHDRS, Item 12). The primary endpoint was the difference in change in the TCS from baseline to the average mean of the combined Week 9 and Week 12 scores (a maintenance phase and an end of treatment score). If either score was missing, the available one was used. If both scores were missing, the last observation carried forward (LOCF) rule was applied. It was analyzed using ANCOVA adjusting for sites and baseline score. All subjects with at least one treatment evaluation were included in the efficacy analysis. Additional analysis was performed to adjust for any significant differences between baseline characteristics. A two-tailed test was used to determine significance. The p-value of 0.05 was selected for a significance level. The ANCOVA was also used to examine secondary endpoints evaluating the change from baseline to week 12 of the UHDRSA (I to V and VII). Rather than change from baseline, CGI Part 2 (Global Improvement) and Part 3 (Efficacy Index) were evaluated by a categorical analysis.

Videotapes of 23 subjects done at Week 12 (on treatment protocol) and again at Week 13 (end of 1 week drug wash-out) had a blinded reviewed review done by a physician specialized in movement disorders who had no other connection to the study. Video monitoring was recommended by the Agency, and agreed to by the Sponsor as a Protocol Amendment. Internal validity of assigned chorea ratings was checked by the videotaping of participants both on study drug (Week 12) and off study drug (Week 13). An independent expert in Huntington's disease ——— MD, PhD), who was blind to drug assignment and week, independently rated the videos of 23 of the subjects at Week 12 and Week 13. Twenty-one of the subjects received ratings for both weeks.

The Dept. of Biostatistics and Computational Biology, University of Rochester handled the statistical analysis of data for the study.

Safety Monitoring

The study was managed by the Huntington Study Group (HSG) Clinical Trials Coordination Center at the University of Rochester. The Principal Investigator (PI) was Frederick Marshall, MD (Dept. of Neurology, University of Rochester). The study sponsor was Prestwick Pharmaceuticals, Inc., Washington, DC. The University of Rochester Institutional Review Board (IRB) reviewed and approved all forms. The local IRBs at each of the 16 study sites monitored the protocol and informed consent procedures. No changes in the protocol or study conduct were allowed without the consent of both the Rochester and local IRBs. An unblinded Data Safety Monitoring Committee (DSMC) consisting of two physicians familiar with clinical research and

a biostatistician had the responsibility of reviewing AEs and advising the PI, Sponsor and Steering Committee if significant risks were occurring.

Results:

Comparison of the Groups

Randomization to groups does not appear to have resulted in any significant imbalances. The demographic characteristics of the drug treatment group and placebo group were comparable in characteristics such as age, education, severity of illness, total chorea scores and functional scores. There were more female than male participants, but they were evenly divided between the treatment and placebo groups. There were only 4 non-whites in the TBZ group (7%) and 1 in the placebo group (3%). Adjusted mean change from baseline in the TCS scores (i.e. decrease in chorea scores) for men in the TBZ group was -5.44 (± 0.68) points, compared to -4.92 (± 0.69) points for the women. There was also similarity within the placebo group (-1.41 ± 0.21 points for men, and -1.81 ± 0.90 points for women).

Dosage levels achieved:

By the end of the treatment period, 22 of 49 (45%) of subjects reached the maximum allowed dose of tetrabenazine, 100 mg/day. The rest of the subjects in the TBZ group ended the study on lower doses (average mean daily dose for the TBZ group at the Week 12 Visit study was 67.5 mg/day). Analysis of the placebo group showed that 4 of the 30 subjects were taking less than the possible maximum of 8 tablets/day at Week 12. It was felt by the investigators that the subjects that reached the 100 mg/day maximum of TBZ might benefit from higher doses. That hypothesis was explored in the open-label extension (TBZ 103,007).

Disposition:

Screening was done of 91 subjects and 84 were enrolled. Reasons for non-admission included: 2 with a chorea score <10 points on the Total Maximal Chorea Score (TCS), 1 with a TFC score < 6, 2 withdrew consent, 1 could not be withdrawn from a neuroleptic treatment, and 1 had unstable diabetes. Of the 54 subjects randomized to the tetrabenazine group, 49 completed the study. The 5 withdrawals from the TBZ group (and approximate day of withdrawal) included one completed suicide (day 65), and 4 subjects with SAEs (one with restlessness attributed to prostatitis, an episode of suicidal ideation, psychosis and paranoia (day 71); one due to a fall with development of a SAH (day 17), and one due to recurrence of breast cancer (day 39). One subject in the group was withdrawn due to an AE of akathisia (day 50). Of the 30 subjects assigned to the placebo group, 29 completed the study. One withdrew consent (day 42), reason not listed. (Table 5.) Another potential cause for withdrawal from the study was non-compliance. The criteria for non-compliance specified that subjects taking less than 70% of their prescribed dose would be judged to be non-compliant, but none of the subjects fit into that category.

Table 5. Reasons for Withdrawal from TBZ 103,004

Reason for Withdrawal	Relationship to Study Drug*	Time of Study Drug Discontinuation (Day after Start of Treatment)	Dose on Last Day of Treatment	Number of Participants Withdrawn	
				Tetrabenazine (N=54)	Placebo (N=30)
Completed Suicide	Possible	65 days	87.5 mg	1	0
Fall, complicated by subarachnoid hemorrhage and confusion	Possible	17 days	25 mg	1	
Suicidal Ideation/ Psychosis/Paranoia	Unrelated	71 days	12.5 mg	1	
Pre-existing mass diagnosed as breast cancer after 39 days on study drug	Unrelated	39 days	87.5 mg	1	
Akathisia	Probable	50 days	37.5 mg	1	0
Withdrawal of consent	Unrelated	42 days	7 placebo tablets	0	1

Side effects (AEs):

AEs were more frequently encountered in the tetrabenazine group than in the placebo group. Forty-nine of the 54 subjects (91%) of the TBZ group experienced one or more AEs at any time during the study. AEs that led to the discontinuation of dose titration and/or reduction in the daily dosage occurred in 28 (52%) of the TBZ group and 1 (3%) of the placebo group. It occurred more frequently in females (61%) than males (38%), but there was no significant difference by age categories of < 55 years or > 55 year.

The most commonly reported AE, according to the Sponsor's evaluation, was fatigue (22%), insomnia (22%), depression (15%), fall (15%), and sedation (15%). Parkinsonism was reported in 6%, depression in 6% and akathisia in 9% of the tetrabenazine subjects, but none of the placebo group. In the placebo group, 21 of the 30 subjects (70%) experienced one or more AEs, the most common being fatigue (13%) and falls (13%). Most of the AEs occurred during the dose adjustment phase of the study. Only 19 of the 54 subjects in the TBZ reported a continuation of the AE at the end of the study. Calculation of the AEs done by the FDA, from the reporting charts of the study, show the most common AE to be sedation from 17 subjects (31%) in the tetrabenazine group, and 1 subject (3%) in the placebo group. There were complaints of fatigue by 14 of the TBZ group (20%), and 4 of the placebo group (13%).

Dosage was decreased for complaints of depression in 3 subjects (all females). For two of the three subjects, the AE resolved with reduction of the dosage. Dosage was reduced due to development of parkinsonism in one male and two females. Reduction in the daily dosage

resolved the AE in two of the three subjects without decreasing efficacy. In the third subject, the reduction reduced efficacy, and the parkinsonism was still present at the end of the study.

Evaluation of the primary objective

The criteria for inclusion on the TBZ study required a baseline chorea score of ≥ 10 units on the TCS. A copy of the Total Maximal Chorea Scale is in Appendix B, Table 31, or in the sample of the questionnaire from the CRF in Appendix C. The mean baseline Total Chorea Score (UHDRS item 12a-g) for the subjects was 14.69 (± 0.52) points (range = 10 to 23 points) for the TBZ group, and 15.20 (± 0.81) points (range = 10 to 26 points) for the placebo group. At the end of the 12 week study, the Total Chorea Scores for TBZ subjects declined by a mean of 5.0 points, while those in the placebo group declined by a mean of 1.5 points. The difference of 3.5 points was statistically significant at p-value = <0.0001 favoring the TBZ group. (Table 6.) The group receiving TBZ showed more decline in their Total Chorea Scores at all but one of the study sites.

Table 6. Total Chorea Score Changes during the Study and after Withdrawal for TBZ 103,004

Treatment	Baseline		End of Week 12		Follow-up Visit	
	N	Mean (\pm SD) Total Chorea Score	N	Mean (\pm SD) Total Chorea Score	N	Mean (\pm SD) Total Chorea Score
Tetrabenazine	54	14.69 \pm 3.84	54	9.41 \pm 4.45	49	15.08 \pm 4.21
Placebo	30	15.20 \pm 4.41	30	14.07 \pm 4.72	29	14.90 \pm 4.47

Response to treatment was also judged by the number of points from baseline chorea scores that the subjects experienced. Table 7 shows the change in chorea scores grouped into categories by the extent of the change. A 3-point decrease in the TCS was considered clinically relevant by the Steering Committee. Fig. 2 shows that $\sim 69\%$ of the subjects in the TBZ group had ≥ 3 -point decrease in their TCS, compared to 23% of the placebo group. Conversely, 11% of the TBZ group showed worsening of chorea compared to 27 % of the subjects in the placebo group.

Table 7. Change from Baseline (to Weeks 9 + 12) in Total Chorea Score (Expressed as Number of Points Decreased) in the TBZ and Placebo Groups

Reduction of Chorea Score	Tetrabenazine (N=54) Number of Participants	Placebo (N=30) Number of Participants	P-Value (Cochran Armitage Trend Test)
≥ 10 points	10 (19%)	1 (3%)	<0.0001
6-9 points	17 (31%)	1 (3%)	
3-5 points	10 (19%)	5 (17%)	
0-2 points	11 (20%)	15 (50%)	
Worsening Chorea	6 (11%)	8 (27%)	

The improvement in the TCS with TBZ, compared to placebo, reached statistical significance from Week 3 until the conclusion of the study. The TCS for both groups showed a decline over

the first 3 weeks of the study. However, the scores of the TBZ group showed a more rapid decline that continued to about Week 7 (with a decline of ~ 5 points in the TCS), then evidenced a leveling effect for the remainder of the study. There was a rapid increase in chorea for the TBZ group following withdrawal of the drug (the post-study Week 13 Visit). The placebo group also showed a decline initially (~ 2 points in the TCS), followed by leveling off from Week 3 and an increasing score (return toward baseline) by the end of the study. (Figure 1.)

Fig. 1. Change from Baseline in Total Chorea Score (Expressed as Number of Points Decreased), TBZ 103,004.

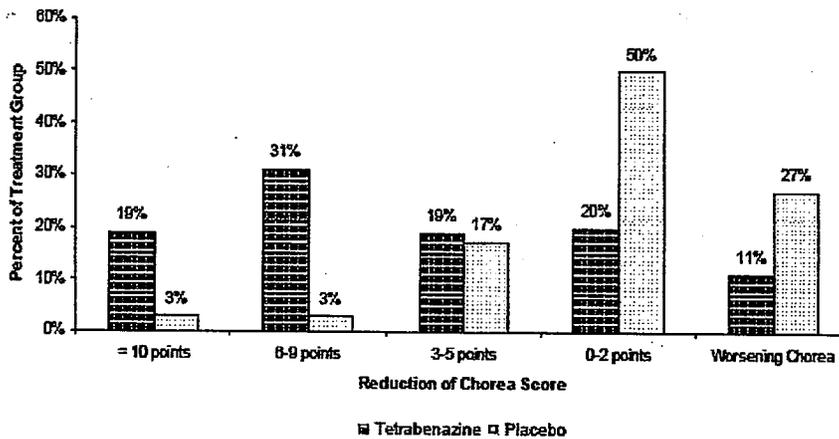
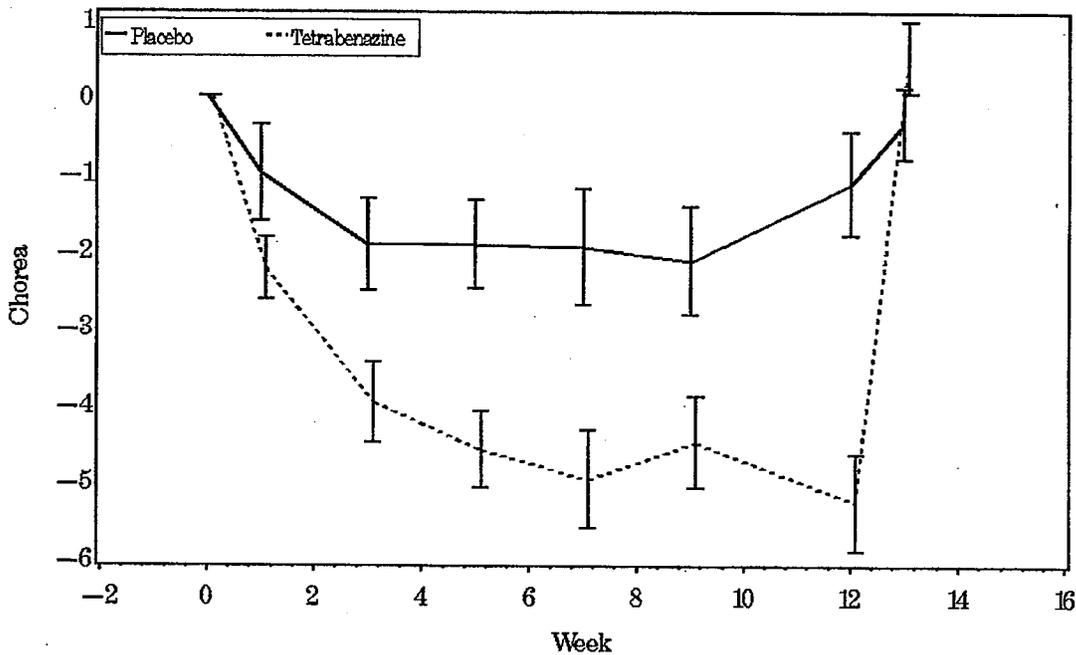


Fig. 2. Mean (\pm s.e.m.) Change in Total Chorea Score (TCS) by Study Week, TBZ 103,004.



Total Chorea Scale score = # of points change from the baseline assessment of chorea using the UHDRS, Item 12

At the end of the study (week 13), after the 7 day drug withdrawal, the mean Total Chorea Scores of the TBZ treated subjects were slightly higher than their mean Chorea Scores at baseline. Three subjects on TBZ and one on placebo had an increase in Total Chorea Scores >3 points. In all others, the chorea scores were either not increased, or were increased by less than 3 points.

The study also did an ad hoc analysis of the effect of TBZ on higher or lower baseline total maximal chorea scores. In Table 8, 41% of the TBZ group and 43% of the placebo group had baseline chorea scores (TCS) of >14 points. The change in the TCS was greater for subjects in the TBZ group with higher (>14 units) baseline chorea scores (-7.35 +0.98), than for those with lower (≤14 units) scores (-2.98 +0.67). More difficult to interpret is the mean difference in the placebo group with those having higher baseline chorea scores also showing a greater treatment effect on the placebo.

Table 8. Change from Baseline (to Weeks 9 + 12) in Total Chorea Score vs. Higher or Lower Baseline Chorea Scores

Total Chorea Score at Baseline	Tetrabenazine (N=54)		Placebo (N=30)		P-Value ANCOVA
	N (%)	Adjusted Mean Changed Score	N (%)	Adjusted Mean Changed Score	
> 14	22 (41%)	-7.35 ± .98	13 (43%)	-2.99 ± 1.25	0.0111
≤ 14	32 (59%)	-2.98 ± .67	17 (57%)	-0.73 ± .86	0.0261

An analysis of responders vs. non-responders was also done. The study definition of a “responder” to the TBZ treatment was a subject whose total maximal chorea score was decreased ≥ 3 points from baseline at the end of the study. This applied to 37 (69%) of the TBZ group, and 7 (23%) of the placebo group. (Table 9.) However, as with the other end-of-study analyses, the entire 54 subjects did not complete the study, so it includes data on those with LOCF scores as well.

Table 9. Number and Percentage of Subjects with a Decrease in TCS (Baseline to Aver. Weeks 9 + 12) of ≥ 3 UHDRS Units (“Responders Analysis”)

Tetrabenazine (N=54)	Placebo (N=30)	P-value (Fisher’s Exact Test)
37 (69%)	7 (23%)	< 0.0001

A score of > 10 points on the TCS was used as part of the inclusion criteria for the study. At the conclusion of the trial, 30 (56%) of the TBZ group had a TCS of < 10 points, compared to 4 (13%) of the placebo group.

Evaluation of the secondary endpoints

Four secondary efficacy endpoints were tested in the specified order given below, and analysis was to be terminated as soon as any p-value was > 0.05. Table 10 lists the change scores from baseline by group, and their level of statistical significance.

Table 10. Change from Baseline for Secondary Outcome Measures, TBZ 103,004

Secondary Outcome Measure	Tetrabenazine (N= 54)	Placebo (N=30)	P-Value (ANCOVA)
CGI Part 2	2.99 ± 0.17	3.73 ± 0.22	0.0074
Total Motor Score (UHDRS 1-15)	-6.84 ± 1.11	-3.51 ± 1.49	0.0752
Functional Assessment Checklist (UHDRS 43-67)	-0.81 ± 0.29	0.37 ± 0.40	0.0183
Gait (UHDRS 13)	0.001 ± 0.05	0.11 ± 0.07	0.2410

(1.) CGI – Clinical Global Improvement (CGI Part 2)

Ratings were done by investigators to assess the overall improvement or worsening in each subject compared to baseline (note – since it was rating change, a rating was not actually obtained at baseline). Investigators were instructed “Compared to baseline, rate total improvement, whether or not, in your judgment, it is due entirely to drug treatment”. The ratings were scored from:

- | | |
|------------------------|---------------------|
| 0 = not assessed | 4 = No change |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved | 6 = Much worse |
| 3 = Minimally improved | 7 = Very much worse |

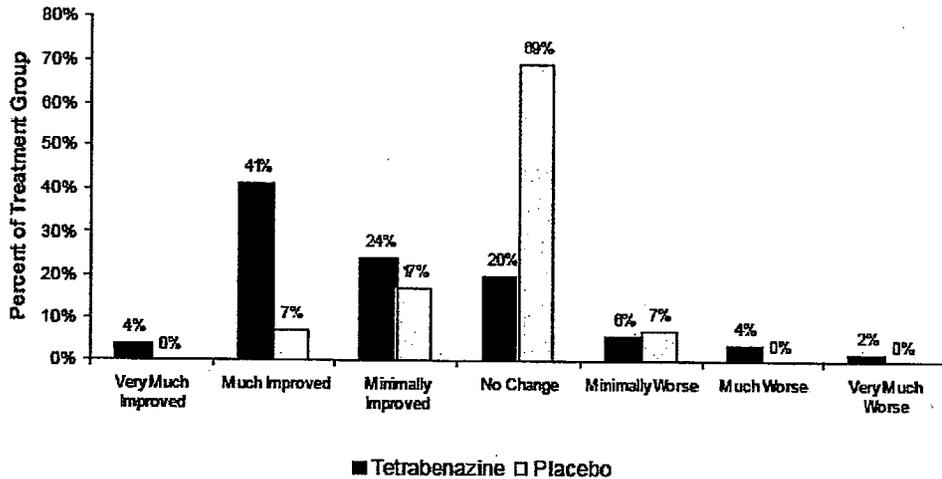
The mean scores in the CGI Part 2 were 2.99 (±0.17) for the TBZ group, compared to 3.73 (±0.22) for the placebo group. The difference between groups of 0.75 point favored the TBZ group, and gave an ANOVA p-value of 0.0074 for statistical significance. (Table 11.)

Table 11. Assessment at Week 12 Visit on the Clinical Global Impression (CGI) Part 2 by Group, TBZ 103,004.

CGI Part 2 Item	Tetrabenazine (N=51)	Placebo (N=29)	P-Value (Cochran-Armitage Analysis for Trend)
	Number of Participants (%)		
Very Much Improved	2 (4%)	0 (0%)	0.0063
Much Improved	21 (41%)	2 (7%)	
Minimally Improved	12 (24%)	5 (17%)	
No change	10 (20%)	20 (69%)	
Minimally Worse	3 (6%)	2 (7%)	
Much Worse	2 (4%)	0 (0%)	
Very Much Worse	1 (2%)	0 (0%)	

CGI Part 2 analysis did show that 35 (69%) of the TBZ subjects had “at least minimal improvement”, compared to 7(24%) of the placebo-treated subjects (p<0.0001). Ratings of “very much improved” and “much improved” were applied to 45% of the TBZ subjects, and 7% of the placebo group subjects. (Fig. 3)

Figure 3. Response at Week 12 Visit on CGI Part 2



(2.) Change in Total Motor Score (UHDRS Part I, items 1-15)

Assessments included motor assessment of : ocular pursuit, saccade initiation, & velocity, dysarthria, tongue protrusion, finger taps, hand pronate/supinate, LURIA, rigidity – arms, bradykinesia – body, maximal dystonia, total maximal chorea (the Total Chorea Score –also evaluated separately as the study’s primary objective), gait (also analyzed separately as an secondary objective), tandem walking and retropulsion pull test. The scores can range from 0 (best) to 124 (worst). The average baseline score was 46 points. The adjusted mean treatment effect of -3.3 UHDRS points (-6.84 for TBZ, -3.51 for placebo) change from the baseline to the average of the Week 9 plus Week 12 scores for the TBZ group in the Total Motor Score was not statistically significant (p-value = 0.0752), although there was a trend in the direction favoring the TBZ group.

(3.) Change in Functional Assessment Checklist (UHDRS Part IV, items 43-67) The questions evaluated the functions of daily living (ADLs) with a rating of how the subject had been handling mixture of simple and complex tasks. They were scored with either 0 = No, or 1 = Yes. The scores could range from 0 (best) to 25 (worst). The average baseline score was 19 points. The information source could be either the participant only or participant and family/caregiver. The change in scores from baseline to Week 12 was -0.81 ((slight worsening) for the TBZ group, and 0.37 (slight improvement) for the placebo group. The difference was estimated to be 1.18 points, a statistically significant outcome (p-value = 0.0183), but favoring the placebo group. The Sponsor attributed the lack of significance to the fact that it was a relatively short study, and all the subjects at enrollment were independently ambulatory (i.e. probably relatively high level functioning) which may have had a “ceiling effect” for the scoring.

(4.) Change in Gait Score (UHDRS Part 1, item 13)

Rated on a 5-point scale ranging from “normal gait” = 0, to “cannot attempt” = 4. Scores for the TBZ group were 0.001 (± 0.05) point, a trace improved, and for the placebo group 0.11 (± 0.07) point, a slight worsening. This gave an ANCOVA p-value of 0.2410 which does not show a

statistically significant treatment effect, and the changes did not show improvement, but were too small to have any clinical meaning.

Evaluation of the exploratory endpoints:

Ten exploratory endpoints were included in the analysis of the data. These included;

- Change in Severity of Illness (CGI Part 1)
- Change on CGI Efficacy Index (CGI Part 3)
- Change in Verbal Fluency (UHDRS 19)
- Change in Symbol Digit Modalities Test (UHDRS 20)
- Change in Stroop Interference Test (colors, UHDRS 21)
- Change in Stroop Interference Test (words, UHDRS 22)
- Change in Stroop Interference Test (interference, UHDRS 23)
- Change in Behavioral Assessment (UHDRS Part III, items 25-35)
- Change in Independence Scale (UHDRS Part V, item 69)
- Change in Total Functional Capacity (UHDRS Part VI, items 70-74)

Table Exploratory Endpoints – LS Mean Change from Baseline (to Aver. Week 9 + 12)

Only on the CGI-Part 3 did the tetrabenazine show statistical superiority to the placebo. This attempted to evaluate the overall assessment of the drug by measuring the therapeutic effect in comparison to the side effects (whether it interferes with patient’s functioning). The therapeutic effect rating reflected the investigator’s impression of improvement (change) in each subject’s condition, so no baseline score was designated for this. The therapeutic effect score was the average of the scores assigned at Week 9 and Week 12, and then matched to the level of side effects experienced by the subject to obtain an overall efficacy index. (Table 12.)

The criteria for “treatment success” on the measure, was a rating of 01 (marked improvement with no side effects); 02 (marked improvement with side effects that do not significantly interfere with patient’s functioning); 05 (moderate improvement with no side effects); or 06 (moderate improvement with side effects that do not significantly interfere with patient’s functioning).

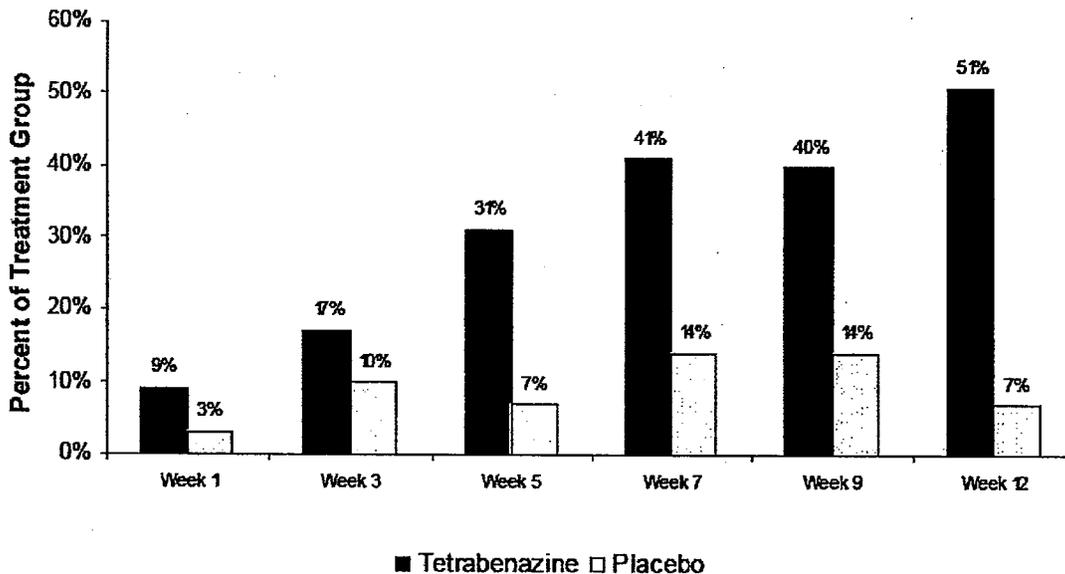
Table 12. Efficacy Index of the Clinical Global Impression (CGI) Part 3.

EFFICACY INDEX – Rate this item on the basis of DRUG EFFECT ONLY			
Select the terms that best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.			
EXAMPLE: Therapeutic effect is rated as "Moderate" and side effects are judged "Do not significantly interfere with patient's functioning." Record 06.			
	SIDE EFFECTS		
	Does not significantly interfere with	Significantly interferes with	Outweighs

THERAPEUTIC EFFECT	None	patient's functioning	patient's functioning	therapeutic effect
MARKED Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
MODERATE Decided improvement. Partial remission of symptoms	05	06	07	08
MINIMAL Slight improvement which doesn't alter status of care of patient	09	10	11	12
UNCHANGED OR WORSE	13	14	15	16
NOT ASSESSED = 00				

The percentage of subjects judged to be a "treatment success" on the CGI Part 3 was higher in the TBZ group from Week 1, and consistently throughout the study. By Week 12, 51% of the TBZ group (compared to 7% of the placebo group), were judged to be a "treatment success", by that criteria, as represented in Fig.4.

Fig. 4. Percentage of Subjects Judged to be a "Treatment Success" on CGI Part 3 by Study Week



None of the other exploratory evaluations showed statistical significance that favored TBZ treatment. Nearly all the remaining analyses trended toward placebo, or in the case of cognitive assessment, was statistically significant favoring placebo.

The CGI Part 1 analysis rated the severity of the illness using the question "Considering your total clinical experience with this particular population, how ill is the patient at this time?"

- | | |
|----------------------------|---|
| 0 = Not assessed | 4 = No change |
| 1 = Normal, not at all ill | 5 = Markedly ill |
| 2 = Borderline ill | 6 = Severely ill |
| 3 = Mildly ill | 7 = Among the most extremely ill patients |

This measure was assessed at the Baseline Visit as well as the subsequent visits.

Table 13. Exploratory Endpoints for CGI (Cognitive Global Impression) - Part 1 and Part 3 scores

Exploratory Outcome Measure	Tetrabenazine		Placebo		P-Value (ANCOVA)
	N	Mean Change Scores	N	Mean Change Scores	
CGI Efficacy Index (CGI Part 3)					
Week 9	50	8.72 ± 3.62	28	11.21±2.99	0.0026
Week 12	51	8.22 ± 4.00	29	11.41±2.88	0.0006
Average Week 9 & Week 12	52	8.63 ± 3.56	29	11.28 ± .67	0.0010
CGI Severity of Illness (Part 1)					
Average of Week 9 & Week 12	54	-0.06 ± 0.48	30	-0.02±0.40	0.9186

Exploratory analyses using the UHDRS (and FIS):

For all of these, the outcome measure was the change between the baseline scores and the average of the Week 9 and Week 12 scores. Table 14 lists the mean change by group on these scales, and the level of statistical significance achieved.

Table 14. Exploratory Endpoints using the UHDRS- Change from Baseline (to Aver. Weeks 9 + 12)

Exploratory Outcome Measure	TBZ (N= 54)	Placebo (N=30)	Difference	P-Value (ANCOVA)
	Mean Change - Baseline (Average Weeks 9 + 12)			
Sum of Cognitive – UHDRS Part II (19 – 23)	-7.7	5.1	12.8	0.025
Verbal Fluency (UHDRS 19)	-2.61 ± 0.77	-1.27 ± 1.05	1.3	0.3045
Symbol Digit Modalities Test (UHDRS 20)	2.15 ± 0.76	3.02 ± 1.05	0.9	0.5087
Stroop Interference Test (Color; UHDRS 21)	-1.69 ± 1.22	1.25 ± 1.74	2.9	0.1767
Stroop Interference Test (Words; UHDRS 22)	-4.84 ± 1.53	1.80 ± 2.09	6.6	0.0123
Stroop Interference Test (Interference; UHDRS 23)	-1.52 ± 0.90	1.47 ± 1.23	3.0	0.0532
Behavioral Assessments (UHDRS 25-35)	-0.96 ± 0.81	-2.22 ± 1.09	1.2	0.3549
Independence Scale (UHDRS 69)	-1.98 ± 1.00	0.55 ± 1.35	2.5	0.1347
Total Functional Capacity (UHDRS 70-74)	-0.43 ± 0.21	-0.06 ± 0.28	0.4	0.2906
Functional Impact Scale (FIS)	0.11	0.13	0.02	0.970

Cognitive Scales

Placebo was statistically better than TBZ on the change in UHDRS Part II (Cognitive Assessment, items 19-23) at p-value = 0.025. That assessment included items on the verbal fluency test, symbol digit modalities test, color naming, word reading, and interference. The exploratory endpoint called for analysis only of the individual items, not the overall score for the Cognitive Assessment. Analysis done on the individual items all at least nominally favored placebo, and achieved statistical significance on the Stroop Interference - Words, and was nearly significant of Stroop Interference - Interference.

Functional Scales:

It seems practical to consider all the functional scales together, especially since there is considerable overlap in the scales of the types of questions asked and the functions evaluated. TBZ did not show a significant beneficial treatment effect on any of the functional scales, as evidenced in Table 15, and nearly all favored placebo either nominally or, for the Functional Assessment Checklist, with statistical significance. The pre-specified endpoint was analysis using the mean of Weeks 9 + 12.

Table 15. Functional Scales – Change from Baseline (to Aver. Weeks 9+12) by Group

Functional Scale	Tetrabenazine (N= 54)	Placebo (N=30)	P-Value (ANCOVA)
	Mean Change from Baseline (Average Week 9 and Week 12)		
Functional Assessment Checklist (UHDRS Part IV; Items 43 to 67)	-0.81 ± 0.29	0.37 ± 0.40	0.0183
Functional Capacity (UHDRS Part VI; Items 70 to 74)	-0.43 ± 0.21	-0.06 ± 0.28	0.2906
Functional Impact Scale (FIS)	0.12 ± 0.17	0.13 ± 0.23	0.9712
Independence Scale	-1.98 ± 1.00	0.55 ± 1.35	0.1347

The Functional Assessment Checklist was the functional scale used as a secondary endpoint. Scoring of the 25 items is done by “yes” = 1, or “no” = 0 for the answers (25 points = fully functional). The TBZ treatment group scores worsened by a mean of -0.81 points, while the placebo group improved their scores by a mean of 0.37 points. Item analysis was done to determine if there were any systematic effects of the TBZ on scores, but no consistent patterns were shown for TBZ either improving or worsening the specific scores.

The three functional scales used for exploratory endpoints did not fare much better. The Total Functional Capacity (TFC) scale deals with a rating for each of 5 topics. Occupation, finances, domestic chores, and ADLs, were rated between 0 = “unable”, to 3 = “normal”, and care level was rated 0 = full-time skilled nursing, to 2 = “home”. Total scores can range from 0 (maximal dysfunction) to 13 (no dysfunction). The baseline scores were quite similar (8.3 for TBZ group, 8.6 for placebo group). Analysis of the TFC scale showed that by the end of the study, both groups had slightly worse scores than at baseline. However, the placebo group declined only 0.03 points, while the TBZ group declined by 0.43 points. The difference between the groups favored the placebo group, but was not large enough to be statistically significant.

The Independence Scale (UHDRS Part V, item 69) is a one number assessment. The mean scores at baseline were 76.9 points for the active treatment group, and 80.2 points for the placebo group on a scale where 100 = no disability, 010 = tube fed, total bed care. Change from the baseline mean was very minimal, but was in a positive direction for the placebo group (0.3 points), and in a negative direction for the TBZ group (-1.7 points).

The Functional Impact Scale was a new scale first used on this study. It was not listed among the 10 exploratory endpoints, but was analyzed there, so it has been included in this review. It was designed to be answered by the caregiver to assess how HD impacts daily functioning. It scores from 0 = "independent", to 15 = "total assistance needed". The baseline scores were quite high for both groups (mean score of 1.3 in TBZ group, 1.27 in placebo group). The mean score of the TBZ group improved by 0.03 points, while the mean score of the placebo group worsened by 0.15 point. There was virtually no change in scores, from baseline to end of study, for either group (a fraction of a point change), and did not show statistical significance.

During the withdrawal phase at the end of the study, the chorea scores for the subjects on tetrabenazine were only slightly higher at 1 week off the drug than the scores obtained at baseline. No significant evidence of a "rebound effect" was found, but the subjects should be cautioned of a possible slight increase of chorea shortly after discontinuation of the drug. The assessments were made 1 week after drug withdrawal (several weeks later in a few cases), and if there was a temporary "rebound effect" that was larger, it may have stabilized by the end of the week. (Table 16.)

Table 16. Total Chorea Score Changes during the Study and after Withdrawal, TBZ 103,004.

Treatment	Baseline		End of Week 12		Follow-up Visit	
	N	Mean (± SD) Total Chorea Score	N	Mean (± SD) Total Chorea Score	N	Mean (± SD) Total Chorea Score
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

Comments

The study was generally balanced in distribution of the demographic groups, although the number of non-white subjects was low. Analysis of the data did show that the baseline demographic variables such as age, gender, length of illness, and concomitant medications did not appear to significantly affect the response to treatment or adverse effects. In addition, refiguring the data to check on the drop-outs showed that they did not have an effect that would have significantly changed the primary conclusions.

The study used flexible dosing. Generally, fixed dosing studies are preferred in drug application studies. The Sponsor argued that the literature has indicated that the flexible dosing is required because of two observations. First, the dose at which efficacy is observed" is only slightly lower than the doses causing troublesome side effects. Second, there is a wide inter-individual

variation of the doses that will produce these troublesome events (50-300 mg daily) with a wide variability of optimal dose. There is also no way to determine who will exhibit low or high optimal doses. Previous studies have also used the flexible dosing approach, and the FDA agreed to its use in this study. A slower titration change was used (dose adjustments every 7 days, rather than the every 3 days schedule used in most prior studies), which may have accounted for the lower incidence of AEs such as dysphagia. It suggests that administration of the drug might be made more efficient by recommendations in the labeling for the slower upward titration with longer intervals between dosing adjustments. The study also documents that the "best dose" varies within a fairly wide range (in this study between 25 to 100 mg/day), and does not correlate to plasma levels. The study tends to confirm the need to flexibly titrate to "best dose" for the HD subjects.

According to the previous studies, up to 50% of the patients exposed to flexible titration experience adverse events that may be readily identifiable as resulting from tetrabenazine (parkinsonism, somnolence, dysphagia, etc.). This may result in a partial unblinding of a significant number of subjects. To counter this, at the recommendation of the FDA, the primary endpoint (chorea) was evaluated by an independent expert physician not involved in other endpoint evaluations, and use of videotape was included in the evaluations. The FDA had assumed that all subjects enrolled after the amendment would be videotaped and receive the outside rating. However, implementation of the plan was inconsistent, and it could not be used as an endpoint. Overall, those ratings were able to show a clear distinction between the chorea scores of the subjects when receiving the TBZ, and after withdrawal of the drug. The pattern was similar to the finding of the site investigators' scores.

Evidence of efficacy was supported in the evaluation of data for the primary objective. There was a reduction in the observed chorea of 3.5 points on the TCS attributable to TBZ effect. The reduction in chorea also followed the anticipated curve showing a steady decrease over the first 5 weeks while doses were being titrated upward, and a leveling during the maintenance period, followed with a return to baseline chorea with drug withdrawal. Comparison to the placebo group was significant by the 3rd week visit and throughout the remainder of the study. The primary determination of efficacy was based on the changes in the Total Chorea Score (UHDRS, Item 12) which had been used in several of the previous studies of HD patients. The treatment effect showing improvement in chorea levels in this study was very similar to those found in previous studies, which suggested that management of chorea was improved in ~ 70% of the subjects with chorea.

Looking at the other efficacy endpoints shows some weaknesses in the study. Evidence of efficacy was supported in only one of the four secondary objectives. Using the Clinical Global Impression (CGI) Part 2 endpoint, a significant number of the TBZ subjects were rated "much" or "very much" improved compared to the placebo group. The CGI is a more subjective assessment, by the investigators, of the subject's symptoms. There is no actual baseline assessment with which to compare it, so the number listed is the assigned score, not a difference in points that occurred. The score of 2.99 on the scale for the TBZ 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 is statistically significant, but not large (less than one point).

Analysis of the cognitive assessment shows that score changes for the section were statistically significant, but favoring the placebo group. The Prestwick did not feel that the changes were attributable to sedation or drowsiness. It is of concern that if cognitive changes are AEs associated with drug use, they could be easily attributed instead to the course of the disease. In that case, dose adjustment or drug discontinuation is likely to occur than with more easily evidenced AEs.

An improvement in mobility and/or functioning would have lent weight to the application. The Gait score was probably not very sensitive to this population or length of study since there were few categories and they were broad. However, with a clinically significant decrease in the chorea, a change in the fairly inclusive Total Motor Score would have seemed likely, but did not occur (especially when only the non-chorea items were evaluated). If the decrease in chorea does not improve mobility scores, then the concern remains that for some patients, the sedation or drowsiness which commonly occurs as side-effects may increase the risk of falls and injuries.

Analysis of the 10 exploratory endpoints showed only one to be statistically significant. The Clinical Global Impression (CGI) Part 3 attempted to weigh clinical improvement in chorea reduction against the side effects of the drug for each subject. It used subjective data from the investigator. The impressions did show a steady improvement in the TBZ group compared to the placebo group but differences between the groups were difficult to interpret with this scale, and it was not clear whether the investigators were rating only chorea changes, or some other factors.

It does seem worthwhile to look at the various tests for functional assessments when they are grouped together. Table 16 combines the secondary endpoint, Functional Assessment Checklist, with the 3 exploratory functional endpoints (Functional Capacity, Functional Impact and Independence). The reduction in the chorea scores with TBZ treatment does not appear to improve ratings on the functional scales. This is a rather surprising finding that goes against logical expectation. The Sponsor's explanation is that the subjects were independently ambulatory and therefore minimally disabled as described on the scales used. So, there may have been little room for functional improvement this group. Four scales of functional abilities were used in the study. Analysis of the Functional Assessment Checklist (items 43 to 67 of the UHDRS, Part IV) was used as a secondary endpoint. It was the most detailed and varied of the functional assessments, and the most specific about the ADLs (activities of daily living). As noted above, the treatment effect favored the placebo group. Item analysis was performed on the scales, but no pattern of effect emerged.

The functional assessments were also notable because it is the area of the study that is evaluated by the subjects and/or caregivers. So, it becomes more significant that none of the scales showed any significant level of benefits with TBZ treatment, and most trended toward placebo. The study lacks any area indicating that the subjects physically or emotionally benefited by the reduction in their chorea.

The Week 13 evaluations showed return of chorea following drug withdrawal for the TBZ group. The TCS scores were slightly higher than at baseline. Since there was a range of time in which the last evaluations were done, it cannot rule out a possible "rebound effect" that may

temporarily influence mobility safety. A longer follow-up after TBZ withdrawal would be helpful to establish the pattern of the chorea return.

In summary, the study was confirmatory of the efficacy of tetrabenazine for the reduction of chorea in Huntington's disease, but not for improvement in mobility or functional activities, and the study cognitive assessment scores were worse on TBZ than placebo.

10.1.2 Study TBZ 103,005 - Phase 3, Efficacy Study

Phase III, trial 11/17/2003 – 12/10/2004, "A Randomized, Double-Blind, Placebo-Controlled, Staggered Withdrawal Study in Patients with Huntington's Disease Treated with Tetrabenazine".

Objective

The stated objective of the study was to examine the efficacy of TBZ for the treatment of Huntington's Disease, and assess the difference in severity of emerging chorea after discontinuation of TBZ. The rationale for the study is based on the premise that since the chorea of HD is chronic, and treatment with tetrabenazine is palliative and temporary, then return of the chorea upon withdrawal of the treatment provides evidence that the treatment is effective in controlling the symptoms of chorea.

Primary objective - to evaluate the efficacy of tetrabenazine in Huntington's chorea by determining whether the withdrawal of the drug from subjects led to the return of chorea. The efficacy parameter was the Total Maximal Chorea Score, Item 12 of the Unified Huntington's Disease Rating Scale (UHDRS) motor portion (12 a through 12 g). The primary outcome measure was the change in the Total Maximal Chorea Score from the Baseline Visit to Day 3 of Group 1 compared to the combined scores of Groups 2 and 3.

Secondary objectives – to evaluate the time-course of the return of chorea; whether chorea observed in patients five (5) days following tetrabenazine discontinuation was more severe than chorea observed in patients three (3) days after tetrabenazine discontinuation. Due to another misunderstanding about the Protocol, the UHDRS measurements were not done on Day 3, so the secondary and exploratory endpoint could not be evaluated. According to the Protocol, the proposed secondary efficacy parameter was to be the Total Functional Capacity Score (TFC – a subscale of the UHDRS, Part VI). The primary outcome measure was the change in TFC from the Baseline Visit to Day 3 where Group 1 was the experimental (drug withdrawn) group and the combined Groups 2 and 3 (not withdrawn) served as the control group. The secondary outcome measure was the difference of the change scores from the Baseline Visit to Day 3, and from Day 3 to Day 5, analyzing the groups separately. In addition, paired t-tests were performed for Group 1 on secondary efficacy parameters (UHDRS Parts I, II, III, IV, V and VII) from Day 1 to Day 5 for each of the three groups.

Exploratory analyses – were not done, as noted above, they were to have included an analysis of covariance (ANCOVA) comparing the three treatment groups on the changes in scores of Parts I, II, III, IV, V and VII of the UHDRS from Day 1 to Day 5 for each of the groups.

Design & Sample Size

The study design was a staggered 5-day drug withdrawal in three unbalanced groups. It was done as a single center, randomized, double-blind, placebo-controlled trial. It enrolled patients who had previously been treated open-label with TBZ under Investigator IND 16,161 (Joseph Jankovic, M.D.). They had to have on-going treatment, and be stabilized on their “best dose” of tetrabenazine, for at least 2 months prior to the start of the study,. The study was done at the Parkinson’s disease Center and Movement Disorder Clinic of Baylor College using 12 males and 18 females, age 18 years or older. Thirty-two patients were screened for this study, and thirty (30) were enrolled. The patients had previously been taking TBZ 25 mg tablets (under the physician IND). For the trial, they were switched to TBZ 12.5 mg (in multiples as needed for their previously established “best dose” or to placebo (identically appearing, and also twice the number of tablets daily that they had previously taken). The staggered withdrawal periods lasted up to 5 days. The protocol called for 12 of the subjects (40%) to be switched to placebo on Day 1 (Group 1), 12 subjects (40%) switched on day 3 (Group 2), and 20% to remain on TBZ (control group). Subjects remained on the trial for the 5 days unless they experienced return of intolerable chorea, at which point they were considered a treatment success, and discontinued from the study. (Figure 5.)

Fig. 5. Proposed Study Design of Tetra Withdrawal TBZ 103,005

Screening (All Patients)	Double-Blind Staggered Withdrawal (5 Day Duration)			
	Treatment Assignment Group	Baseline Visit	Day 3	Day 5
Within 2 weeks prior to randomization	Group 1 (12)	Switches to placebo	Continues on placebo	Continues on placebo
	Group 2 (12)	Remains on tetrabenazine	Switches to placebo	Continues on placebo
	Group 3 (6)	Remains on tetrabenazine	Remains on tetrabenazine	Remains on tetrabenazine

At the end of the study, resumption of “best dose” was resumed with no titration to assess whether it would be well-tolerated, or suggest the need for titration for tolerance. Following the completion of the trial, the subjects were given the possibility of continuing in an open-label, long-term extension of the TBZ study for an additional six (6) months on Prestwick TBZ Protocol 103,006.

Table 17 lists the demographic characteristics of the groups included in the study. No significant differences were found in the distributions.

Table 17. Demographic Characteristics of 30 HD Subjects –TBZ 103,005

Demographic Characteristic	Group 1 (N= 12)	Group 2 (N=12)	Group 3 (N=6)	Statistical Test; p-value
Gender *				
Male	5 (42%)	4 (33)	3 (50%)	Fischer Exact 0.8912
Female	7 (58%)	8 (67)	3 (50%)	
Age (years)				
Mean	56.08	55.92	59.83	ANCOVA 0.7171
Median	59.50	58.00	59.50	
Std Dev	9.69	8.48	14.22	
Range	39 – 70	41 - 68	39 - 75	
Race *				
White	12 (100%)	10 (83%)	6 (100%)	Fischer Exact 0.3379
Other	0	2 (17%)	0	
Years of Education				
Mean	14.08	13.83	15.00	ANCOVA 0.6231
Median	14.50	14.00	15.00	
Std Dev	2.43	2.52	2.10	
Range	10 - 18	9 - 18	12 - 18	

Table 18 lists the baseline illness characteristics of the study groups which were generally well randomized except that Group 3 had a higher average baseline chorea score, more in the markedly and severely ill categories, and rather worse ratings on the TMS. This was probably due to randomization difficulties with such a small number included in the group.

Table 18. Baseline Illness Characteristics by Groups – Tetra Withdrawal TBZ 103,005

Baseline Illness Characteristic	Group 1 (N= 12)	Group 2 (N=12)	Group 3 (N=6)	Statistical Test; p-value
Disease Duration (yrs)				
Mean	10.22	9.18	11.41	ANOVA 0.6925
Std. Dev	4.51	6.10	4.77	
Range	4.07 – 21.22	.48 – 19.28	6.71 – 18.87	
CGI Part 1; number of patients				
Not Ill	0	0	0	Fisher's Exact 0.2411
Borderline Ill	0	0	0	
Mildly Ill	0	2 (17%)	0	
Moderately Ill	7 (58%)	7 (58%)	2 (33%)	
Markedly Ill	4 (33%)	1 (8%)	1 (17%)	
Severely Ill	1 (8%)	2 (17%)	3 (50%)	
Among the most extremely ill patients	0	0	0	
Primary Efficacy End-Point				
Total Maximal Chore Score; (UHDRS Item 12)				
Mean ± SD	9.42 (±1.42)	9.08 (±1.79)	11.17 (±1.82)	ANOVA 0.7337
Median	8.50	8.50	11.00	
Std Dev	4.91	6.22	4.45	

Range	2 - 19	3 - 25	6 - 16	
Secondary Efficacy Endpoint				
TFC				
Mean ± SD	6.25 (±0.75)	7.58 (±1.01)	5.00 (±1.15)	ANOVA 0.2340
Median	6.00	7.00	4.50	
Std Dev	2.60	3.50	2.83	
Range	2 - 12	2 - 13	2 - 10	
Exploratory End-Points				
Total Motor Score; (UHDRS 43-67)				
Mean ± SD	34.75(±2.81)	28.00 (±3.79)	50.00 (±3.57)	ANOVA 0.0016
Median	34.50	25.50	53.00	
Std Dev	9.74	12.00	8.74	
Range	19 - 55	12 - 47	34 - 59	
Gait; (UHDRS 13)				
Mean ± SD	1.50 (±0.15)	1.33 (±0.31)	2.33 (±0.33)	ANOVA 0.0675
Median	1.50	1.00	2.50	
Std Dev	.52	1.07	.82	
Range	1 - 2	0 - 4	1 - 3	

Ratings of the chorea (before and after tetrabenazine withdrawal) were done using the UHDRS Item 12, the maximal chorea score, a sub-set of the UHDRS Part 1 Motor Assessment. This is the same rating tool that had been used as the primary efficacy objective in the preceding trial, Prestwick Protocol TBZ 103,004.

Figure 6 lists the additional scales used in the secondary and exploratory analyses for the study.

Fig. 6. List of Scales used in Tetra Withdrawal TBZ103,005

Efficacy	Tolerability
<ul style="list-style-type: none"> • UHDRS (parts I, II, III, IV, V, and VII) • TFC (subscale of the UHDRS; part VI) 	<ul style="list-style-type: none"> • UHDRS (parkinsonism and part VIII) • TFC (subscale of the UHDRS; part VI) • HAM-D (at the discretion of the Investigator)

HAM-D = 17-item Hamilton Depression Rating Scale; TFC = Total Functional Capacity;
 UHDRS = Unified Huntington's Disease Rating Scale.

Definitions

Same as those listed in the TetraHD 103,004 study. In this study, the ratings were referred to as the Maximal Chorea Score or Total Maximal Chorea Score, but the rating used was the same as in the primary objective of Protocol TBZ 103,004 where the score was referred to as the Total Chorea Score (TCS).

Key Inclusion Criteria

Males and females 18 years of age or older

Clinical diagnosis of Huntington's disease with an expanded CAG repeat (n≥37)

Receiving treatment with tetrabenazine for at least two months
 Subjects who had responded well to tetrabenazine treatment
 Subjects who were stabilized on the “best dose” of tetrabenazine (as judged by the Investigator) for at least two months prior to their enrollment in the study

Key Exclusion Criteria

An unstable, serious medical or psychiatric illness
 Concomitant treatment with other dopamine (DA) depletors, DA D2 receptor blockers, selective and non-selective monamine oxidase inhibitors (MAOIs), levodopa and DA agonists
 Change in the dosage of any concomitant antidepressant within 8 weeks of the Baseline Visit
 Lack of a caregiver

Concomitant Medications

Same criteria as the TetraHD 103,004 trial. The most common psychotropic medications were antidepressants and benzodiazepines. (Table 19.)

Table 19. Total Number of Subjects on Concomitant Medications at Study Entry

Treatment Assignment Group	Number of Participants	Statistical Test; p-value
Group 1	10 (83%)	0.7872
Group 2	11 (92%)	
Group 3	6 (100%)	

Four of the participants in the study were taking neuroleptic medications at the start of the study and these were continued, which was a protocol deviation. These subjects were included in the efficacy, safety and pharmacokinetics analyses. (Table 20.)

Table 20. Summary Data of Subjects Taking Neuroleptics – TBZ 103,005

Participant Identification	“Best Dose” of Tetrabenazine at Study Entry (mg)	Treatment Assignment Group	Generic Neuroleptic Medication (stated indication)	Daily Dosage
547-408	25/12.5 b.i.d.	Group 2	Fluphenazine (chorea)	0.5 mg po qAM
547-410	25 t.i.d.	Group 1	Fluphenazine (HD)	6 mg po per day
547-413	25 qd	Group 2	Haloperidol (chorea)	0.25 mg po t.i.d.
547-427	25 t.i.d.	Group 3	Quetiapine (insomnia)	100 mg po qhs

Dosage

A wide range of doses was involved in the study. Most were between 50 and 150 mg/day. The mean daily dosage for the combined groups at the start of the study was 52.92 (± 27.4) mg/day.

Tetrabenazine 12.5 mg tablets given to previous “best dose” for each subject, or a dose of placebo to mimic the subject’s dose prior to the study. The subjects had previously been taking the same dosages of TBZ but using the 25 mg tablets, so the number of tablets was doubled for both TBZ and placebo groups. (Table 21.)

Table 21. Daily Tetrabenazine Dosages at the Study Entry –TBZ 103,005

Treatment Assignment Group	Mean (\pm SD) Daily Dosage (mg/day)	Median Daily Dose (mg/day)	Minimum (mg/day)	Maximum (mg/day)
Group 1 (N = 12)	59.38 \pm 35.0	50.0	12.5	150
Group 2 (N = 12)	45.83 \pm 19.46	37.5	25.0	75.0
Group 3 (N = 6)	54.17 \pm 24.58	62.5	25.0	75.0
Groups 1, 2 and 3, combined (N = 30)	52.92 \pm 27.4	50.0	12.5	150

Schedule

Safety and tolerability were evaluated for each subject at each visit and blood samples were drawn at baseline, and Days 3 & 5 to check plasma concentrations of TBZ and its two metabolites. More extensive blood testing was done on a subset of 10 subjects for pharmacokinetic profiles of b.i.d. and t.i.d. dosing regimens.

Table 22. Study Schedule (Study Flow Chart) – Tetra Withdrawal TBZ 103,005

Assessment	Study Visit			
	Screening • Day – 14 to Day 0	Randomization (Baseline) Day 1•	Day 3	End-of- Study Day 5
Informed Consent	X			
Demographic	X			
Medical & History; Neurological Previous Meds	X			
Neurological & Physical Exam	X			X
Clinical Global Impression (CGI)	X			
CAG Repeat Analysis†		X		
12-Lead ECG	X			X
Laboratory Tests (including serum pregnancy test)	X			X
Inclusion/Exclusion	X	X		
Randomization Call-CTCC		X		
First Dose Study Drug		X		
Vital Signs	X	X	X	X
Blood Plasma Level for PK		X	X	X
UHDRS	X	X		X
Total Maximal Chorea Score (UHDRS, q12a- 12g)			X	
TFC (subscale of UHDRS-part VI)	X		X	
Subject Disposition Form	X			
Visit Signature Form	X	X	X	X

Adverse Events Log		X	X	X
Concomitant Medications Log	X	X	X	X
Study Drug Log		X	X	X
Study Drug Dispensing -Compliance Log		X	X	X

The flow chart for the study is represented on Table 22. The study design called for tetrabenazine to be withdrawn from Group 1 and replaced by the placebo on Day 1 of the study. Group 2 was to remain on their “best dose” of the drug until after the morning dose on Day3, at which time the drug would be discontinued and placebo substituted. The control group (Group 3) was to continue taking tetrabenazine at their “best dose” as usual throughout the study. On Day 5, the subjects were to be evaluated after taking their assigned drugs.

Analysis

Statistical Methods – The primary analysis used the intent-to-treat principle with all randomized subjects within their groups. The two-sided Type 1 error rate is 0.05. For both the primary and secondary efficacy endpoints, analysis of covariance (ANCOVA) was used to compare Group the groups to each other and to their baseline Total Maximal Chorea scores. The same analysis was also done adjusting for unbalanced baseline covariants. The exploratory analyses used ANCOVA analysis to compare the three groups on the change in scores in all efficacy parameters from the Baseline Visit to Day 5.

Results –

There were no premature discontinuations. Analysis of the randomization to the groups showed that Group 3 had the highest number of severely ill subjects, 3 of the 6 subjects (50%), compared to 1 subject (8%) in Group 1, and 2 subjects (17%) in Group 2. Correspondingly, the scores on the Total Maximal Chorea score (TCS), the Total Functional Capacity score (TFC), TotalMotor Score and Gait all showed that the Group 3 subjects were slightly more impaired. In view of the type of study, and the study design, the differences were not significant enough to affect the study interpretation or outcome.

Primary efficacy evaluation – the pre-determined endpoint for this study did not reach statistical significance. The Sponsor feels that it is due to a misunderstanding of the protocol by the Study Coordinator at the site and the Project Coordinator at HSG. Group 1 was to discontinue the tetrabenazine on Day 1, but Group 2 was to have remained on the drug until after the morning dose of Day 3. After breaking the blind for the study, they determined that the subjects in Group 2 had their tetrabenazine discontinued on the evening of Day 2 and had been “washed out” from the drug for 12 to 18 hours before the Day 3 evaluations were done. As a result, the protocol implementation was flawed, and the Group 2 subjects were not an appropriate comparison group.

The pre-specified primary endpoint for efficacy evaluation was the comparison of the change in TCS of Group 1 compared to the mean scores of Groups 2 and 3 combined. Group 1 (off TBZ), had an increase in the TSC of 5.33 (+3.47) points by Day 3, and comparison to the combined other groups (mean TCS change 2.94 +3.52), gave an ANCOVA p-value = 0.0779. Combining Group 1 and Group 2 (since both were off TBZ), and comparing their Day 3 mean TCS to Group 3 gave a p-value = 0.135. Leaving Group 2 out of the calculations, and just comparing Group 1

(off TBZ) to Group3 (on TBZ) on Day 3, gave a p-value = 0.11. None of the calculations using variants of the specified endpoint were statistically significant. Table 23 lists the TCS for each group, and Table 24 lists the mean change in TCS for each group.

Table 23. Total Maximal Chorea Scores (TCS) by Withdrawal Group and Study Day

Treatment Assignment Group	Day 1	Day 3		Day 5
	On Tetrabenazine	On Tetrabenazine	Off 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 24. Mean Change in TCS from Baseline to Day 3, and Baseline to Day 5

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

Other measures were also done to evaluate the data. The Sponsor felt that a retrospective ad hoc trend analysis was more appropriate, considering Group 2 as a “middle group”, and it gave a p-value = 0.0486. Combining Groups 1 and 2 at Day 3 (both off TBZ) for comparison to their own baseline in TSC change (rather than comparison to Group 3) showed statistical significance (p-value = <0.001), as shown in Table 25. In Table 26, the same analysis was done combining all the groups at the end of study to compare to the baseline score. These analyses indicated that within group differences could show statistically significant change.

Table 25. Mean Change of TCS Baseline to Day 3 for Groups 1 and 2 Combined

Treatment Group	Baseline Visit	Day 3	Mean Change (± SD)	T-test, P-value
Groups 1 + 2 (N = 24)	9.25 ± 5.48	13.71 ± 5.3	4.46 ± 3.20	P < 0.0001

Table 26. Mean Change of TCS (Baseline to Day 5) for All Subjects, TBZ 103,005

Baseline Visit	Day 5	Mean Change (± SD)	T-Test, p-value
9.6 ± 5.3	14.8 ± 6.0	5.13 ± 3.43	p < 0.0001

When evaluating individual participants, only one subject in Group 1 did not have an increased chorea score (the Day 5 reading was the same as the Baseline Visit), the other 11 subjects all showed increases in their TCS. The range for the entire group of 12 subjects was 0 to 11 points, with a mean 5.33 point TCS increase. For Group 2, all the subjects had increased chorea scores by Day 5 with a range of 1 to 11 points, and a mean of 5.92 points. The total range for Group 3 was 0 to 9 points, with a mean 4.0 increase in the chorea score. See Table 37, Appendix B.

The increase in the TCS for Group 1 was stable between Day 3 and Day 5, and Group 2 had a very similar score on Day 5, suggesting that washout of the drug is done within 2-3 days. The score on Day 3 for Group 2, when they had been off TBZ for 12 to 18 hours, was similar to the score for Group 3 when they had been off TBZ for 12 to 18 hours.

Secondary Efficacy Assessment: As noted above, the secondary endpoints could not be used since the UHDRS was not done as scheduled on Day 3. Instead, an analysis was included of the TFC (Total Functional Capacity, UHDRS Part VI) as the secondary efficacy measurement. In the Protocol, it had been listed as a measurement of safety and tolerability for the study. The new outcome measure became the change in the TFC from Baseline Visit to Day 3 where Group 1 was the experimental group, and compared to the combined Groups 2 and 3 as the control group. (Table 27.) For 26 of the 30 subjects, there was no change in their TFC score from Baseline Visit to Day 3. Analysis of the data showed that the drug withdrawn Group 1, who might have been expected to show a decrease in functioning, had no change in their TFC by Day 3 (0.00 ± 0.00). On the other hand, the control group (combined Group 2 and 3) did show a slight decrease (-0.389 ± 1.20) which was not well explained, but was probably just overly influenced by the very small number of subjects involved.

Table 27. Secondary Efficacy Analysis: Mean Change of Total Functional Capacity (TFC) Scores - Baseline to Day 3 (Comparing Group1 to Aver. Groups 2 + 3)

Mean Change (\pm SD) of Total Maximal Chorea Score; Baseline to Day 3		
Group 1 (N = 12)	Groups 2 + 3 (N = 18)	p-Value; T-test
0.00 \pm 0.00	-0.389 \pm 1.29	0.2180

The secondary outcome measure was the difference of the change scores from Baseline Visit to Day 3, and from Day 3 to Day 5 with each group analyzed separately. (Table 28.) For 18 of the 30 subjects, there was no change in their TFC from the Baseline Visit to Day 5.

Table 28. Mean TFC Change by Group – Baseline to Day 3, and Day 3 to Day 5

Treatment Assignment Group	Study Day	
	Day 3 to Baseline Visit	Day 5 to Day 3
Group 1 (N=12)	0.0 \pm 0.0	-0.50 \pm 0.79
Group 2 (N=12)	-0.17 \pm 0.72	-0.50 \pm 0.67
Group 3 (N=6)	-0.83 \pm 2.04	0.0 \pm 0.0

An additional secondary outcome measure was done (ad hoc analysis), combining all the groups and comparing the Baseline Visit to Day 5 TFC scores. This gave a statistically significant decline (p-value = 0.0093), but only ~ half of one point on the 19 point scale, which would lack clinical significance. (Table 29.)

Table 29. Mean TFC Change for All Subjects – Baseline to Day 5

Baseline Visit	Day 5	Mean Change (\pm SD)	p-value, T-test
6.53 \pm 3.09	5.90 \pm 3.17	-0.63 \pm 1.25	p = 0.0093

As noted in the discussion on choice of endpoints (Section 5.1.2), the Total Functional Capacity (TFC) score was probably not an adequately sensitive measure for such a short study. Of the five items, 3 (occupation, finances or care level) were not likely to change over a 5 day period, and the scoring of other two items (domestic chores and ADLs) involved large shifts in function to go from one ranking to another. Analysis of TFC did not appear to contribute to the study. As discussed above, the Protocol for the study had planned to use the TFC analysis as a safety and tolerability assessment, not a measure of efficacy.

The pre-specified secondary endpoints were the analyses of the UHDRS Parts I, II, III, IV, V, and VII. In the study write-up, these were referred to as exploratory endpoints. It was explained that due to an administrative error, the complete UHDRS was not performed on Day 3 of the study, and as a result, the planned analyses could not be performed. Section 11.4.1.3.1 of the TBZ 103,005 study (Exploratory Efficacy Analyses) states: “An additional ANCOVA analysis was performed comparing the three treatment groups on the changed scores in the same efficacy parameters from the Baseline Visit to Day 5. The treatment effect was not statistically significant in any of these analyses”. No data or additional comment was provided in the analyses.

Comments

The laboratory and physical evaluations were appropriate. The Total Maximal Chorea Score (TCS) was an appropriate measurement device for the study, and had the added benefit of easier comparisons to the multi-center study which used the same primary efficacy measurement.

The withdrawal study can be used to show efficacy for a drug, but generally the most useful information involves the length of time the subjects had been receiving the drug prior to its withdrawal. This gives an indication of whether it had maintained effectiveness over time. All of the subjects had been on their “best dose” of TBZ for at least 2 months by the inclusion criteria of the study. The information on length of prior use of the drug was not collected on the subject CRFs, or included in the report. When the information was requested, it was provided by a review of Baylor medical records. The average duration of prior TBZ treatment was 2.5 years for the combined groups with a range of 0.21 to 7.07 years. Of the 30 subjects, 13 had been taking TBZ for < 1 year, 5 were in the 1 to 2 year range, 8 in the 2 to 5 year range, and 4 had been on the drug for > 5 years. Return of chorea in subjects that had been on the drug for several years is suggestive that efficacy is maintained. One of the perplexing questions about the

withdrawal study is why there should be such a rapid return of chorea after withdrawal of the tetrabenazine. The drug has a short half-life, however its proposed method of action is dopamine depletion. It seems surprising that, after years of continued use of TBZ, the depletion would not preclude the return of chorea within a matter of hours.

The pre-specified number of subjects for the study had been set at 45. The Sponsor cited difficulties with enrolling subjects into the study, stating that those currently on the medication did not want to be withdrawn from it even temporarily. However, periodic withdrawal of the drug is routinely done to assess whether the patients are still benefiting from it, since as Huntington's disease progresses, the chorea is usually replaced by rigidity. The protocol was amended, and the FDA agreed to limitation of the study to one site, at Baylor College of Medicine, and reduction of the enrollment to 30 subjects. This increased the need for the study to be conducted flawlessly at that site.

Communication of the protocol was obviously very problematic:

There was an apparent miscommunication on Day 3 when all groups were to have taken their morning medications from the Bottle 1 prior to evaluations, and switched to Bottle 2 drugs afterward. Instead all of the subjects were started on the Bottle 2 drugs prior to evaluations, so Group 2 was off the TBZ for 12 to 18 hours when the exams were done. This caused major difficulties with analysis of the data, and precluded any meaningful interpretation of the study's main endpoints. The problems occurred again on Day 5, when subjects were to have been evaluated after taking their assigned morning drug, but instead, evaluations were done before taking the drugs. As a result, even Group 3 scores reflected 12 to 18 hours since the last TBZ dose, and they could no longer be used as a control group for the study. Another protocol deviation was that four of the subjects were taking neuroleptic medications, excluded by the inclusion criteria, throughout the study.

Statistical analysis of the pre-specified primary efficacy endpoint was done, despite the flawed design, but did not reach statistical significance, yielding a p-value of 0.077. The argument was presented by the Sponsor that in view of the changed circumstances, a trend analysis was more appropriate. A retrospective, ad hoc trend analysis was applied to the data, using Group 2 as a middle group, and was statistically significant (p-value = 0.048).

The Total Functional Capacity (TFC) score was substituted for the initially proposed secondary efficacy measurement. The TFC was not a very sensitive scale to have used for this analysis. It can give an assessment that would indicate change over a year in the course of the disease, but there are only 5 items evaluated, and several of the indicators, such as work status, financial, and residence (home or nursing home) are unlikely to change during a 5 day clinical trial even if the chorea increased dramatically.

There was a problem with data management in the interpretation of results. Charts for primary endpoints analyses were displayed in the middle of data analysis of the secondary endpoints and referenced their figures incorrectly. The references to the supporting raw data charts showed that it was not just a result of typos, the raw data charts for primary endpoints were embedded in the middle of the secondary endpoints data. In other areas, the discussions and charts do not correlate on the designated dates.