

Overall, TBZ 103,005 was a very flawed study, and lacking a control presents problems with statistical analysis of the data collected.

Prestwick also submitted the interim reports on their two follow-on studies. Both of these were done as safety and tolerability studies, but some data analysis for efficacy was done. Since they were both open-label studies, the results of their efficacy evaluations based on the interim data could not be used to support the efficacy claims for this indication.

#### **10.1.2 Study TBZ 103,007 and Study TBZ 103,006**

Both studies were done as open-label extension studies designed primarily to support safety and tolerability claims. The FDA has received only the interim data for each study. Some efficacy analysis has also been done on the data collected.

Prestwick TBZ Protocol 103,007 was the extension study of TBZ Protocol 103,004. Only an interim report at week 24 has been received for inclusion in the efficacy review. The study used the same 16 sites, and eligible subjects from the previous study for a 48 week open-label follow-on study (including a temporary drug wash-out at Visit 3, Week 25). Of the subjects that completed Protocol TBZ 103,004, 75 of the 78 participated. Since the subjects that had been in the placebo group (not yet exposed to TBZ) were included, escalation titration to “best dose” was used for all subjects.

In TBZ 103,004, 22 of 49 subjects (45%) reached the maximum allowable dose of the study, 100 mg/day, which suggested that higher doses for these subjects might provide additional benefits. That was tested in the follow-on open-label study where the maximum allowable dose was increased to 200 mg/day. Of the 22 enrolled from the previous study taking the highest dose, their “best dose” on this study was lower than 100 mg/d for 12, between 100 to 150 mg/day for 8 patients, and equal to 200 mg/day for 1 patient. Between Week 24 and Week 28, 98% of all subjects were treated with doses  $\leq$  150 mg/day, and 70% were treated with doses  $\leq$  100 mg/day. The mean TBZ dose for all the study participants, at the time of the 24-week interim report, was 72.8 mg/day.

Information on withdrawal from the study was available on only 19 of the subjects. The reasons cited were withdrawal due to administrative reasons =4, lack of efficacy =1, worsening HD =2, adverse events =7. Another five withdrew at the 24 weeks point, 1 each due to depression, non-compliance, fatigue & dislike of travel, to avoid a drug wash-out and too many problems-no specifics given. The administrative reasons included (1 each): lost to follow-up, lose of caregiver, an exclusionary medication, and withdrawn consent. The adverse events included: death due to metastatic breast cancer, a fall from unsteady gait & balance with hip fracture, vocal tics, abnormal bilirubin, akathisia (2).

Efficacy for the purposes of the interim study was measured only by the change from baseline to the end of Week 36 (Visit 7) in the Total Maximal Chorea Score (UHDRS Part I – motor portion, item 12, q. 12a – 12g). At the start of the study, the mean baseline TCS was 14.95 ( $\pm$ 3.67) with a range of 8.0 to 23.0 on the 28 point scale. The mean change in the TCS was -7.27

( $\pm 4.51$ ) UHDRS points at Visit 7, Week 36 (n=30). At Visit 4 (n=69), the mean TCS change was -5.80 ( $\pm 4.98$ ) points. The study interprets the comparison of scores at Visit 4 and Visit 7 as indication that efficacy has been maintained over time. With such a large number of subjects withdrawn from the study in the interim, the maintenance of changed scores (and the increase) could easily be attributable to only subjects responsive to the drug remaining in the study.

The response to TBZ by subjects with either high or low baseline chorea scores was investigated. The 43 subjects with a baseline score of  $> 14$  UHDRS points had a mean change in TCS of -9.17 ( $\pm 4.34$ ) on Visit 7 (when n=18 subjects). By contrast, the 30 subjects with a mean baseline TCS of  $\leq 14$  had a mean TCS of -4.42 ( $\pm 3.12$ ) on Visit 7 (n=12 subjects). Overall, the cumulative percentage of chorea scores  $> 3$  (their level of clinical significance) was  $> 60.27\%$  at Visits 1 through 4 and Visit 7.

The study report repeatedly states that 56 subjects remain enrolled in the study, but the charts used in the efficacy evaluation provide data for only 30 subjects (or, on the male:female chart, only 29 subjects) as of Visit 7, Week 36

Study TBZ 103,006 was designed as an open-label extension study of the tetrabenazine withdrawal study, Prestwick TBZ 103,005 at Baylor College of Medicine. The study began 11/17/03 and is reported as on-going. Subjects were treated for up to 80 weeks, however the FDA has received only the data from an interim analysis based on evaluation of the data at the 24 Weeks Visit (Visit 2). The objective was to examine the tolerability and safety of TBZ for HD chorea over time. A secondary objective was to examine the tolerability of rapidly resuming the subjects' "best dose" treatment without titration. Twenty-seven of the 30 subjects in the Prestwick Tetra Withdrawal Protocol TBZ 103,005 were enrolled (1 declined due to lack of drug efficacy, 2 enrolled late so were included in the update of SAEs and deaths, but not in the efficacy and safety analyses). Enrollment criteria required successful completion of the previous study, including a relapse of chorea after withdrawal of the tetrabenazine. At the time of the interim report, 25 of the subjects remained on the study. One withdrew after 120 days due to placement in a nursing home, and one withdrew after 27 days due to nausea and weight loss requiring hospitalization. Both had been receiving 37.5 mg/day of TBZ.

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. Most of the subjects, 25 of the 27 (92.6%), were able to resume their "best dose" without adjustments. One subject was restarted on a lower dose due to mild parkinsonism, and another misunderstood the dosing instructions and took more than the prescribed dose.

#### Efficacy Results:

The efficacy evaluation of the study used the change from baseline on the Total Maximal Chorea Score. The mean baseline TCS was 14.44 ( $+6.34$ ), range = 3-27 UHDRS points. The report states that due to staggered enrollment in the study, there were fewer data points for the later visits resulting in n = 17 for Visit 2 (the 24 Week Visit). 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  $\geq 3$  points units on the Maximal Chorea Score (TCS).

The subjects that had baseline TCS of  $> 14$  UHDRS points again showed the larger changes in the TCS. The 8 subjects with baseline TCS  $> 14$  points had a mean change of  $-9.33 (+6.56)$  points at Week 24 (Visit 2). The 11 subjects with baseline TCS of  $\leq 14$  points showed a mean change of  $-4.09 (+3.36)$  UHDRS points. Overall, the cumulative percentage of score reductions that were  $\geq 3$  points (the study criteria for clinical significance) was 76.5% at Visit 2. Decrease in the TCS was greater for the 8 females ( $-7.8 \pm 5.8$  points) than for the 9 male subjects ( $-4.3 \pm 4.3$  points) on this study, but with the very small number involved, no interpretations are possible.

### **10.1.3 Baylor Chorea Database**

Information from the Baylor Database also accompanied the application (TBZ Project 103,011). It consisted of a review of information extracted from the records of chorea patients that had been treated with tetrabenazine at the Baylor College of Medicine by Dr. Joseph Jankovic under Investigator IND 16,161, Protocol H-721. The treatment dates for the patients occurred between January, 1979 to February, 2004. The data extraction was done April, 2004 to December, 2004. From a potential data base of 162 patients, the records of 145 patients were deemed sufficiently complete for evaluation. Of these, 98 patients had chorea associated with HD, and 47 with chorea of various etiologies. Tetrabenazine 25 mg tablets were used. The drug was started at 12.5 mg/day, and titrated by 25 mg/day increments every 3-7 days to "best dose" (max. = 300 mg/day). "Best dose" for 85% of the patients was between 12.5 mg/day to 100 mg/day (in divided doses if  $\geq 25$  mg/day), and the mean "best dose" was  $65.3 \pm 35.4$  mg/day. Only 2 patients had a "best dose" of  $> 200$  mg/day. Concomitant medications were used by 97% of the patients, including antidepressants (62%), benzodiazepines (46%) or neuroleptics (47%). Patients were usually evaluated every 3 – 6 months. Duration of treatment varied from 1 day to many years; mean duration =  $2.6 \pm 2.5$  years.

Of the cohort of 145 patients, 118 were withdrawn from treatment (including 14 who died, 17 withdrew to enter another TBZ protocol, 29 withdrew due to AEs). The duration of treatment for patients withdrawn from the study included 72 with  $\geq 1$  year of treatment; 55 with  $\geq 2$  years of treatment. As of, February, 2004, 27 patients continued treatment under the original open-label protocol.

Effectiveness: Efficacy was measured by the number and percentages of patients with a response grade of 1 (marked or complete relief of chorea) through 5 (worsening of chorea). The Investigator 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.

#### **Comments:**

Collectively, the open-label studies all show a trend that is supportive of the effectiveness of tetrabenazine for chorea. These are not controlled studies, and with the large number of withdrawals, randomization is lost, and treatment bias is likely to occur. Such factors are probably inevitable in a studies using patients that have to travel to the study sites for the

evaluations, and compounded by mobility difficulties for these subjects, and the progression of the illness over time. However, it does severely complicate interpretation of the data in uncontrolled trials.

## **10.2 LINE-BY-LINE LABELING REVIEW**

**APPEARS THIS WAY  
ON ORIGINAL**

## **APPENDIX B**

Table 30. Number of Participants Enrolled and Completing TBZ 103,004 by Sites

| Site No.     | Investigator and Site  | Number of Participants |                                 |
|--------------|--|------------------------|---------------------------------|
|              |  | Enrolled               | Completed 12 weeks of Treatment |
| 005          | Kathleen Shannon, MD, Rush Presbyterian – Saint Luke's Medical Center, Department of Neurological Sciences | 4                      | 3                               |
| 007          | William Ondo, MD, Baylor College of Medicine, Department of Neurology                                      | 5                      | 5                               |
| 018          | Amy Cocher, MD, Pennsylvania Hospital, Penn Neurological Institute   | 4                      | 3                               |
| 019          | Juan Sanchez-Ramos, MD, James Haley VA Hospital, University of South Florida College of Medicine           | 6                      | 6                               |
| 020          | Sandra Kostyk, MD, PhD, Ohio State University, Parkinson's Center  | 6                      | 6                               |
| 032          | Claudia Testa, MD, PhD, Emory University, Department of Neurology  | 6                      | 6                               |
| 037          | Donald Higgins, MD, Albany Medical College, Parkinson's Disease and Movement Disorders Center              | 7                      | 7                               |
| 045          | Joanne Wojcieszek, MD, Indiana University School of Medicine; Outpatient Clinical Research Facility        | 8                      | 6                               |
| 051          | Jody Corey-Bloom, MD, PhD, University of California – San Diego School of Medicine                         | 9                      | 8                               |
| 055          | Andrew Feigin, MD, North Shore University Hospital   | 6                      | 6                               |
| 071          | Martha Nance, MD, Park Nicollet Clinic, Department of Neurosciences  | 6                      | 6                               |
| 073          | Michael Geschwind, MD, PhD, University of California San Francisco, UCSF Memory and Aging Center           | 5                      | 4                               |
| 104          | Karen Blindauer, MD, Medical College of Wisconsin, Department of Neurology                                 | 3                      | 3                               |
| 123          | Karen Anderson, MD, University of Maryland School of Medicine, Department of Neurology                     | 2                      | 2                               |
| 145          | Tetsuo Ashizawa, MD, University of Texas Medical Branch at Galveston                                       | 6                      | 6                               |
| 151          | Phillip Hanna, MD, JFK Medical Center, Neuroscience Institute  | 1                      | 1                               |
| <b>Total</b> |  | 84                     | 78                              |

Table 31. Total Maximal Chorea Score (TCS) - United Huntington's Disease Rating Scale, Item 12

| <b>12. MAXIMAL CHOREA</b> |                                      |     |             |
|---------------------------|--------------------------------------|-----|-------------|
| 0 =                       | Absent                               | 12a | FACE _____  |
| 1 =                       | Slight/intermittent                  | 12b | BOL _____   |
| 2 =                       | Mild/common or moderate/intermittent | 12c | TRUNK _____ |
| 3 =                       | Moderate/common                      | 12d | RUE _____   |
| 4 =                       | Marked/prolonged                     | 12e | LUE _____   |
|                           |                                      | 12f | RLE _____   |
|                           |                                      | 12g | LLE _____   |

BOL = bucco-oro-lingual; LLE = Left Lower Extremity; LUE = Left Upper Extremity; RLE = Right Lower Extremity; RUE = Right Upper Extremity

Table 32. The Clinical Global Impression (CGI) - Part 3 (Efficacy Index)

| <b>EFFICACY INDEX – Rate this item on the basis of DRUG EFFECT ONLY</b>  |              |   |   |                              |
|--|--------------|---|---|------------------------------|
| 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. |              |   |   |                              |
| THERAPEUTIC EFFECT   | SIDE EFFECTS |   |   |                              |
|  | None         | Does not significantly interfere with patient's functioning | Significantly interferes with patient's functioning | Outweighs therapeutic effect |
| <b>MARKED</b> – Vast improvement. Complete or nearly complete remission of all symptoms  | 01           | 02  | 03  | 04                           |
| <b>MODERATE</b> -Decided improvement. Partial remission of symptoms  | 05           | 06  | 07  | 08                           |
| <b>MINIMAL</b> -Slight improvement which doesn't alter status of care of patient   | 09           | 10  | 11  | 12                           |
| <b>UNCHANGED OR WORSE</b>  | 13           | 14  | 15  | 16                           |
| <b>NOT ASSESSED = 00</b>   |              |   |   |                              |

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|                                  | Screening                 |                         | Titration                |                         |                          |                          |                          | Maintenance Phase        |                       |                           | Washout                   |
|----------------------------------|---------------------------|-------------------------|--------------------------|-------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------|---------------------------|---------------------------|
|                                  | Screening Day - 14 to - 1 | Baseline Visit 00 Day 0 | Visit 01 Week 1 ± 2 days | Day 10-14 Phone contact | Visit 02 Week 3 ± 3 days | Visit 03 Week 5 ± 3 days | Visit 04 Week 7 ± 3 days | Visit 05 Week 9 ± 3 days | Week 11 Phone contact | Visit 06 Week 12 ± 3 days | Visit 07 Week 13 ± 2 days |
| ASSESSMENTS                      |                           |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| Informed Consent                 | X                         |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| Screening/Baseline Confirmation  | X                         |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| Randomization Call-CTCC          |                           | X                       |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| First Dose Study Drug            |                           | X                       |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| Medical History/Demographics     | X                         |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| Neurological & Physical Exam     | X                         |                         |                          |                         |                          |                          |                          |                          | X                     |                           |                           |
| Dysphagia Dysarthria             | X                         | X                       | X                        | X                       | X                        | X                        | X                        | X                        | X                     | X                         | X                         |
| Vital Signs                      | X                         | X                       | X                        | X                       | X                        | X                        | X                        | X                        | X                     | X                         | X                         |
| 12 Lead ECG                      | X                         |                         |                          |                         |                          |                          |                          |                          | X                     |                           |                           |
| Laboratory Tests                 | X                         |                         |                          |                         |                          |                          |                          |                          | X                     |                           |                           |
| Pregnancy Test                   | X                         | X*                      |                          |                         |                          |                          |                          |                          | X                     |                           |                           |
| Plasma Level (Population PK)     |                           |                         |                          |                         |                          |                          |                          | X                        |                       |                           |                           |
| Blood draw -Blinded CAG          | X                         |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| I7-item HAM-D                    |                           | X                       | X                        |                         | X                        | X                        | X                        | X                        | X                     | X                         |                           |
| Clinical Global Impression       |                           | X                       | X                        |                         | X                        | X                        | X                        | X                        | X                     | X                         |                           |
| Screening UHDRS (I, II)          | X                         |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           |
| UHDRS (I, III, IV, V, VII, VIII) |                           | X                       | X                        |                         | X                        | X                        | X                        | X                        | X                     | X                         | X                         |
| UHDRS (Part II)                  |                           | X                       |                          |                         |                          |                          |                          |                          | X                     |                           |                           |
| TFC (Part VI of UHDRS)           | X                         | X                       |                          |                         |                          |                          |                          |                          | X                     |                           |                           |

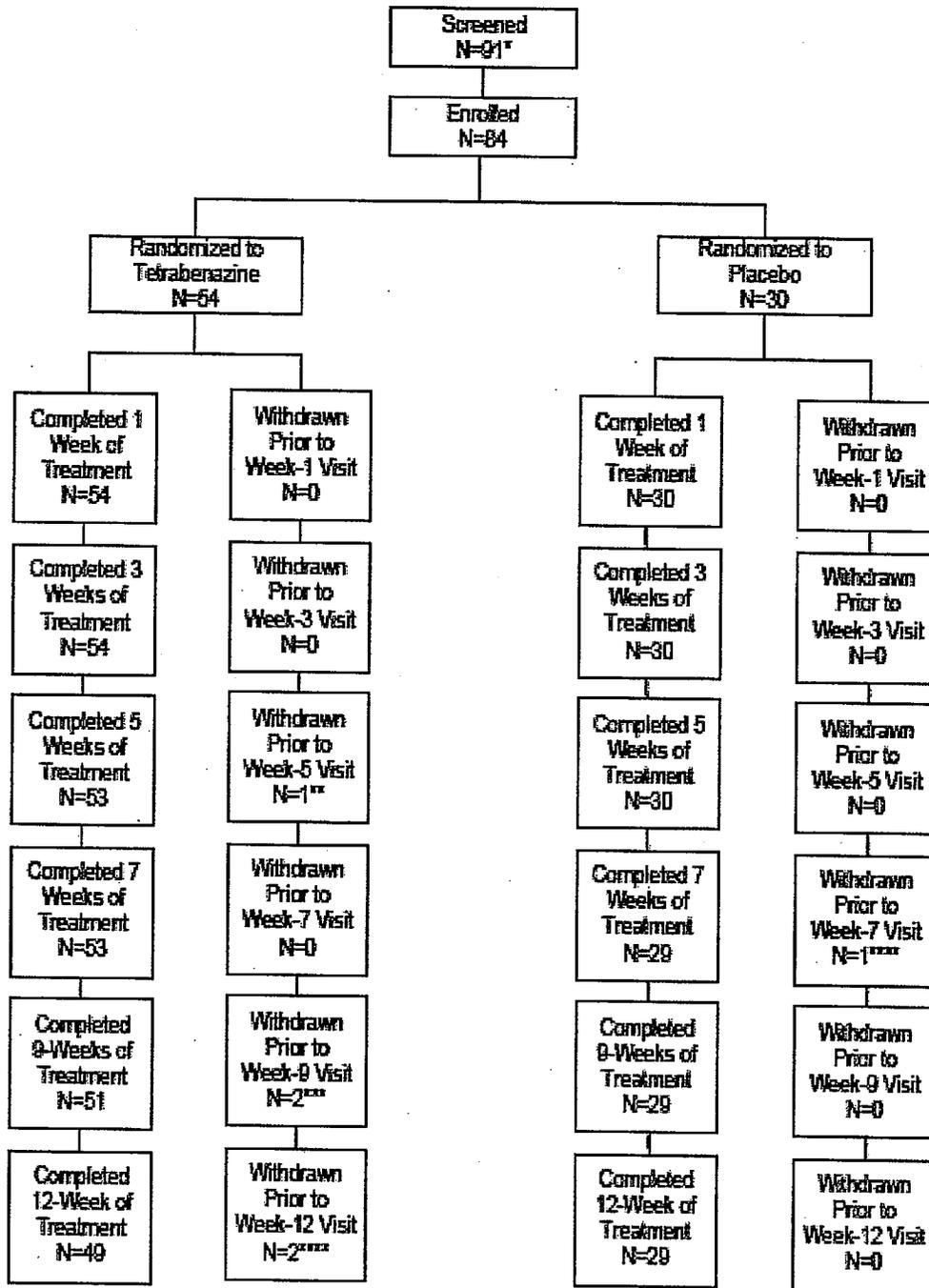
Table 33. Study Schedule (Study Flow Chart) for Tetra HD TBZ 103,004

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Table 33 Study Schedule (Study Flow Chart) for Tetra HD TBZ 103,004 (cont.)

|  | Screening                 |                         | Titration                |                         |                          |                          |                          |                          | Maintenance Phase     |                           |                           |   | Washout |
|--|---------------------------|-------------------------|--------------------------|-------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------|---------------------------|---------------------------|---|---------|
|  | Screening Day - 14 to - 1 | Baseline Visit 00 Day 0 | Visit 01 Week 1 ± 2 days | Day 10-14 Phone contact | Visit 02 Week 3 ± 3 days | Visit 03 Week 5 ± 3 days | Visit 04 Week 7 ± 3 days | Visit 05 Week 9 ± 3 days | Week 11 Phone contact | Visit 06 Week 12 ± 3 days | Visit 07 Week 13 ± 2 days |   |         |
| ASSESSMENTS                              |                           | X                       |                          |                         |                          |                          | X                        |                          |                       |                           |                           | X |         |
| BARNES                                   |                           | X                       |                          |                         |                          |                          | X                        |                          |                       |                           |                           | X |         |
| Epworth Sleepiness Scale                 |                           | X                       |                          |                         |                          |                          | X                        |                          |                       |                           |                           | X |         |
| Functional Impact Scale (piloting scale) |                           | X                       |                          |                         |                          |                          | X                        |                          |                       |                           |                           | X |         |
| Conclusion of Study Partic               |                           |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           | X |         |
| Visit Signature Form                     | X                         | X                       | X                        |                         | X                        | X                        | X                        | X                        |                       |                           |                           | X | X       |
| Adverse Events Log                       |                           | X                       | X                        | X                       | X                        | X                        | X                        | X                        |                       |                           |                           | X | X       |
| Adverse Events Follow-up Log             |                           |                         |                          |                         |                          |                          |                          |                          |                       |                           |                           | X | X       |
| Concomitant Meds Log                     | X                         | X                       | X                        | X                       | X                        | X                        | X                        | X                        | X                     | X                         | X                         | X | X       |
| Study Drug Titration Log                 |                           | X                       | X                        | X                       | X                        | X                        | X                        | X                        | X                     | X                         | X                         | X |         |
| Study Drug Dispensing -Compliance Log    |                           | X                       | X                        | X                       | X                        | X                        | X                        | X                        | X                     | X                         | X                         | X |         |
| Telephone Contact                        |                           |                         |                          | X                       |                          |                          |                          |                          |                       |                           | X                         |   |         |

Figure 7. Disposition of Subjects for Protocol TBZ 103,004

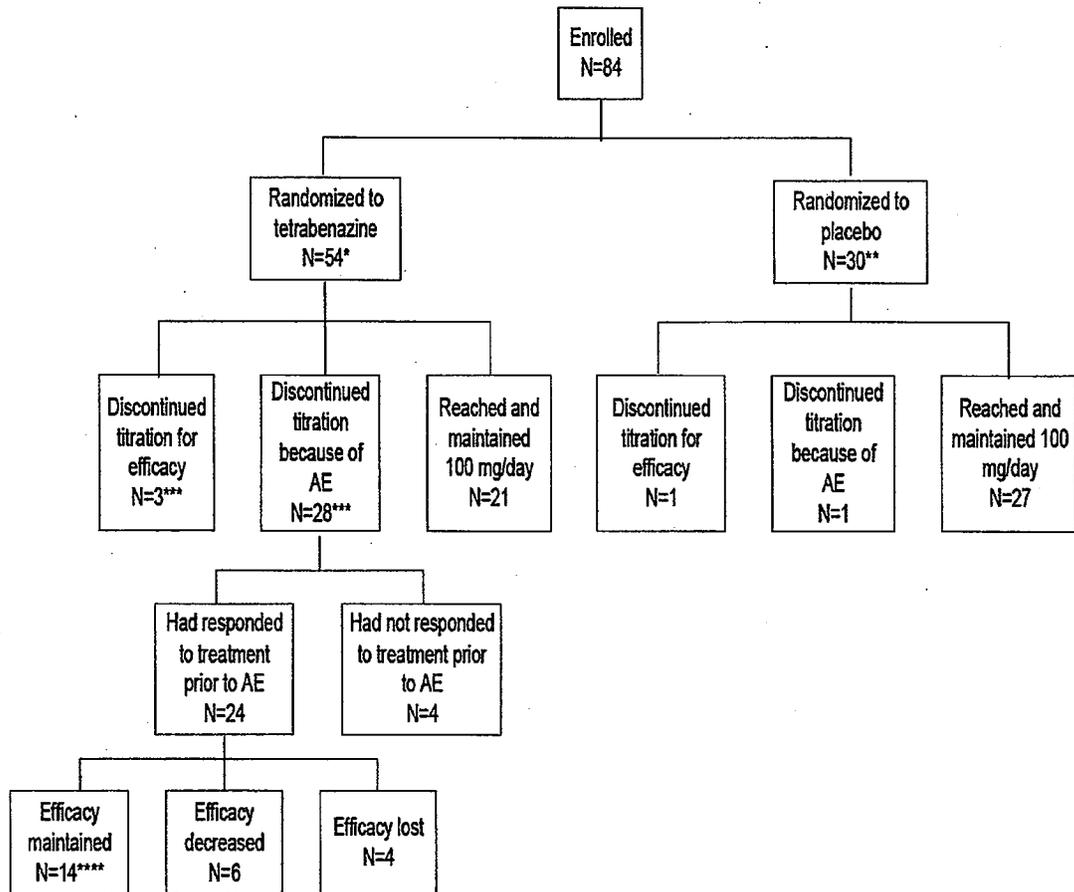


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Tetrabenazine (TBZ)

Figure 8. Reasons for Discontinuation of Upward Titration and Subsequent Response to Treatment in TBZ 103,004.



\* 3 participants in the tetrabenazine group prematurely discontinued (ID 447-206, ID 447-254, ID 447-271) but did not have any AEs causing dose reduction, nor did they reach efficacy.

\*\* 1 participant (ID 447-317) in the placebo group withdrew consent prior to completing the study

\*\*\* 1 participant (ID 447-288) had an AE (sedation) which caused a temporary dose decrease from 62.5 mg to 50 mg per day, but then the dose was increased back to 62.5 mg per day and efficacy was achieved, therefore this participant is counted twice in the figure.

\*\*\*\* 1 participant (ID 447-246) experienced akathisia which led to premature withdrawal from the study despite achieving efficacy.

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Table 34. Adverse Effects by Body System for Tetra HD TBZ 103,004

| Body System           | AE Preferred Term       | Tetrabenazine<br>N=54<br>n (%) | Placebo<br>N=30<br>n (%) | Total<br>N=84<br>n (%) |        |
|-----------------------|-------------------------|--------------------------------|--------------------------|------------------------|--------|
| GRAND TOTAL           | TOTAL                   | 49 (91%)                       | 21 (70%)                 | 70 (83%)               |        |
| PSYCHIATRIC DISORDERS | TOTAL                   | 39 (72%)                       | 4 (13%)                  | 43 (51%)               |        |
|                       | Insomnia                | 12 (22%)                       |                          | 12 (14%)               |        |
|                       | Depression              | 8 (15%)                        |                          | 8 (10%)                |        |
|                       | Sedation                | 8 (15%)                        |                          | 8 (10%)                |        |
|                       | Restlessness Aggravated | 7 (13%)                        |                          | 7 (8%)                 |        |
|                       | Irritability            | 5 (9%)                         | 1 (3%)                   | 6 (7%)                 |        |
|                       | Anxiety                 | 4 (7%)                         | 1 (3%)                   | 5 (6%)                 |        |
|                       | Anxiety Aggravated      | 4 (7%)                         |                          | 4 (5%)                 |        |
|                       | Somnolence              | 4 (7%)                         |                          | 4 (5%)                 |        |
|                       | Drowsiness              | 3 (6%)                         |                          | 3 (4%)                 |        |
|                       | Appetite Decreased      | 2 (4%)                         |                          | 2 (2%)                 |        |
|                       | Obsessive Reaction      | 2 (4%)                         |                          | 2 (2%)                 |        |
|                       | Sleepiness              | 2 (4%)                         | 1 (3%)                   | 3 (4%)                 |        |
|                       | Aggressiveness          | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Agitation               | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Anger                   | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Anorexia                | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Anxiety Attack          | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Apathy                  | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Bradyphrenia            | 1 (2%)                         |                          | 1 (1%)                 |        |
|                       | Compulsive Reaction     |                                |                          | 1 (3%)                 | 1 (1%) |
|                       | Concentration Impaired  | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Confusion               | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Disorientation          | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Dreaming Abnormal       |                                |                          | 1 (3%)                 | 1 (1%) |
|                       | Emotional Liability     | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Forgetfulness           | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Lethargy                | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Listless                | 1 (2%)                         |                          |                        | 1 (1%) |
|                       | Nervousness             |                                |                          | 1 (3%)                 | 1 (1%) |
| Paranoid Reaction     | 1 (2%)                  |                                |                          | 1 (1%)                 |        |
| Psychosis             | 1 (2%)                  |                                |                          | 1 (1%)                 |        |
| Sleep Difficult       | 1 (2%)                  |                                |                          | 1 (1%)                 |        |
| Sleep Disturbed       | 1 (2%)                  |                                |                          | 1 (1%)                 |        |
| Thoughts of Self Harm | 1 (2%)                  |                                |                          | 1 (1%)                 |        |

|  |                                 |        |  |        |
|--|---------------------------------|--------|--|--------|
|  | Withdrawal from Social Contacts | 1 (2%) |  | 1 (1%) |
|--|---------------------------------|--------|--|--------|

| Body System                               | AE Preferred Term        | Tetrabenazine<br>N=54<br>n (%) | Placebo<br>N=30<br>n (%) | Total<br>N=84<br>n (%) |
|---|--------------------------|--------------------------------|--------------------------|------------------------|
| CENTRAL &<br>PERIPHERAL<br>NERVOUS SYSTEM | TOTAL                    | 19 (35%)                       | 3 (10%)                  | 22<br>(26%)            |
|   | Akathisia                | 5 (9%)                         |                          | 5 (6%)                 |
|   | Balance Difficulty       | 5 (9%)                         |                          | 5 (6%)                 |
|   | Bradykinesia             | 3 (6%)                         |                          | 3 (4%)                 |
|   | Dizziness                | 2 (4%)                         |                          | 2 (2%)                 |
|   | Dysarthria               | 2 (4%)                         |                          | 2 (2%)                 |
|   | Gait Unsteady            | 2 (4%)                         |                          | 2 (2%)                 |
|   | Headache                 | 2 (4%)                         | 1 (3%)                   | 3 (4%)                 |
|   | Chorea                   | 1 (2%)                         |                          | 1 (1%)                 |
|   | Clumsiness               | 1 (2%)                         |                          | 1 (1%)                 |
|   | Coordination Abnormal    | 1 (2%)                         |                          | 1 (1%)                 |
|   | Dystonia                 | 1 (2%)                         | 1 (3%)                   | 2 (2%)                 |
|   | Light-Headed Feeling     | 1 (2%)                         | 1 (3%)                   | 2 (2%)                 |
|   | Migraine                 | 1 (2%)                         |                          | 1 (1%)                 |
|   | Muscle Stiffness         | 1 (2%)                         |                          | 1 (1%)                 |
|   | Muscular Tone Increased  | 1 (2%)                         |                          | 1 (1%)                 |
| Parkinsonism                              | 1 (2%)                   |                                | 1 (1%)                   |                        |
| Speech Disorder                           | 1 (2%)                   |                                | 1 (1%)                   |                        |
| Walking Difficulty                        | 1 (2%)                   |                                | 1 (1%)                   |                        |
| GASTROINTESTINAL<br>SYSTEM DISORDERS      | TOTAL                    | 19 (35%)                       | 3 (10%)                  | 22<br>(26%)            |
|   | Nausea                   | 7 (13%)                        | 2 (7%)                   | 9 (11%)                |
|   | Diarrhea                 | 3 (6%)                         | 3 (10%)                  | 6 (7%)                 |
|   | Vomiting                 | 3 (6%)                         | 1 (3%)                   | 4 (5%)                 |
|   | Abdominal Discomfort     | 1 (2%)                         |                          | 1 (1%)                 |
|   | Blood in Stool           | 1 (2%)                         |                          | 1 (1%)                 |
|   | Constipation             | 1 (2%)                         |                          | 1 (1%)                 |
|   | Cramp Abdominal          | 1 (2%)                         |                          | 1 (1%)                 |
|   | Diverticulitis           | 1 (2%)                         |                          | 1 (1%)                 |
|   | Dysphagia                | 1 (2%)                         | 1 (3%)                   | 2 (2%)                 |
|   | Gastroesophageal Reflux  | 1 (2%)                         |                          | 1 (1%)                 |
|   | Heartburn                |                                | 1 (3%)                   | 1 (1%)                 |
|   | Mouth Dry                | 1 (2%)                         |                          | 1 (1%)                 |
|   | Mouth Ulceration         |                                | 1 (3%)                   | 1 (1%)                 |
|   | Parotid Duct Obstruction | 1 (2%)                         |                          | 1 (1%)                 |

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|  |                      |        |  |        |
|--|----------------------|--------|--|--------|
|  | Salivation           | 1 (2%) |  | 1 (1%) |
|  | Stomach Upset        | 1 (2%) |  | 1 (1%) |
|  | Stools Loose         | 1 (2%) |  | 1 (1%) |
|  | Ulcers Aphthous Oral | 1 (2%) |  | 1 (1%) |

| Body System                         | AE Preferred Term                 | Tetrabenazine<br>N=54<br>n (%) | Placebo<br>N=30<br>n (%) | Total<br>N=84<br>n (%) |
|-------------------------------------|-----------------------------------|--------------------------------|--------------------------|------------------------|
| BODY AS A<br>WHOLE -GENERAL         | TOTAL                             | 13 (24%)                       | 7 (23%)                  | 20<br>(24%)            |
|                                     | Fatigue                           | 12 (22%)                       | 4 (13%)                  | 16<br>(19%)            |
|                                     | Back Pain                         | 1 (2%)                         |                          | 1 (1%)                 |
|                                     | Death                             | 1 (2%)                         |                          | 1 (1%)                 |
|                                     | Feeling of Warmth                 | 1 (2%)                         |                          | 1 (1%)                 |
|                                     | Hot Flashes                       |                                | 1 (3%)                   | 1 (1%)                 |
|                                     | Pain                              | 1 (2%)                         | 1 (3%)                   | 2 (2%)                 |
|                                     | Sacro-Iliac Pain                  | 1 (2%)                         |                          | 1 (1%)                 |
|                                     | Temperature Elevation             |                                | 1 (3%)                   | 1 (1%)                 |
| SECONDARY<br>TERMS                  | TOTAL                             | 11 (20%)                       | 4 (13%)                  | 15<br>(18%)            |
|                                     | Fall                              | 8 (15%)                        | 4 (13%)                  | 12<br>(14%)            |
|                                     | Inflicted Injury                  | 3 (6%)                         |                          | 3 (4%)                 |
|                                     | Eye Burns                         | 1 (2%)                         |                          | 1 (1%)                 |
| RESPIRATORY<br>SYSTEM<br>DISORDERS  | TOTAL                             | 9 (17%)                        | 7 (23%)                  | 16<br>(19%)            |
|                                     | Upper Respiratory Tract Infection | 6 (11%)                        | 2 (7%)                   | 8 (10%)                |
|                                     | Coughing                          | 3 (6%)                         | 3 (10%)                  | 6 (7%)                 |
|                                     | Breath Shortness                  | 2 (4%)                         |                          | 2 (2%)                 |
|                                     | Bronchitis                        | 2 (4%)                         |                          | 2 (2%)                 |
|                                     | Crackles                          | 1 (2%)                         |                          | 1 (1%)                 |
|                                     | Pneumonia                         | 1 (2%)                         |                          | 1 (1%)                 |
|                                     | Rhinitis                          |                                | 1 (3%)                   | 1 (1%)                 |
|                                     | Sinusitis                         |                                | 1 (3%)                   | 1 (1%)                 |
| Throat Sore                         | 1 (2%)                            | 1 (3%)                         | 2 (2%)                   |                        |
| PLATELET,<br>BLEEDING &<br>CLOTTING | TOTAL                             | 7 (13%)                        | 2 (7%)                   | 9 (11%)                |
|                                     | Bruise                            | 4 (7%)                         | 2 (7%)                   | 6 (7%)                 |
|                                     | Ecchymosis                        | 3 (6%)                         |                          | 3 (4%)                 |
|                                     | Epistaxis                         | 1 (2%)                         |                          | 1 (1%)                 |
| URINARY SYSTEM<br>DISORDERS         | TOTAL                             | 3 (6%)                         | 1 (3%)                   | 4 (5%)                 |
|                                     | Dysuria                           | 2 (4%)                         |                          | 2 (2%)                 |
|                                     | Bladder Infection                 |                                | 1 (3%)                   | 1 (1%)                 |

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|                                   |                           |        |        |        |
|-----------------------------------|---------------------------|--------|--------|--------|
|                                   | Blood in Urine            |        | 1 (3%) | 1 (1%) |
|                                   | Urinary Tract Infection   | 1 (2%) |        | 1 (1%) |
|                                   | Urinary Urgency           | 1 (2%) |        | 1 (1%) |
| SKIN AND APPENDAGES DISORDERS     | TOTAL                     | 2 (4%) |        | 2 (2%) |
|                                   | Skin Dry                  | 1 (2%) |        | 1 (1%) |
|                                   | Skin Infection            | 1 (2%) |        | 1 (1%) |
| MUSCULO-SKELETAL SYSTEM DISORDERS | TOTAL                     | 2 (4%) | 2 (7%) | 4 (5%) |
|                                   | Bone Fracture Spontaneous | 1 (2%) | 1 (3%) | 2 (2%) |
|                                   | Muscle Ache               | 1 (2%) |        | 1 (1%) |
|                                   | Tendon Injury             |        | 1 (3%) | 1 (1%) |

| Body System                       | AE Preferred Term       | Tetrabenazine<br>N=54<br>n (%) | Placebo<br>N=30<br>n (%) | Total<br>N=84<br>n (%) |
|-----------------------------------|-------------------------|--------------------------------|--------------------------|------------------------|
| VISION DISORDERS                  | TOTAL                   | 1 (2%)                         | 1 (3%)                   | 2 (2%)                 |
|                                   | Conjunctivitis          | 1 (2%)                         |                          | 1 (1%)                 |
|                                   | Eye Irritation          |                                | 1 (3%)                   | 1 (1%)                 |
| VASCULAR (EXTRACARDIAC) DISORDERS | TOTAL                   | 1 (2%)                         |                          | 1 (1%)                 |
|                                   | Subarachnoid Hemorrhage | 1 (2%)                         |                          | 1 (1%)                 |
| REPRODUCTIVE DISORDERS, MALE      | TOTAL                   | 1 (2%)                         |                          | 1 (1%)                 |
|                                   | Prostatitis             | 1 (2%)                         |                          | 1 (1%)                 |
| REPRODUCTIVE DISORDERS, FEMALE    | TOTAL                   | 1 (2%)                         |                          | 1 (1%)                 |
|                                   | Breast Pain Female      | 1 (2%)                         |                          | 1 (1%)                 |
| NEOPLASM                          | TOTAL                   | 1 (2%)                         |                          | 1 (1%)                 |
|                                   | Carcinoma               | 1 (2%)                         |                          | 1 (1%)                 |
| RESISTANCE MECHANISM DISORDERS    | TOTAL                   |                                | 1 (3%)                   | 1 (1%)                 |
|                                   | Abscess                 |                                | 1 (3%)                   | 1 (1%)                 |

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Table 35. Demographic and Other Characteristics of Subjects in TBZ 103,005

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

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Table 36. Baseline Illness Characteristics of Subjects in TBZ 103,005.

| Baseline Illness Characteristic                | Group 1<br>(N= 12) | Group 2<br>(N=12) | Group 3<br>(N=6) | Statistical Test;<br>p-value |
|--|--------------------|-------------------|------------------|------------------------------|
| <b>Disease Duration (yrs)</b>                  |                    |                   |                  |                              |
| Mean   | 10.22              | 9.18              | 11.41            | ANOVA<br>0.6925              |
| Std. Dev                                       | 4.51               | 6.10              | 4.77             |                              |
| Range  | 4.07 – 21.22       | .48 – 19.28       | 6.71 – 18.87     |                              |
| <b>CGI Part 1; number of patients*</b>         |                    |                   |                  |                              |
| Not Ill  | 0                  | 0                 | 0                | Fisher's Exact<br>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 patient           | 0                  | 0                 | 0                |                              |
| <b>HD-Affected Parent; number of patients*</b> |                    |                   |                  |                              |
| Mother   | 5 (42%)            | 5 (42%)           | 3 (50%)          | Fisher's Exact<br>1.00       |
| Father   | 6 (50%)            | 7 (58%)           | 3 (50%)          |                              |
| Unspecified                                    | 1 (8%)             | 0                 | 0                |                              |
| <b>Primary Efficacy End-Point</b>              |                    |                   |                  |                              |
| 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           |                              |
| <b>Secondary Efficacy Endpoint</b>             |                    |                   |                  |                              |
| 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           |                              |
| <b>Exploratory End-Points</b>                  |                    |                   |                  |                              |
| 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          |                              |
| <b>Gait; (UHDRS 13)</b>                        |                    |                   |                  |                              |
| 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            |                              |

Table 37. Comparison of Baseline Visit and Day 5 Total Maximal Chorea Scores with Change Scores for 30 HD Subjects – Tetra Withdrawal 103,005

| Participant ID          | Baseline Visit Score | Day 5 Score<br>(n descending order, by treatment group) | Day 5 to Baseline Visit Change ( $\Delta$ ) |
|-------------------------|----------------------|---|---|
| <b>Group 1 (N = 12)</b> |                      |   |   |
| 547-410                 | 15                   |   |   |
| 547-406                 | 19                   |   |   |
| 547-403                 | 11                   |   |   |
| 547-424                 | 15                   |   |   |
| 547-430                 | 5                    |   |   |
| 547-418                 | 10                   |   |   |
| 547-419                 | 5                    |   |   |
| 547-426                 | 7                    |   |   |
| 547-412                 | 7                    |   |   |
| 547-414                 | 8                    |   |   |
| 547-405                 | 9                    |   |   |
| 547-422                 | 2                    |   |   |
| <b>Group 2 (N = 12)</b> |                      |   |   |
| 547-402                 | 25                   |   |   |
| 547-404                 | 10                   |   |   |
| 547-420                 | 9                    |   |   |
| 547-417                 | 15                   |   |   |
| 547-413                 | 8                    |   |   |
| 547-428                 | 3                    |   |   |
| 547-425                 | 7                    |   |   |
| 547-411                 | 10                   |   |   |
| 547-408                 | 11                   |   |   |
| 547-409                 | 3                    |   |   |
| 547-421                 | 4                    |   |   |
| 547-429                 | 4                    |   |   |
| <b>Group 3 (N = 6)</b>  |                      |   |   |
| 547-427                 | 16                   |   |   |
| 547-416                 | 16                   |   |   |
| 547-401                 | 13                   |   |   |
| 547-415                 | 7                    |   |   |
| 547-407                 | 9                    |   |   |
| 547-423                 | 6                    |   |   |

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**MEMORANDUM**      **DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

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**DATE:**                    March 6, 2006

**TO:**                        Teresa Wheelous, Regulatory Project Manager  
                                 Carole Davis, M.D., Medical Officer  
                                 Elizabeth McNeil, M.D., Medical Officer  
                                 Russell Katz, M.D., Director  
                                 Division of Neurology Products

**THROUGH:**                Constance Lewin, M.D., M.P.H., Acting Branch Chief  
                                 Good Clinical Practice Branch I  
                                 Division of Scientific Investigations

**FROM:**                     Jose Javier Tavarez, M.S.  
                                 Good Clinical Practice Branch I, HFD-46  
                                 Division of Scientific Investigations

**SUBJECT:**                 Evaluation of Clinical Inspections

**NDA:**                        21-894

**SPONSOR:**                 Prestwick Pharmaceuticals, Inc.

**DRUG:**                     Tetrabenazine

**CHEMICAL CLASSIFICATION:**    Type 1

**THERAPEUTIC CLASSIFICATION:**        Priority

**INDICATION:**                Treatment of Huntington's chorea

**CONSULTATION REQUEST DATE:**    October 18, 2005

**PDUFA GOAL DATE:**    March 26, 2006

**I. BACKGROUND**

Clinical investigator inspections were conducted at four clinical sites that performed studies for which the sponsor submitted data in NDA 21-894. The inspections were conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocols TBZ 103,004 and TBZ 103,011.

Tetrabenazine is a new molecular entity (NME) product intended for treatment of Huntington's Chorea.

In this NDA, the sponsor has included results of protocols TBZ 103,004 (efficacy study) and 103,011 (long term safety study). Study TBZ 103,004 was a multi-center, randomized, doubleblind, placebo-controlled study in two parallel unbalanced (2:1) groups (tetrabenazine titrated to "best dose"; placebo) of HD subjects. The main objective of the study was to demonstrate the efficacy and tolerability of tetrabenazine for the treatment of chorea associated with HD. The study was conducted at 16 sites across the US. A total of 84 subjects were enrolled; 54 were randomized to tetrabenazine, 30 were randomized to placebo. Treatment duration was 12 weeks.

Protocol TBZ 103,011 was a retrospective study designed to assess long-term safety of tetrabenazine used to treat subjects with chorea enrolled in Baylor Protocol H-721. Data was retrieved from a review of patient records for those consecutive patients identified with chorea including HD and treatment with tetrabenazine at Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic between January 1, 1979 and February 29, 2004. A total of 162 chorea subjects have been treated with tetrabenazine at Baylor College since January 1979. Medical records were missing for 17 of these subjects. Thus, a total of 145 subjects (98 with HD, 47 with chorea of other etiologies) were evaluated.

**Basis for Sites Selection:** Four clinical sites were inspected: Drs. Corey-Bloom, Wojcieszek, Ondo, and Jankovic's sites. These sites enrolled a large number of subjects for protocol TBZ 103,004 or TBZ 103,011. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

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**II. RESULTS (by site):**

| Clinical Investigator   | Location   | Protocol    | Inspection Date | EIR Received Date | Final Classification |
|-------------------------|--|-------------|-----------------|-------------------|----------------------|
| Jody Corey-Bloom, M.D.  | UCSD School of Medicine, 9500 Gilman Drive, La Jolla, CA                                     | TBZ 103,004 | 1/3-10/2006     | 1/31/2006         | NAI                  |
| Joanne Wojcieszek, M.D. | Indiana University Outpatient Clinical Research Facility 535 Barnhill Drive Indianapolis, IN | TBZ 103,004 | 1/4-11/2006     | 1/23/2006         | VAI                  |
| William Ondo, M.D.      | Baylor College of Medicine, Department of Neurology, 6550 Fannin St. Houston, TX             | TBZ 103,004 | 1/9-11/2006     | 2/9/2006          | VAI                  |
| Joseph Jankovic, M.D.   | Baylor College of Medicine, Department of Neurology, 6550 Fannin St. Houston, TX             | TBZ 103,011 | 1/11-13/2006    | 2/21/2006         | VAI                  |

Key to Classifications

NAI = No deviation from regulations. Data acceptable  
 VAI = Minor deviation(s) from regulations. Data acceptable  
 OAI = Significant deviations from regulations. Data unreliable  
 Pending = Inspection not completed

**(1) Jody Corey-Bloom, M.D. Site #51 – 17 subjects**  
**UCSD School of Medicine**  
**9500 Gilman Drive**  
**La Jolla, CA**

- a. What was inspected?  
 Nine (9) subjects were enrolled into the study TBZ 103,004. The FDA field investigator reviewed the records for all 9 subjects enrolled in the study. The FDA field investigator reviewed the source documents, case report forms and compared these with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.
- b. Limitations of inspection: None.
- c. General observations/commentary:  
 No Form FDA 483, Inspectional Observations, was issued at the close of the inspection. The inspection did not reveal any significant issues regarding the conduct of the study. No underreporting of adverse events noted. Data in

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sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Data from this clinical site appear acceptable for use in support of this NDA.

**(2) Joanne Wojcieszek, M.D. Site #45 – 14 subjects**  
**Indiana University Outpatient Clinical Research Facility**  
**535 Barnhill Drive**  
**Indianapolis, IN**

a. What was inspected?

Eight (8) subjects were enrolled into the study TBZ 103,004. The FDA field investigator reviewed the records for all 8 subjects enrolled in the study. The FDA field investigator reviewed the source documents, case report forms and compared these with the data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary

A two-item FDA 483, Inspectional Observations, was issued noting inadequate drug accountability records, and the failure of the informed consent forms to include a statement regarding confidentiality of the participant's records. No underreporting of adverse events noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

Recommendation: Overall, data from this site appear acceptable for use in support of this NDA.

**3) William Ondo, M.D. Site #7 – 10 subjects**  
**Baylor College of Medicine**  
**Department of Neurology**  
**6550 Fannin St.**  
**Houston, TX**

a. What was inspected?

Five (5) subjects were enrolled into the study TBZ 103,004. The FDA field investigator reviewed the records for all 5 subjects enrolled in the study. The FDA field investigator reviewed the source documents, case report forms and compared with data listing provided by the sponsor as part of the NDA submission. The inspection encompassed an audit of all subjects' consent forms.

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d. Limitations of inspection: None.

e. General observations/commentary

A four-item FDA 483, Inspectional Observations, was issued at the close of this inspection, noting the failure to adhere to protocol. Based on the Form FDA 483 and the establishment inspection report (EIR), inspectional findings are as follows:

1. The protocol required adverse events to be recorded throughout the study. Source notes dated 10/29/2003 document that subject 207 "Passed out today – No TBZ taken. Hit head on car door yesterday & cut." However, this adverse event was not reported to the sponsor.
2. Source notes dated 1/12/2004 document that subject 209 had a dull headache for one week after starting study medication; however, this adverse event was not reported to the sponsor.
3. The protocol required that the clinical investigator immediately notify the Medical Monitor by telephone and by fax of any treatment suspension. Source documents record that subject 207's treatment was stopped from 10/25/2003 to 10/29/2003; however, the Medical Monitor was not notified of this treatment suspension.
4. The protocol required that subjects taking 5 to 8 tablets per day were to be instructed to reduce the number of tablets to 4 per day for 2 days and then discontinue. Subjects 208, 210, and 211 took 2 tablets for 2 days as reduction to protocol's active treatment and then discontinued.

Recommendation: Overall, data from this site appear acceptable for use in support of this NDA.

**4) Joseph Jankovic, M.D. Site – 145 subjects**

**Baylor College of Medicine  
Department of Neurology  
6550 Fannin St.  
Houston, TX**

a. What was inspected?

Inspection confirmed the inclusion of 145 subjects in this retrospective study (TBZ 103,011). The FDA field investigator reviewed the records for 25 subjects.

b. Limitations of inspection: None.

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c. General observations/commentary

No Form FDA 483, Inspectional Observations, was issued at the close of the inspection. However, the clinical investigator did not report the adverse event of increased dysphagia for subjects 414, 347, and 8. The reason given for not reporting these AEs was that they were related to the subject's underlying disease.

Recommendation: Overall, data from this site appear acceptable for use in support of this NDA.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

As detailed above, inspection revealed that there were two unreported adverse events and two protocol deviations at Dr. Ondo's site; that at Dr. Jankovic's site, the AE of increased dysphagia for three subjects was not reported; and that at Dr. Wojcieszek's site, an informed-consent document deficiency. At Dr. Corey-Bloom's site, no regulatory deficiencies were noted in the conduct of the study. In general, for the four clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. None of the inspectional findings adversely impact acceptability of the data generated at this sites. Therefore, data from these clinical sites appear acceptable for use in support of NDA 21-894.

Jose Javier Tavarez, M.S.  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, M.D., M.P.H.  
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### 10.3 APPENDIX C

**SAMPLE CRF QUESTIONNAIRES FOR:**

**UNITED HUNTINGTON'S DISEASE RATING SCALE (UHDRS)  
GLOBAL CLINICAL IMPRESSION (GCI) SCALE  
FUNCTIONAL IMPACT SCALE  
HAMILTON DEPRESSION SCALE (HAMD)  
BARNES AKATHESIA RATING SCALE (BARS)  
UNITED PARKINSON'S DISEASE RATING SCALE – PART II  
(SWALLOWING AND SPEECH)**

**TETRA-HD**  
**UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99**

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All items must be completed. Use U if information is Unavailable. Use N if information is Not Applicable.

|                 |                      |            |                      |                      |                      |
|-----------------|----------------------|------------|----------------------|----------------------|----------------------|
| PARTICIPANT NO. | <input type="text"/> | SITE NO.   | <input type="text"/> | VISIT NO.            | <input type="text"/> |
| INITIALS        | <input type="text"/> | VISIT DATE | <input type="text"/> | <input type="text"/> | <input type="text"/> |
|                 |                      |            | MM                   | DD                   | YEAR                 |

**I. MOTOR ASSESSMENT**

|  |                          |                          |                         |
|--|--------------------------|--------------------------|-------------------------|
|  | Horizontal               | Vertical                 |                         |
| 1. OCULAR PURSUIT  | 1a. <input type="text"/> | 1b. <input type="text"/> |                         |
| 0 = complete (normal)<br>1 = jerky movement<br>2 = interrupted pursuits/full range<br>3 = incomplete range<br>4 = cannot pursue  |                          |                          |                         |
|  | Horizontal               | Vertical                 |                         |
| 2. SACCADE INITIATION  | 2a. <input type="text"/> | 2b. <input type="text"/> |                         |
| 0 = normal<br>1 = increased latency only<br>2 = suppressible blinks or head movements to initiate<br>3 = unsuppressible head movements<br>4 = cannot initiate saccades |                          |                          |                         |
|  | Horizontal               | Vertical                 |                         |
| 3. SACCADE VELOCITY  | 3a. <input type="text"/> | 3b. <input type="text"/> |                         |
| 0 = normal<br>1 = mild slowing<br>2 = moderate slowing<br>3 = severely slow, full range<br>4 = incomplete range  |                          |                          |                         |
| 4. DYSARTHRIA  |                          |                          | 4. <input type="text"/> |
| 0 = normal<br>1 = unclear, no need to repeat<br>2 = must repeat to be understood<br>3 = mostly incomprehensible<br>4 = anarthria                                       |                          |                          |                         |

|   |                          |                          |
|---|--------------------------|--------------------------|
| 5. TONGUE PROTRUSION  |                          | 5. <input type="text"/>  |
| 0 = can hold tongue fully protruded for 10 seconds<br>1 = cannot keep fully protruded for 10 seconds<br>2 = cannot keep fully protruded for 5 seconds<br>3 = cannot fully protrude tongue<br>4 = cannot protrude tongue beyond lips   |                          |                          |
|   | Right                    | Left                     |
| 6. FINGER TAPS  | 6a. <input type="text"/> | 6b. <input type="text"/> |
| 0 = normal ( $\geq 15/5$ sec.)<br>1 = mild slowing and or reduction in amplitude (11-14/5 sec.)<br>2 = moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5sec.)<br>3 = severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements (3-6/5 sec.)<br>4 = can barely perform the task (0-2/5 sec.) |                          |                          |
|   | Right                    | Left                     |
| 7. PRONATE/SUPINATE-HANDS   | 7a. <input type="text"/> | 7b. <input type="text"/> |
| 0 = normal<br>1 = mild slowing and/or irregular<br>2 = moderate slowing and irregular<br>3 = severe slowing and irregular<br>4 = cannot perform   |                          |                          |
| 8. LURIA (fist-hand-palm test)  | 8. <input type="text"/>  |                          |
| 0 = $\geq 4$ in 10 seconds, no cue<br>1 = $< 4$ in 10 seconds, no cue<br>2 = $\geq 4$ in 10 seconds with cues<br>3 = $< 4$ in 10 seconds with cues<br>4 = cannot perform  |                          |                          |

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 NDA 21,894  
 Tetrabenazine (TBZ)



TETRAHD  
LEADERS '99

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**II. COGNITIVE ASSESSMENT**

19. VERBAL FLUENCY TEST (raw score)

19. 

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20. SYMBOL DIGIT MODALITIES TEST (raw score)

20. 

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**STROOP INTERFERENCE TEST**

21. Color Naming (number correct)

21. 

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22. Word Reading (number correct)

22. 

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23. Interference (number correct)

23. 

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24. Cognitive Examiner

24. 

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- 111 -

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**III. BEHAVIORAL ASSESSMENT**

**Instructions:** Please rate the frequency and severity of the behavior. Ratings should be based on all information available including the clinician's impression and the report of the participant and the informant for the past month. Please be sure to use the written UHDRS '99 Guidelines which have statements for each specific item that will allow you to make ratings of frequency and severity. Words in *italics* in the guidelines are useful for framing questions to the participant or informant; other descriptors are useful ideas of behaviors to look for in your observation.

**DEPRESSED MOOD**

25a. Frequency

- 0 = never or almost never
- 1 = seldom, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

25a.

25b. Severity

- 0 = no mood disturbance
- 1 = questionable or equivocal
- 2 = mild, responds to redirection and reassurance
- 3 = moderately depressed, expresses distress
- 4 = severe, significant suffering and loss of functioning

25b.

**LOW SELF-ESTEEM/GUILT**

26a. Frequency

- 0 = never or almost never
- 1 = seldom, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

26a.

26b. Severity

- 0 = no evidence
- 1 = questionable or equivocal
- 2 = mild, definitely present
- 3 = moderate, some distress
- 4 = severe

26b.

**ANXIETY**

27a. Frequency

- 0 = never or almost never
- 1 = seldom, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

27a.

27b. Severity

- 0 = no evidence
- 1 = questionable or equivocal
- 2 = mild, responds to reassurance
- 3 = moderate, impacts on everyday life
- 4 = severe, causing a profound restriction of activities

27b.

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**SUICIDAL THOUGHTS**

28a. Frequency

28a. 

28b. Severity

28b. 

- 0 = not thinking about suicide or self harm
- 1 = seldom thinking about suicide-less than once a month
- 2 = sometimes thinking about suicide-at least once a month
- 3 = frequently thinking about suicide-at least once a week
- 4 = often thinks about suicide-sometimes for days and weeks on end

- 0 = no suicidal thoughts
- 1 = no thoughts at current time, but person talks about suicide as a potential option
- 2 = fleeting thoughts about it
- 3 = seriously considered suicide but has no plan
- 4 = has a plan and is actively preparing

**DISRUPTIVE OR AGGRESSIVE BEHAVIOR**

29a. Frequency

29a. 

29b. Severity

29b. 

- 0 = never or almost never
- 1 = seldom, less than once a month
- 2 = sometimes, at least once a month
- 3 = frequently, at least once a week
- 4 = very frequently, everyday

- 0 = behavior well-controlled
- 1 = verbal threats or intimidating behavior
- 2 = mild physically or verbally threatening behavior
- 3 = clear physical threat (moderately aggressive), bumping, shoving, verbal outburst
- 4 = clear physical threat, (severe aggression) striking/hitting, or definite intention to cause injury

**IRRITABLE BEHAVIOR**

30a. Frequency

30a. 

30b. Severity

30b. 

- 0 = never or almost never
- 1 = seldom, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

- 0 = behavior well-controlled
- 1 = questionable or equivocal
- 2 = definite but mild
- 3 = moderate, others change their behavior to avoid irritating participant
- 4 = severe irritability

**PERSEVERATIVE/OBSSIONAL THINKING**

31a. Frequency

- 0 = never or almost never
- 1 = seldom, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

31a. 

31b. Severity

- 0 = thinking is always flexible
- 1 = questionable or equivocal
- 2 = gets stuck on certain ideas but can be easily redirected
- 3 = moderate-gets stuck on certain ideas, difficult to redirect
- 4 = severe-gets stuck on certain ideas, and does not respond to redirection

31b. **COMPULSIVE BEHAVIOR**

32a. Frequency

- 0 = never or almost never
- 1 = seldom, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

32a. 

32b. Severity

- 0 = behavior always well-controlled
- 1 = equivocal-has a mild impulse not sufficient to act on
- 2 = mild-has impulse, acts on impulse, but can stop
- 3 = moderate-has impulse, acts on it and sometimes cannot stop
- 4 = severe-has impulse, acts on it and cannot stop

32b. **DELUSIONS**

33a. Frequency

- 0 = no evidence
- 1 = seldom, less than once a month
- 2 = sometimes, at least once a month
- 3 = frequently, at least once a week
- 4 = very frequently, sometimes for days on end

33a. 

33b. Severity

- 0 = no evidence
- 1 = has delusional idea(s), not sure it is true
- 2 = convinced of idea(s) but allows that the idea is not true
- 3 = utterly convinced of the idea(s)
- 4 = utterly convinced of the idea(s), behavior is determined by the delusion(s)

33b.

**HALLUCINATIONS**

34a. Frequency

34a.

- 0 = no evidence of hallucinations
- 1 = seldom, less than once a month
- 2 = sometimes, at least once a month
- 3 = frequently, at least once a week
- 4 = often, sometimes for days on end

34b. Severity

34b.

- 0 = no evidence
- 1 = has hallucinations, but doubts they are real
- 2 = convinced of the reality of the hallucinations but allows that it is possible that they are not real
- 3 = utterly convinced of the hallucinations being real, but not acting on them
- 4 = severe-has hallucinations that are vivid, participant is utterly convinced they are real and the hallucinations severely disrupt behavior

**APATHY**

35a. Frequency

35a.

- 0 = never
- 1 = seldom apathetic, less than once a week
- 2 = sometimes, at least once a week
- 3 = frequently, several times a week
- 4 = very frequently, most all the time

35b. Severity

35b.

- 0 = no evidence
- 1 = equivocal
- 2 = mild apathy-participant not initiating conversation or activity but is responsive
- 3 = moderate apathy-sometimes responds to efforts to get involved in conversation/activities
- 4 = severe apathy-generally unresponsive to attempts to involve participant in activities or conversation

36. Does the examiner believe the participant is confused? (0 = No, 1 = Yes)

36.

37. Does the examiner believe the participant is demented? (0 = No, 1 = Yes)

37.

38. Does the examiner believe the participant is depressed? (0 = No, 1 = Yes)

38.

39. Does the participant require pharmacotherapy for depression? (0 = No, 1 = Yes)

39.

40. Does the participant require pharmacotherapy for irritability? (0 = No, 1 = Yes)

40.

**INFORMATION SOURCES**

41. Was the Behavioral Assessment information obtained from:

41.

- 1 = Participant only
- 2 = Participant and family/companion

42. Behavioral Examiner

42.

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1/24/03

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NDA 21,894  
Tetrabenazine (TBZ)

TETRAHD  
UNDRS '99

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**IV. FUNCTIONAL ASSESSMENT** questions 43 - 67 (0 = No, 1 = Yes) *(only choices)*

43. Could participant engage in gainful employment in his/her accustomed work? 43.
44. Could participant engage in any kind of gainful employment? 44.
45. Could participant engage in any kind of volunteer or non gainful work? 45.
46. Could participant manage his/her finances (monthly) without any help? 46.
47. Could participant shop for groceries without help? 47.
48. Could participant handle money as a purchaser in a simple cash (store) transaction? 48.
49. Could participant supervise children without help? 49.
50. Could participant operate an automobile safely and independently? 50.
51. Could participant do his/her own housework without help? 51.
52. Could participant do his/her own laundry (wash/dry) without help? 52.
53. Could participant prepare his/her own meals without help? 53.
54. Could participant use the telephone without help? 54.
55. Could participant take his/her own medications without help? 55.
56. Could participant feed himself/herself without help? 56.
57. Could participant dress himself/herself without help? 57.
58. Could participant bathe himself/herself without help? 58.
59. Could participant use public transportation to get places without help? 59.

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Tetrabenazine (TBZ)

TETRA-HD  
UDRS '91

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**IV. FUNCTIONAL ASSESSMENT (CONT)** questions 43 - 67 (0 = No, 1 = Yes) *only choices*

60. Could participant walk to places in his/her neighborhood without help? 60.
61. Could participant walk without falling? 61.
62. Could participant walk without help? 62.
63. Could participant comb hair without help? 63.
64. Could participant transfer between chairs without help? 64.
65. Could participant get in and out of bed without help? 65.
66. Could participant use toilet/commode without help? 66.
67. Could participant's care still be provided at home? 67.
- INFORMATION SOURCES**
68. Was the Functional Assessment information obtained from: 68.
- 1 = Participant only
- 2 = Participant and family/companion

**V. INDEPENDENCE SCALE**

Please indicate the most accurate current level of participant's independence **69.**

*(only increments of 5 are acceptable)*

- 100: No special care needed
- 090: No physical care needed if difficult tasks are avoided
- 080: Pre-disease level of employment changes or ends; cannot perform household chores to pre-disease level, may need help with finances
- 070: Self-care maintained for bathing, limited household duties (cooking and use of knives), driving terminates; unable to manage finances
- 060: Needs minor assistance in dressing, toileting, bathing; food must be cut for participant
- 050: 24-hour supervision appropriate; assistance required for bathing, eating, toileting
- 040: Chronic care facility needed; limited self feeding, liquified diet
- 030: Participant provides minimal assistance in own feeding, bathing, toileting
- 020: No speech, must be fed
- 010: Tube fed, total bed care

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Tetrabenazine (TBZ)

TETRAHD  
UDRS 34

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**VI. FUNCTIONAL CAPACITY**

**70. OCCUPATION**

70.

- 0 = unable
- 1 = marginal work only
- 2 = reduced capacity for usual job
- 3 = normal

**71. FINANCES**

71.

- 0 = unable
- 1 = major assistance
- 2 = slight assistance
- 3 = normal

**72. DOMESTIC CHORES**

72.

- 0 = unable
- 1 = impaired
- 2 = normal

**73. ADL**

73.

- 0 = total care
- 1 = gross tasks only
- 2 = minimal impairment
- 3 = normal

**74. CARE LEVEL**

74.

- 0 = full time skilled nursing
- 1 = home or chronic care
- 2 = home

**INFORMATION SOURCES**

**75. Was the Functional Capacity information obtained from:**

75.

- 1 = participant only
- 2 = participant and family/companion

**76. Functional Examiner**

76.

STAFF CODE

**VII. CLINICAL SUMMARY**

**77. What was the purpose of this visit?**

77.

- 1 = Participant in an at risk study
- 2 = Participant in a manifest HD study
- 3 = Presymptomatic genetic testing
- 4 = Determine if person is symptomatic
- 5 = Known manifest HD
- 6 = Other (please specify) \_\_\_\_\_

**78. Since your last assessment of the participant, in your opinion, has the participant:**

78.

- 1 = improved
- 2 = worsened
- 3 = stayed about the same
- 4 = not applicable (never seen before)

**79. Since your last assessment does the participant feel:**

79.

- 1 = improved
- 2 = worsened
- 3 = about the same
- 4 = not applicable (never seen before)

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Tetrabenazine (TBZ)

TETRAHD  
UHDRS 99

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**VII. CLINICAL SUMMARY (CONT)**

80. Based on the entire UHDRS (Motor, Cognitive, Behavioral and Functional components) do you believe with a confidence level  $\geq 99\%$  that this participant has manifest HD? (0 = No, 1 = Yes)

80.

81. Comments

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**SIGN-OFF**

82. Examiner

82.

STAFF CODE

**VIII. CLINICAL DISPOSITION**

83a. Since the last visit, has the participant been permanently institutionalized? (0 = No, 1 = Yes)

83a.

83b. If the participant was institutionalized will the participant continue to be assessed for this database? (0 = No, 1 = Yes)  
If No, the participant Disposition Form must be completed.

83b.

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NDA 21,894  
Tetrabenazine (TBZ)



**TETRA - HD**  
**FUNCTIONAL IMPACT SCALE IN HD (FIS)**



All items must be completed. Use U if information is Unavailable. Use N if information is Not Applicable.

PARTICIPANT NO. 447-         SITE NO.         VISIT NO.

INITIALS         VISIT DATE:

MM                      DD                      YEAR

**Directions:** Questions to be answered by caregiver. Please note how each of the following domains impact average daily functioning over the past week.

**1. BATHING** 1.   
 0 = Independent  
 1 = Able to bath self, but requires minor assistance  
 2 = Able to participate in bathing, but requires moderate assistance  
 3 = Needs complete assistance

**2. DRESSING** 2.   
 0 = Independent  
 1 = Needs minor assistance with dressing, such as with small items (buttons, zippers, etc.)  
 2 = Able to participate in dressing, but requires moderate assistance  
 3 = Needs complete assistance

**3. FEEDING** 3.   
 0 = Independent  
 1 = Can feed self independently, but is slow and sloppy  
 2 = Needs moderate assistance with cutting and using utensils  
 (e.g., can use spoon but cannot cut foods, avoids hot items)  
 3 = Unable to feed self

**4. SOCIAL ISOLATION** 4.   
 0 = No difficulty going outside of home (excluding physical limitations)  
 1 = Unlimited activities but embarrassed by HD  
 2 = Accomplishes activities only when accompanied by others  
 3 = Markedly withdrawn, rarely, if ever engages in activities outside the home;  
 certain activities impossible or given up

**5. TOILETING** 5.   
 0 = Independent  
 1 = Can mostly self-toilet, but requires minor assistance  
 2 = Can help with toileting, but requires moderate assistance  
 3 = Needs complete assistance

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TETRA - HD

22

HAMILTON DEPRESSION SCALE (HAMD)

Page 1 of 3

Hamilton, M.: Development of a rating scale for primary depressive illness, 1967.

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable.

PARTICIPANT NO 447-    SITE NO.    VISIT NO.

INITIALS    VISIT DATE:

MM DD YEAR

1. DEPRESSED MOOD (sadness, hopeless, helpless, worthless) 1. 
  - 0 = Absent
  - 1 = These feelings are indicated only on questioning
  - 2 = These feelings are spontaneously reported verbally
  - 3 = These feelings are communicated non-verbally, i.e., through facial expression, posture, voice, and tendency to weep
  - 4 = Patient reports VIRTUALLY ONLY these feelings in his/her spontaneous verbal and non-verbal communication
  
2. FEELING OF GUILT 2. 
  - 0 = Absent
  - 1 = Self-reproach, feels he/she has let people down
  - 2 = Ideas of guilt or rumination over past errors or sinful deeds
  - 3 = Present illness is a punishment. Delusions of guilt
  - 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
  
3. SUICIDE 3. 
  - 0 = Absent
  - 1 = Feels life is not worth living
  - 2 = Wishes he/she were dead or any thoughts of possible death to self
  - 3 = Suicidal ideas or gesture
  - 4 = Attempts at suicide (any serious attempt rates 4)
  
4. INSOMNIA EARLY 4. 
  - 0 = No difficulty falling asleep
  - 1 = Complains of occasional difficulty falling asleep, i.e. more than 1/2 hour
  - 2 = Complains of nightly difficulty falling asleep
  
5. INSOMNIA MIDDLE 5. 
  - 0 = No difficulty
  - 1 = Patient complains of being restless and disturbed during the night
  - 2 = Waking during the night - any getting out of bed rates 2 (except for purposes of voiding)
  
6. INSOMNIA LATE 6. 
  - 0 = No difficulty
  - 1 = Waking in early hours of the morning but goes back to sleep
  - 2 = Unable to fall asleep again if gets out of bed

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NDA 21,894  
Tetrabenazine (TBZ)

ENCLOSURE

**7. WORK AND ACTIVITIES**

7.

- 0 = No difficulty
- 1 = Thoughts and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies
- 2 = Loss of interest in activity, hobbies, or work - either directly reported by patient, or indirectly in listlessness, indecision and vacillation (feels he/she has to push self to work or join activities)
- 3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours per day in activities (hospital job or hobbies) exclusive of ward chores
- 4 = Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores; or if the patient fails to perform ward chores unassisted

**8. RETARDATION: Slowness of thought and speech; impaired ability to concentrate; decreased motor activity**

8.

- 0 = Normal speech and thought
- 1 = Slight retardation at interview
- 2 = Obvious retardation at interview
- 3 = Interview difficult
- 4 = Complete stupor

**9. AGITATION**

9.

- 0 = None
- 1 = Fidgetiness
- 2 = "Playing with" hands, hair, etc.
- 3 = Moving about, can't sit still
- 4 = Hand-wringing, nail-biting, hair-pulling, biting of lips

**10. ANXIETY (PSYCHIC)**

10.

- 0 = No difficulty
- 1 = Subjective tension and irritability
- 2 = Worrying about minor matters
- 3 = Apprehensive attitude apparent in face or speech
- 4 = Fears expressed without questioning

11. **ANXIETY (SOMATIC):** *Physiological concomitants of anxiety, such as:*  
*Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching;*  
*Cardiovascular - palpitations, headaches;*  
*Respiratory-hyperventilation, sighing;*  
*Urinary frequency; sweating.* 11.
- 0 = Absent  
1 = Mild  
2 = Moderate  
3 = Severe  
4 = Incapacitating
12. **SOMATIC SYMPTOMS/GASTRO-INTESTINAL** 12.
- 0 = None  
1 = Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen  
2 = Difficulty eating without staff urging
13. **SOMATIC SYMPTOMS/GENERAL** 13.
- 0 = None  
1 = Heaviness in limbs, back or head. Backaches, headaches, muscle aches.  
Loss of energy and fatigability  
2 = Any clear-cut symptom rates 2
14. **GENITAL SYMPTOMS:** *Loss of libido, menstrual disturbances.* 14.
- 0 = Absent  
1 = Mild  
2 = Severe
15. **HYPOCHONDRIASIS** 15.
- 0 = Not present  
1 = Self-absorption (bodily)  
2 = Preoccupation with health  
3 = Frequent complaints, requests for help, etc.  
4 = Hypochondrial delusions
16. **LOSS OF WEIGHT** 16.
- 0 = No weight loss or weight loss NOT caused by present illnesses  
1 = Weight loss probably caused by present illness  
2 = Definite (according to patient) weight loss caused by present illness
17. **INSIGHT** 17.
- 0 = Acknowledges being depressed and ill  
1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus,  
need for rest, etc.  
2 = Denies being ill at all

**TETRA - HD**  
**BARNES AKATHISIA RATING SCALE (BARS)**

(26)

Page 1 of 2

All items must be completed. Use U if information is Unavailable. Use N if information is Not Applicable.

PARTICIPANT NO 447-          SITE NO.          VISIT NO.

INITIALS          VISIT DATE:

MM                      DD                      YEAR

**Instructions for Assessment**

Patients should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of two minutes in each position). Symptoms observed in other situations, for example, while engaged in routine activities, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

**1. Objective**

1.

- 0 = Normal, occasional fidgety movements of the limbs.
- 1 = Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg, while sitting, and/or rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed.
- 2 = Observed phenomena, as described in (1) above, which are present for a least half the observation period.
- 3 = The patient is constantly engaged in characteristic restless movements, and/or is unable to remain seated or standing without walking or pacing, during the time observed.

**1b. Objective**

1b.

- 0 = Normal, occasional fidgety movements of the limbs, not attributable to HD.
- 1 = Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg, while sitting, and/or rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed.
- 2 = Observed phenomena, as described in (1) above, which are present for a least half the observation period.
- 3 = The patient is constantly engaged in characteristic restless movements, and/or is unable to remain seated or standing without walking or pacing, during the time observed.

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

**TETRA-HD**  
**ACTIVITIES OF DAILY LIVING (ADL)**  
**EXTRACTED QUESTIONS FROM UPDRS-PART II**

(20)

Page 1 of 1

All items must be completed. Use U if information is Unavailable. Use N if information is Not Applicable.

|                |                      |                      |                      |                      |             |                      |                      |                      |                      |                      |                      |
|----------------|----------------------|----------------------|----------------------|----------------------|-------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| PARTICIPANT NO | 447-                 | <input type="text"/> | <input type="text"/> | <input type="text"/> | SITE NO.    | <input type="text"/> | <input type="text"/> | <input type="text"/> | VISIT NO.            | <input type="text"/> | <input type="text"/> |
| INITIALS       | <input type="text"/> | <input type="text"/> | <input type="text"/> |                      | VISIT DATE: | <input type="text"/> |
|                |                      |                      |                      |                      |             | MM                   | DD                   |                      | YEAR                 |                      |                      |

When completing this section, indicate the subject's level of function during the past week.

**1. Swallowing: (Dysphagia inclusion criteria question)**

- 0 = Normal.
- 1 = Rare choking.
- 2 = Occasional choking.
- 3 = Requires soft food.
- 4 = Requires NG tube or gastrostomy feeding.

1.

**2. Speech: (Dysarthria inclusion criteria question)**

- 0 = Normal.
- 1 = Mildly affected. No difficulty being understood.
- 2 = Moderately affected. Sometimes asked to repeat statements.
- 3 = Severely affected. Frequently asked to repeat statements.
- 4 = Unintelligible most of the time.

2.

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

-----  
Carole Davis  
3/24/2006 09:00:30 AM  
MEDICAL OFFICER

John Feeney  
3/24/2006 10:57:51 AM  
MEDICAL OFFICER  
see my cover memo

## 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 23 2006

Reviewer Name D. Elizabeth McNeil, MD  
Review Completion Date March 3 2006

Established Name Tetrabenazine  
(Proposed) Trade Name Xenazine  
Applicant Prestwick Pharmaceuticals

Priority Designation P

Formulation Tablet  
Dosing Regimen 12.5 to 100 mg/day  
Indication Chorea associated with  
Huntington's disease  
Intended Population Adults

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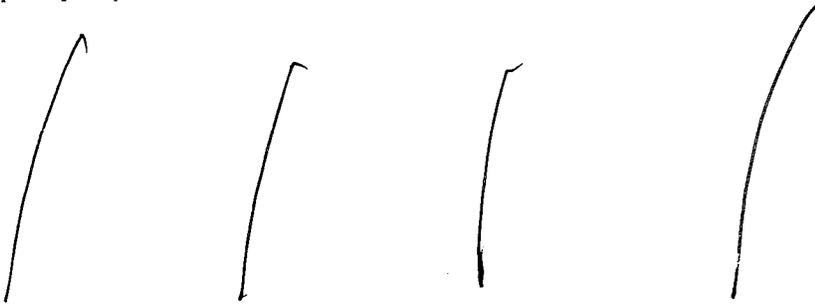
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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

Based upon the safety data, I would recommend an approvable action at this time. Prior to approval I would want to see the following:

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



If this product is approved, I would recommend the following:



- Active long-term surveillance of the incidence of parkinsonism with long-term use, including surveillance of patients who had stopped drug to make certain that whatever parkinsonism did occur was reversible at the time of discontinuation. The preclinical data indicates that dopamine depletion may continue, in animals, after drug discontinuation. I would want to know whether that was an expected consequence of drug use in humans.

### 1.2 Recommendation on Postmarketing Actions

This is addressed in the efficacy review done by Dr. Carole Davis, DNP.

### 1.3 Summary of Clinical Findings

#### 1.3.1 Brief Overview of Clinical Program

This is addressed in the efficacy review done by Dr. Carole Davis, DNP.

#### 1.3.2 Efficacy

This is addressed in the efficacy review done by Dr. Carole Davis, DNP.

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### 1.3.3 Safety

Tetrabenazine may be considered capable of producing the following adverse effects:

- Somnolence
- Parkinsonism
- Insomnia
- Depression
- Dysphagia
- Hyperprolactinemia

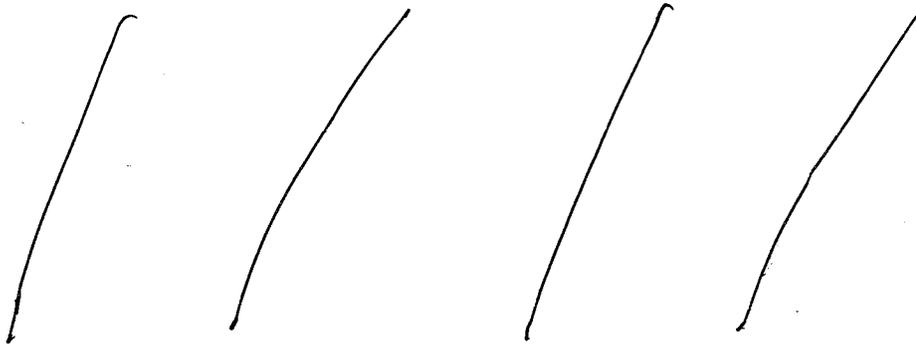
While causality is less certain, Tetrabenazine may be associated with the following adverse effects:

- Suicide/suicidal ideation
- Pneumonia
- Dystonia

There does not appear to be a risk of intentional misuse of tetrabenazine for recreational purposes, based upon the clinical trial data. In the setting of drug overdose, neuroleptic malignant syndrome (NMS) has been described.

The major limitation of the data provided is that it describes 84 patients with Huntington's disease-associated chorea who were exposed to tetrabenazine in a placebo-controlled trial; 54 of whom received study drug. This is a small number upon which to base major conclusions. Many of the assessments related to potential adverse events are based upon the entire database which included patients who were on placebo-controlled trials, prospective data from patients who received open label therapy as well as retrospective data from patients who were participants in a long-term open label compassionate use trial: a total database of 651 patients. Exposure data ranged from up to 12 weeks (n=651) to over 10 years (n=20) at doses which varied from 12.5 mg to 300 mg per day.

The safety profile of this product is acceptable in light of the intended indication, the treatment of chorea in patients with Huntington's disease,



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If marketed, tetrabenazine would be the only product indicated for use in the treatment of chorea associated with Huntington's disease.

#### 1.3.4 Dosing Regimen and Administration

This is addressed in the efficacy review done by Dr. Carole Davis, DNP.

#### 1.3.5 Drug-Drug Interactions

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

#### 1.3.6 Special Populations

There were no apparent differences in response based upon gender or age. This product was not adequately assessed in non-Caucasians so it is not possible to comment on potential ethnic differences.

**APPEARS THIS WAY  
ON ORIGINAL**

## 2 INTRODUCTION AND BACKGROUND

This may be found in the efficacy review done by Dr. Carole Davis, DNP.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

These findings are addressed in the efficacy review done by Dr. Carole Davis, DNP.

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

These are addressed in the efficacy review done by Dr. Carole Davis, DNP.

## 5 CLINICAL PHARMACOLOGY

These findings are in the efficacy review done by Dr. Carole Davis, DNP.

## 6 INTEGRATED REVIEW OF EFFICACY

The efficacy review was done by Dr. Carole Davis, DNP.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

#### 7.1.1 Deaths

*[Reviewer's note: I have listed the findings in this section by study since this application included controlled studies and uncontrolled long-term studies in patients with chorea as well as supplementary information from studies of tetrabenazine in persons without chorea. I reviewed the narratives for all deaths. I reviewed the provided CRFs for these patients. I have highlighted the cause of death, when provided, in bold font.]*

*This section reflects an assessment of all deaths that either occurred during the period of drug exposure or within 4 weeks of cessation of drug use. The deaths described during the development program for this product appear to be consistent with what is described in the literature. It is not clear whether the known risk of parkinsonism predisposes the patients to aspiration pneumonia and subsequent complications including morbidity/mortality; the two are sufficiently intertwined that causality is difficult to attribute. While Huntington's disease patients are known to be at increased risk for depression, it is unclear whether the medication is additive to or synergistic with the underlying predisposition.*

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*The sponsor has provided a table summarizing all literature reports of deaths in patients exposed to tetrabenazine. This table has been reproduced in this review and placed in Appendix 10.5. ]*

#### 7.1.1.1 Clinical Pharmacology studies

No deaths were reported during the Phase I clinical pharmacology studies, which enrolled a total of 140 patients.

#### 7.1.1.2 Study TBZ 103, 004: A randomized, double-blind, placebo-controlled study of Tetrabenazine for the treatment of Huntington's chorea

*[Reviewer's note: This study enrolled a total of 84 patients; one death was reported.]*

A 40 year old man with Huntington's disease (HD), who had a history of suicidal ideation, committed **suicide** by drowning: Pt 447-271. — He had been receiving tetrabenazine for 65 days and was on a dose of 87.5 mg at the time of his death. By report, this patient was seen for a study visit 2 weeks prior to his suicide. At the time of his visit, his HAM-D revealed no abnormality: total score was 1 (one) due to early morning awakening. His family noted a change in behavior once he decided to stop working; he became reclusive. By report, the patient was found drowned on the day that he terminated his employment due to disease related disability. The available information makes it impossible to completely rule out an association with study drug.

#### 7.1.1.3 Study TBZ 103, 007: An open-label, up to 80-week extension study of Tetrabenazine for the treatment of Huntington's chorea. Follow-on protocol to Protocol TBZ 103, 004.

*[Reviewer's note: This study enrolled a total of 75 patients; one death was reported.]*

A 55 year old woman with Huntington's disease died of **metastatic breast cancer**: Pt 747-211, — She had been receiving tetrabenazine for 451 days and was on a dose of 75 mg at the time of her death. She had had prolactin-negative breast cancer diagnosed two years prior to her enrollment in study TBZ 103, 004. She had a mastectomy in — followed by chemotherapy including tamoxifen. During a routine follow-up examination in January 2004, she was found to have a suspicious lesion on her lumbar spine as well as a rising tumor marker antigen titer. Her Huntington's disease was noted to be worsening. She was treated with anti-neoplastic agents and continued in the tetrabenazine study for 12 months before evidence of aspiration and lung metastases were found. She died shortly after the recurrence was detected. The available information makes it impossible to completely rule out an association with study drug.

#### 7.1.1.4 Study TBZ 103, 005: A randomized, double-blind, placebo-controlled, staggered withdrawal study in patients with Huntington's disease treated with Tetrabenazine

No deaths were reported during this five-day study, which enrolled 30 patients, or its subsequent extension TBZ 103, 006.

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7.1.1.5 Study TBZ 103,011: An analysis of a prospective, open-label dose-titration study of tetrabenazine in the treatment of patients with chorea

The available patient data for patients with chorea treated at Baylor was transcribed onto CRFs and entered into a database for analysis as study TBZ 103, 011. Archival records were available for 145 of the 162 patients with chorea. Eighteen deaths were recorded as tabulated below:

Table 1: Deaths during TBZ 103, 011

| Patient ID | Age at Time of Death | Sex | Diagnosis      | Reported cause of death                                 | Duration of Treatment (days) | Dose at SAE onset                             |
|------------|----------------------|-----|----------------|---|------------------------------|---|
| 00987      | 54                   | M   | Non-HD Chorea  | Creutzfeldt-Jakob disease with pneumonia                | 20                           | Patient was no longer receiving tetrabenazine |
| 01020      | 42                   | F   | SLE            | Pneumonitis and respiratory failure                     | 36                           | 12.5  |
| 00750      | 68                   | F   | HD             | Metastatic lung carcinoma                               | 193                          | 37.5  |
| 00039      | 42                   | M   | HD             | End-stage HD  | 269                          | Unknown                                       |
| 00650      | 57                   | F   | HD             | Unknown   | 226                          | Patient was no longer receiving tetrabenazine |
| 00683      | 64                   | F   | HD             | Myocardial infarction                                   | 579                          | 75  |
| 00596*     | 64                   | F   | HD             | Dysphagia and aspiration pneumonia                      | 756                          | Patient was no longer receiving tetrabenazine |
| 00990      | 71                   | F   | HD             | Presumed end-stage HD                                   | 884                          | 62.5  |
| 00720*     | 75                   | F   | HD             | End-stage HD  | 1,204                        | 37.5  |
| 00108      | 74                   | F   | Tardive Chorea | Peptic ulcer complicated by gastrointestinal hemorrhage | 1,308                        | 50  |
| 00306      | 47                   | F   | HD             | Choreoathetosis (End-stage HD)                          | 1,926                        | 50  |
| 00066      | 38                   | F   | HD             | End-stage HD  | 2,112                        | Unknown                                       |
| 00089      | 61                   | M   | HD             | End-stage HD with COPD                                  | 2,084                        | Unknown                                       |
| 00026*     | 57                   | M   | HD             | End-stage HD with aspiration pneumonia                  | 2,256                        | Patient was no longer receiving tetrabenazine |
| 00468      | 55                   | F   | HD             | Myocardial infarction                                   | 3,061                        | 150   |
| 00088      | 83                   | F   | HD             | End-stage HD with aspiration pneumonia                  | 3,097                        | 50  |
| 00157      | 84                   | F   | Tardive Chorea | Unknown   | 4,603                        | 37.5  |
| 00426*     | 60                   | M   | HD             | End-stage HD  | Unknown                      | Patient was no longer receiving tetrabenazine |

Data from Tables 8-4 and 9-4 from the ISS

The patients denoted with \* died >30 days after withdrawal from the study.

[Reviewer's note: This represented a retrospective analysis. The narratives provided did not provide any more information than what is shown in the table. We have no means of determining whether the deaths denoted as "end-stage Huntington's disease" were associated with aspiration pneumonia or other morbidity.]

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#### 7.1.1.6 Study H-721 (an open-label study in patients without chorea)

This reflects the available patient data for 280 patients without chorea treated at Baylor between 1979 and 2001.

##### 7.1.1.6.1 Subject 212

A male with Tourette's syndrome was noted to have had a suicidal gesture, manifest as an overdose of tetrabenazine tablets. He had somnolence, nausea and vomiting reported as AEs in association with that overdose. He also was in a motor vehicle accident in which he sustained rib fractures. He committed **suicide** in —, more than one month after cessation of tetrabenazine therapy. It is not possible to completely rule out an association with study drug.

##### 7.1.1.6.2 Subject 4190

A woman with past medical history notable for tardive dyskinesia, tardive dystonia, gastroesophageal reflux and dementia developed parkinsonism while receiving tetrabenazine therapy. She ultimately discontinued tetrabenazine therapy due to lack of efficacy. She died of unspecified **cardiovascular disease** 3 years after her final study evaluation. Her death was probably not related to study drug, though her parkinsonism probably was.

##### 7.1.1.6.3 Subject 9059

A woman with past medical history notable for tardive dyskinesia, cardiovascular disease, congestive heart failure, and a history of colon resection. She received tetrabenazine for 6 months but ultimately discontinued therapy due to parkinsonism. She died of unspecified **cardiovascular disease** 1 year after her final study evaluation. Her death was probably not related to study drug, though her parkinsonism may have been.

##### 7.1.1.6.4 Subject 13942

This woman, with past medical history notable for tardive dyskinesia, congestive heart failure, coronary artery disease, and diabetes, received tetrabenazine for 7 months but ultimately discontinued therapy due to parkinsonism. She died of unspecified **cardiovascular disease** months after her final study evaluation. Her death was probably not related to study drug though her parkinsonism may have been.

#### 7.1.1.7 Nitoman 003 (an open label study in patients with hyperkinetic disorders)

This open label study was performed in Canada prior to Prestwick obtaining rights to this compound and so was not part of the Prestwick development program. CRFs and summary death reports were provided for the majority of the patients (541 of the 757 patients) but the available information was incomplete. The causes of death, where known, are presented in table 2 below; narratives are provided in Appendix 10.2. In the Huntington's Disease patients, who represented 22% of the patients who died (n=10), 60% died of dysphagia/aspiration pneumonia; one third of the other patients died for this reason.

Table 2: Deaths from the Canadian Nitoman study

| Probable cause of death                          | Number (%)        |
|--|-------------------|
| <b>Huntington's disease patients</b>             | <b>10 (22.2%)</b> |
| Dysphagia and aspiration pneumonia               | 6 (13)            |
| "End-stage" disease                              | 3 (7)             |
| Sub-arachnoid hemorrhage                         | 1 (2)             |
| <b>Other hyperkinetic movement disorders</b>     | <b>35 (77.8%)</b> |
| Dysphagia and aspiration pneumonia               | 10 (22)           |
| Cerebrovascular disease and/or its complications | 4 (9)             |
| Myocardial infarction or cardiac arrest          | 4 (9)             |
| Diabetic peripheral vascular disease             | 2 (4)             |
| Dementia   | 1 (2)             |
| Gastrointestinal bleeding                        | 1 (2)             |
| Pre-existing metastatic prostatic carcinoma      | 1 (2)             |
| Cancer NOS                                       | 1 (2)             |
| Unknown  | 11 (24)           |
| <b>Total</b>                                     | <b>45 (100%)</b>  |

Data from Table 3 from the study report (p. 14/39)

#### 7.1.1.8 Summary of deaths

In work done by Drs. Schoenfeld (1984) and Farrer (1986), the three leading causes of death in Huntington disease patients were pneumonia (31-32%), cardiovascular causes (15-17%), and suicide (6-13%). The deaths described during the development program for this product appear to be consistent with what is described in the literature.

The sponsor has provided a summary table of the deaths seen during this development program. Although information regarding the Nitoman study was provided, that study was not part of the current development program. The information was provided by the sponsor to demonstrate the causes of death determined during an open-label compassionate use study which enrolled patients with hyperkinetic movement disorders of all types. As previously described, there were 45 deaths seen during the Nitoman study, a study which enrolled 757 patients. Since data is missing on 216 patients, it is impossible to determine what percentage of those patients died or make any comments regarding the cause of their demise. We can only say that fewer than 10% of the patients, upon whom we have information, died, i.e. 45 patients out of the 541 with available data.

The data from the Baylor program, which comprises TBZ103, 011 and H-721, is also incomplete as it reflects retrospective data analysis based on information from the medical records and from the investigator's memory.

Table 3: Summary of deaths seen during current development program

| Study                           | Number of Subjects/<br>Patients<br>Enrolled | Number of<br>Subjects/Patients<br>Treated with |         | Number of<br>Patients<br>Who Died | Cause of Death               |
|---------------------------------|---|--|---------|-----------------------------------|------------------------------|
|                                 |   | TBZ  | Placebo |                                   |                              |
| Clinical Pharmacology Studies   | 140   | 137  | -       | 0                                 | NA                           |
| TBZ 103,004                     | 84  | 54   | 30      | 1                                 | Completed Suicide            |
| TBZ 103,005                     | 30  | 30   | 24      | 0                                 | NA                           |
| TBZ 103,006                     | 29  | 29   | 0       | 0                                 | NA                           |
| TBZ 103,007                     | 75  | 75   | 0       | 1                                 | Metastatic Breast Cancer     |
| CSR TBZ 103,011                 | 145   | 145  | 0       | 9                                 | End Stage HD                 |
|                                 |   |  |         | 2                                 | Cardiovascular Disease       |
|                                 |   |  |         | 3                                 | Pneumonia/ Pulmonary Disease |
|                                 |   |  |         | 1                                 | Peptic Ulcer & GI Hemorrhage |
|                                 |   |  |         | 1                                 | Metastatic Lung Carcinoma    |
|                                 |   |  |         | 2                                 | Unknown                      |
| H 721: Baylor Non-Chorea Report | 280   | 280  | 0       | 3                                 | Cardiovascular Disease       |
|                                 |   |  |         | 1                                 | Completed Suicide            |

Table 9-1 from the ISS

### 7.1.2 Other Serious Adverse Events (SAEs)

*[Reviewer's note: I have listed the findings in this section by study since this application included controlled studies, and uncontrolled long-term studies in patients with chorea as well as supplementary information from studies of tetrabenazine in persons without chorea.]*

*No SAEs were reported in the subjects who participated in the clinical pharmacology studies.*

*I have elected to divide the available information on subjects with serious adverse events into two groups. In section 7.1.2.1, I discuss all of the patients who had serious adverse events which led to discontinuation. I reviewed the CRFs for all of these patients. In section 7.1.2.2, I discuss all of the patients who had serious adverse events which did not lead to discontinuation.]*

#### 7.1.2.1 Serious adverse events which led to discontinuation

##### 7.1.2.1.1 TBZ103, 004 (a 12-week placebo controlled trial)

There were four patients who discontinued due to serious adverse events. One patient committed suicide, patient 447-271. A second patient (447-206) was withdrawn after a fall led to subarachnoid hemorrhage and confusion. A third person (447-213) experienced two SAEs, restlessness which lessened after a decrease in the tetrabenazine dose to 12.5 mg and suicidal

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ideation attributed to the increase in chorea seen after the decrease in tetrabenazine dose. The suicidal ideation was associated with paranoia and psychosis. The latter symptoms resolved after hospitalization and treatment with antipsychotics.

The fourth was a woman (447-254) who had a (pre-existing) breast mass biopsied during this study. Upon discovery that the mass was a prolactin-receptor negative infiltrating ductal carcinoma, the patient was withdrawn from the study. She was subsequently granted a waiver and allowed to enroll in the open label extension, study TBZ 103,007.

*7.1.2.1.2 TBZ103, 005 (a 5-day staggered withdrawal study)*

There were no discontinuations due to SAEs during this trial.

*7.1.2.1.3 TBZ103, 006 (a 48-week open label extension of trial TBZ 103, 005)*

One woman was withdrawn from the study due to nausea and dehydration (pt. 447-422).

*7.1.2.1.4 TBZ103, 007 (an up to 80-week open label extension of trial TBZ 103, 004)*

One woman (747-211) died of metastatic breast cancer. She had a prior history notable for prolactin-receptor negative breast cancer.

A man, while on a maintenance dose of 75 mg/day of tetrabenazine, experienced increased depression, agitation, anxiety and akathisia. He was hospitalized for evaluation. He resumed his medication upon discharge but after three days, he decided to discontinue all medications leading to study withdrawal.

*7.1.2.1.5 Nitoman 003 (an Canadian open label study in patients with hyperkinetic disorders)*

There were five patients who discontinued due to serious adverse events (SAEs); one of whom had Huntington's chorea. The latter patient was hospitalized for treatment of aspiration pneumonia, dehydration, gastrointestinal hemorrhage and quadriparesis. The other patients were discontinued for "intercurrent illness," dystonia, depression (with suicidal ideation/gestures) and confusion.

**7.1.2.2 Serious adverse events which did not lead to discontinuation**

*7.1.2.2.1 TBZ103, 006 (a 48-week open label extension of trial TBZ 103, 005)*

Seven participants in this study had SAE which did not lead to discontinuation. One woman had a fall for which she was hospitalized. One woman had recurrent diarrhea (having had a bout during TBZ103, 005) and depression. Two men had infections: pneumonia/empyema (647-405); urinary tract infection and prerenal azotemia (647-415). Another man had non-cardiac chest pain which was attributed to increased anxiety.

One woman, who had had previous hospitalizations for depression, discontinued her antidepressant therapy and developed delusions as well as suicidal ideation. Her tetrabenazine was suspended during her three day hospitalization for resumption of antidepressant medications.

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7.1.2.2.2 TBZ103, 007 (an up to 80-week open label extension of trial TBZ 103, 004)

Three patients reported falls which led to hospitalization. One woman fell down the stairs and sustained a fracture of the left femoral neck, which was subsequently treated surgically. A man was hospitalized due to a fall and during the course of his evaluation, he was found to have pneumonia. A second woman also had pneumonia detected as an incidental finding during an evaluation after a fall. She was treated for ongoing dysphagia during that hospitalization.

In addition to the patient who died, two other patients had cancer detected while participating in this study. During routine screening, patient 747-264 was found to have prostate cancer which was subsequently treated surgically. Patient 747-254 had a local recurrence of her breast cancer for which she received chemotherapy and radiation.

Patient 747-275 was hospitalized for an elective hip replacement.

7.1.2.2.3 TBZ103, 011 (An open-label study in patient with chorea of any etiology)

These patients were treated from 1979 to 2004. Archival records were available for review from 145 patients; 98 of whom had Huntington's disease. At the time that the protocol was instituted there were no guidelines for SAE reporting. When the available data was abstracted for inclusion in the database, the study staff coded adverse events that would meet the current definition for SAEs as such.

Table 4: SAE (retrospectively assigned)

| Patient ID | Age | Sex | Adverse Event (Verbatim term)          | Onset (month) | Dose at onset (mg/day) |
|------------|-----|-----|--|---------------|------------------------|
| 00026a     | 52  | M   | •Fall                                  | 36            | 75                     |
|            |     |     | •Pulmonary congestion                  | 42            | 112.5                  |
|            |     |     | •Dysphagia, severe                     | 48            | 75                     |
|            |     |     | •Pneumonia                             | 50            | 75                     |
| 00051      | 59  | F   | •Decubitus ulcer                       | 14            | 25                     |
|            |     |     | •Deep vein thrombosis , malnutrition   | 15            | 25                     |
|            |     |     | •Sepsis (Staphylococcus, Enterococcus) |               |                        |
| 00558      | 42  | F   | •Suicidal gesture                      | 14            | 50                     |
| 00568      | 66  | F   | •Diarrhea                              | 3             | 50                     |
|            |     |     | •Dehydration                           | 4             | 50                     |
|            |     |     | •Delirium                              |               | 50                     |
| 00574      | 52  | F   | •Aspiration pneumonia                  | 18            | 75                     |
| 00584      | 69  | M   | •Hallucinations                        | 1             | 75                     |
|            |     |     | •Psychosis                             |               | 75                     |
|            |     |     | •Insomnia                              |               | 75                     |
| 00596a     | 63  | F   | •Dysphagia                             | 11            | 75                     |
|            |     |     | •Emesis                                |               | 75                     |
| 00687      | 86  | F   | •Ankle fracture                        | 23            | 37.5                   |
| 00884      | 45  | M   | •Dehydration                           | 36            | 75                     |
| 00984      | 60  | F   | •Hyponatremia                          | 7             | 37.5                   |
|            |     |     | •Aspiration pneumonia                  | 10            | 37.5                   |
| 01020      | 42  | F   | •Optic atrophy due to lupus            | 1             | 12.5                   |

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Table 4 (continued): SAE (retrospectively assigned)

| Patient ID | Age | Sex | Adverse Event (Verbatim term)   | Onset (month) | Dose at onset (mg/day) |
|------------|-----|-----|---|---------------|------------------------|
| 00846      | 53  | F   | •Appendectomy due to appendicitis<br>•Diverticulitis with perforation   | 32            | 62.5                   |
| 00884      | 45  | M   | •Dehydration  | 36            | 75                     |
| 00984      | 60  | F   | •Hyponatremia   | 7             | 37.5                   |
|            |     |     | •Aspiration pneumonia   | 10            | 37.5                   |
| 00057      | 37  | M   | •Severe low back pain   | 32            | 75                     |
|            |     |     | •Sciatica   |               | 75                     |
|            |     |     | •Suicidal ideation  |               | 300                    |
|            |     |     | •Worsening of cervical spondylosis  |               | 300                    |
|            |     |     | •Possible staphylococcal infection  | 33            | 150                    |
|            |     |     | •Severe low back pain   | 34            | 150                    |
|            |     |     | •Renal failure<br>•Cardio respiratory arrest<br>•Dehydration<br>•Hyperkalemia<br>•Hypotension<br>•Lactic acidosis<br>•Rhabdomyolysis<br>•Staphylococcus Infection | 38            | 300                    |
| 00066      | 37  | F   | Aspiration pneumonia  | 44            | 300                    |
| 00088      | 83  | F   | •Ptosis with surgery •Left scapula fracture   | 52            | 37.5                   |
|            |     |     |   |               | 37.5                   |
|            |     |     | •Adrenal insufficiency •Cataract surgery •Dehydration   | 64            | 50                     |
|            |     |     |   |               | 50                     |
|            |     |     |   |               | 50                     |
| 00089      | 61  | M   | •Suicidal ideation  | 7             | 150                    |
|            |     |     | •Suicidal ideation  | 40            | 150                    |
|            |     |     | •Kidney stone   | 46            | 37.5                   |
|            |     |     | •Fecal impaction  | 57            | 100                    |
|            |     |     | •Motor vehicle accident   | 59            | 100                    |
| 00093      | 58  | M   | •Subdural hematoma  | 20            | 75.0                   |
| 00108      | 74  | F   | •Left eye surgery   | 27            | 50                     |
|            |     |     | •Pneumonia  | 34            | 50                     |
| 00258      | 71  | F   | •Tetrabenazine overdose   | 1             | 25                     |
| 00284      | 54  | F   | •Severe dehydration<br>•Comatose  | 13            | 75                     |
| 00426a     | 59  | M   | •Esophageal hemorrhage  | 49            | 75                     |
|            |     |     | •Hemorrhagic cystitis   | 55            | 25                     |

Data from table 8-4 from the ISS. The deaths were tabulated above in section 7.1.1 so they are not shown here.

7.1.2.2.4 *Nitoman 003 (an open label study in patients with hyperkinetic disorders)*

There were eight patients who reported serious adverse events (SAEs) that did not lead to discontinuation; one of whom had Huntington’s chorea. The latter patient was hospitalized for treatment of “over sedation.” While most of the other patients had conditions known to be associated with tetrabenazine such as insomnia, sedation and dysphagia, two patients had conditions which were not: Patient 117 developed a left breast carcinoma; Patient 325, who began treatment in September 1989, was hospitalized in \_\_\_\_\_ due to renal and hepatic failure, pancreatitis. We are not given sufficient information to draw conclusions regarding the possible association with use of tetrabenazine.

7.1.2.3 Summary table of SAE from select studies: TBZ103, 004; TBZ 103,005; 103,006; 103, 007.

All SAEs were reported in the active drug group. There were no SAE reported from the placebo group during 12-week placebo-controlled TBZ103, 004. There were no SAE reported from either the active or the placebo group during 5-day placebo-controlled TBZ 103, 005.

Table 5: Summary of SAE in placebo-controlled and extension studies

| Patient ID  | Age | Sex | SAE   | Dose   | Days on treatment | Discontinued due to SAE? |
|---|-----|-----|---|--------|-------------------|--------------------------|
| <b>SAE from study 103, 004 (a 12 week placebo-controlled, double-blind study)</b> |     |     |   |        |                   |                          |
| 447-271   | 40  | M   | Suicide   | 87.5mg | 65                | no                       |
| 447-213   | 62  | M   | Restlessness  | 100    | 52                | no                       |
|   |     |     | Suicidal ideation, psychosis, paranoia              | 12.5   | 68                | yes                      |
| 447-206   | 51  | F   | Fall with subarachnoid hemorrhage and confusion     | 25mg   | 16                | yes                      |
| 447-254   | 38  | F   | Breast cancer                                       | 87.5   | 39                | yes                      |
|   |     |     | Chest wall recurrence of breast cancer              | 75     | 377               | no                       |
| <b>SAE from study 103, 007 (an extension of TBZ 103, 004)</b>                     |     |     |   |        |                   |                          |
| 747-275   | 74  | M   | Elective hip replacement                            | 87.5   | 247               | no                       |
| 747-274   | 68  | M   | Fall, pneumonia                                     | 100    | 196               | no                       |
| 747-264   | 56  | M   | Prostate cancer                                     | 50     | 175               | no                       |
| 747-245   | 53  | M   | Increased depression, akathisia, anxiety, agitation | 75     | 239               | yes                      |
| 747-257   | 63  | F   | Pneumonia, dysphagia                                | 50     | 377               | no                       |
| 747-226   | 63  | F   | Fall, left femoral neck fracture                    | 67.5   | 506               | no                       |
| 747-211   | 55  | F   | Death due to metastatic breast cancer               | 75     | 451               | yes                      |

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Table 5 (continued): Summary of SAE in placebo-controlled and extension studies

| Patient ID   | Age | Sex | SAE                                     | Dose | Days on treatment | Discontinued due to SAE? |
|--|-----|-----|---|------|-------------------|--------------------------|
| <b>SAE from study 103, 006 (an extension of study TBZ 103,005)</b> |     |     |   |      |                   |                          |
| 647-430  | 53  | F   | Suicidal ideation, delusions            | 37.5 | 67                | no                       |
| 647-415  | 66  | M   | Urinary tract infection                 | 25   | 230               | no                       |
| 647-426  | 42  | M   | Chest pain                              | 37.5 | 54                | no                       |
| 647-419  | 60  | F   | Fall                                    | 100  | 284               | no                       |
| 647-405  | 61  | M   | Pneumonia, empyema, respiratory failure | 75   | 381               | no                       |
| 647-402  | 45  | F   | Diarrhea, depression                    | 50   | 17                | no                       |
| 647-422  | 47  | F   | Nausea, dehydration                     | 37.5 | 26                | yes                      |

Data from tables in section 8 of the ISS

#### 7.1.2.4 Reviewer's summary

While all of the SAE were reported in persons who had received the active drug product, most of the serious adverse events reported were not inconsistent with what has been reported in the literature for this drug.

#### 7.1.3 Dropouts and Other Significant Adverse Events

##### 7.1.3.1 Overall profile of dropouts

###### 7.1.3.1.1 Clinical Pharmacology studies

There were no withdrawals from study TBZ 201,001. All six participants completed the trial.

There were three withdrawals from study TBZ 103,003; twenty-five subjects completed the trial. The three withdrawals, all of whom were all discontinued for administrative reasons, had each completed the first arm of this crossover study:

- Subject 347-012: Presumed positive drug screen (subsequently found to be negative)
- Subject 347-025: Subject withdrew consent "for personal reasons."
- Subject 347-026: Drug screen positive for alcohol

There were five withdrawals from study TBZ 104,012; twenty-three subjects completed the trial. The withdrawals, all of whom were all discontinued for administrative reasons, had each completed the first arm of this crossover study:

- Subject 1247-112: Positive drug screen for marijuana
- Subject 1247-117: Positive drug screen for cocaine

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- Subject 1247-123: Positive drug screen for propoxyphene
- Subject 1247-126: Self medication with an excluded medication (naprosyn)
- Subject 1247-132: Subject withdrew consent “for personal reasons.”

There were no withdrawals from study CL1700114 (A). All 12 participants completed the trial.

There was one withdrawal from study TBZ 203,008; 12 subjects completed the trial. The one withdrawal had completed the first arm of this crossover study:

- Subject 847-042: Treated with an excluded medication (azithromycin) for urethritis

There was one withdrawal from study CL1700114 (B); this occurred after the ingestion of the last dose of tetrabenazine:

- Subject 032: Subject withdrew consent because she did not want further blood draws. She had previously reported three adverse events, specifically asthenia (4 episodes), somnolence (1 episode) and a deep laceration of her right hand.

There were four withdrawals from study TBZ 203,009; 12 subjects completed the trial. Three of the 4 withdrawals were discontinued due to adverse events:

- Subject 947-051: Other: Subject withdrew consent “for personal reasons” prior to receiving her first dose of tetrabenazine
- Subject 947-052: AE: Elevated AST and ALT detected during the digoxin alone phase of the study. She did not receive tetrabenazine.
- Subject 947-058: AE: Elevated ALT detected after ingestion of 50 mg of tetrabenazine. This AE began during the digoxin treatment period immediately preceding her discontinuation.
- Subject 947-066: AE: Near syncope occurring prior to administration of study drug

There had been no withdrawals from ongoing study TBZ 203,010 as of the data cut-off, February 28 2005.

#### 7.1.3.1.2 *Double-blind studies in patients with Huntington disease-associated chorea (TBZ 103,004; 103,005)*

There were 6 withdrawals from study TBZ 103,004. Five of the 6 withdrawals were discontinued due to adverse events:

##### Placebo group

- Patient 447-317: Other: Subject withdrew consent 42 days after beginning therapy

##### Tetrabenazine group

- Patient 447-271: SAE: Death ( after 65 days of treatment, final dose 87.5 mg)
- Patient 447-206: SAE: Fall with complicating subarachnoid hemorrhage and confusion (after 17 days of treatment, final dose 25 mg)
- Patient 447-213: SAE: Psychosis/paranoia (after 71 days of treatment, final dose 12.5 mg)
- Patient 447-254: SAE: Preexisting breast mass found to be cancer (after 39 days of treatment, final dose 87.5 mg)
- Patient 447-246: AE: Akathisia ( after 50 days of treatment, final dose 37.5 mg)

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There were no withdrawals from study TBZ 103,005.

#### *7.1.3.1.3 Long term extension studies (TBZ 103,006; 103,007)*

##### TBZ 103,006

Although all 30 patients were eligible to continue from study TBZ 103,005, one patient decided not to enter the extension study due to difficulty in traveling to Houston from Mexico. The CRF for this patient reports that the treatment was not providing sufficient benefit but a subsequent contact with the patient revealed the travel difficulties.

As of the data cut-off date (February 28 2005), there were 2 withdrawals from study TBZ 103,006.

- Patient 647-422: SAE : nausea and dehydration (after 27 days of treatment)
- Patient 647-420 : Other: withdrew from the study after placement in a nursing home (after 120 days of treatment)

##### TBZ 103,007

Although 74 of the 84 patients were eligible to continue from study TBZ 103,004, four patients decided not to enter the extension study:

##### Placebo group

- Patient 447-234: Other: Patient returned home to ~~na~~ having moved to Atlanta to participate in the initial study.
- Patient 447-269: Other: PI questioned patient's ability to comply with study requirements

##### Tetrabenazine group

- Patient 447-240: Other: Patient choice, no further information available
- Patient 447-286: Other: Patient choice, no further information available

During this study 19 patients discontinued prior to completion of 48 weeks of therapy. All participants had previously participated in the 12-week double-blind study TBZ 103, 004. The on-treatment times given below represent time of participation in TBZ 103, 007.

- Patient 747-211: SAE: Death (after 350 days of treatment, final dose 37.5 mg)
- Patient 747-262: AE: Suicidal ideation (after 145 days of treatment, final dose 12.5 mg)
- Patient 747-247: AE: Depression, akathisia (after 113 days of treatment, final dose 37.5 mg)
- Patient 747-248: AE: Akathisia (after 175 days of treatment, final dose 50 mg)
- Patient 747-232: AE: Vocal tics (after 140 days of treatment, final dose 50 mg)
- Patient 747-224: AE: Abnormal coordination, unsteady gait, balance difficulty (after 7 days of treatment, final dose 12.5 mg)
- Patient 747-237: AE: Abnormal liver function tests (after 87 days of treatment, final dose 25 mg)
- Patient 747-244: AE: Abnormal bilirubin (after 174 days of treatment, final dose 50 mg)
- Patient 747-202: Other: used excluded medication (after 65 days of treatment, final dose 75 mg)
- Patient 747-201: Other: lost to follow-up (after 4 days of treatment, final dose 12.5 mg)
- Patient 747-260: Other: Disease progression (after 147 days of treatment, final dose 150 mg)

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- Patient 747-274: Other: Lost to follow-up (after 171 days of treatment, final dose 100 mg)
- Patient 747-229: Other: Consent withdrawn (after 167 days of treatment, final dose 50 mg)
- Patient 747-238: Other: Consent withdrawn (after 167 days of treatment, final dose 62.5 mg)
- Patient 747-243: Other: Consent withdrawn (after 176 days of treatment, final dose 50 mg)
- Patient 747-245: Other: Consent withdrawn (after 153 days of treatment, final dose 25 mg). This patient had experienced a SAE of increased depression, agitation, anxiety and akathisia as described earlier in this review.
- Patient 747-261: Other: Consent withdrawn (after 167 days of treatment, final dose 25 mg)
- Patient 747-268: Other: Consent withdrawn (after 70 days of treatment, final dose 150 mg). He reached a maximum dose of 200 mg/day but was later reduced to 150 mg/day due to somnolence. This patient had severe anxiety noted at week 24 and decided at that visit not to continue with tetrabenazine therapy.

Brief narratives for discontinuations of note

Patient 747-232 was noted to have vocal tics after 140 days of treatment. These did not resolve upon cessation of tetrabenazine use. The patient was treated with aripiprazole. At the time of this review, there are no reports in the literature linking tetrabenazine with irreversible adverse events, so this appears to be a novel finding.

Patient 747-237, who was taking Lipitor as a concomitant medication, had been noted to have an elevated ALT of 83 IU/L (normal 6-43) when he completed study TBZ103,004. Approximately two months after beginning the open label extension, his ALT was 231 IU/L, his AST was 68 IU/L (normal 11-36). His Lipitor was discontinued. His tetrabenazine had previously been lowered from 100 mg/day (his dose at completion of study 103, 004) to 50 mg/day because of sedation. Subsequently his LFTs were shown to remain high: ALT 289 IU/L; AST 76 IU/L; GGT 131 IU/L (normal 10-61). His CPK was 684 U/L (normal 22-269). His hepatitis screen was negative. Once these results were known, the tetrabenazine was stopped. Three weeks later, with the exception of an elevated GGT (75 IU/L), his liver function tests were all within normal limits. This case may reflect an effect of tetrabenazine on the liver function test but it could reflect potential liver injury with concomitant drug use. The injury appears to have been reversible and responsive to drug discontinuation.

Patient 747-244 was noted to have had an elevated bilirubin at the end of TBZ 103,004: 1.42 mmol/ml (normal 0.2-1.2). After approximately six months of open-label treatment his bilirubin was 1.75 mmol: he was withdrawn from the study. This case may reflect an effect of tetrabenazine on hepatic function.

Patient 747-247 had been receiving tetrabenazine 75 mg for 2.5 months when he was noted to have had an increase in HAM-D score to 22 from his usual range of 8-10. He was reported at the time to have a severe depression; his chorea score was 7, improved from 14 at baseline. Despite

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reduction of his tetrabenazine from 75 mg to 62.5 mg to 37 mg/day and finally to zero, his depression persisted. After a week of no therapy, he was challenged with tetrabenazine again, beginning at 12.5 mg and increasing to 37.5 mg. He was withdrawn from the study due to continued depression and mild akathisia.

*7.1.3.1.4 Baylor College of Medicine protocol (composed of CSR TBZ 103,011 and the Baylor non-chorea report: H-721)*

The discontinuation data from these studies comes from a review (partially retrospective) of patient records from January 1979 to February 2004.

*[Reviewer's note: We were notified on March 2, 2006 that a DSI investigation revealed that Dr. Jankovic did not report increased dysphagia in a number of patients due to his belief that the dysphagia was related to the underlying disease. We may fairly assume that the incidence of dysphagia in the patients from Baylor has been underreported in the database. It is not known which other adverse events experienced were not incorporated into the database due to the PI's determination that these were disease related and not drug-related.]*

TBZ103,011

Study 103, 011 is the analysis of the subset of patients who were treated for chorea at Baylor College of Medicine (n=145). This study is ongoing and 27 of the patients are still being treated under Protocol H-721. Of the 118 patients who are not still participating in protocol H-721, 22 withdrew to enroll in TBZ 103,005. Fourteen patients died and twelve withdrew due to hardship caused by financial constraints or by travel. Ten patients withdrew due to insufficient efficacy. In four patients the chorea resolved so no further treatment was warranted.

Thirty-three patients cited "other" reasons for study withdrawal:

- Transfer of care to another physician (n=16)
- Patient placed in hospice or nursing home (n=6)
- Lost to follow-up (n=6)
- Disease progression (n=4)
- Surgical treatment of movement disorder (n=1)

Information which pertained to adverse events as reason for individual withdrawal was not consistently captured in the CRFs. The investigator provided additional information on some cases after the database was closed, however, in my opinion, this information would be subject to recall bias. In any event, the information below represents all AEs reported by the patient at the time of discontinuation. It is not always clear which was the AE that caused the discontinuation.

- Patient 00069: AE: Depression (after 23 days of treatment, final dose 75 mg). This patient did not have Huntington's chorea.
- Patient 00156: AE: Depression, somnolence (after 13 days of treatment, final dose 75 mg). This patient did not have Huntington's chorea.
- Patient 00332: AE: Depression (after 320 days of treatment, final dose unknown). This patient did have Huntington's chorea.
- Patient 00436: AE: Depression (after 2050 days of treatment, final dose 25 mg). This patient did have Huntington's chorea.
- Patient 00439: AE: Depression, Parkinsonism (after 324 days of treatment, final dose 37.5 mg). This patient did not have Huntington's chorea.

- Patient 00578: **AE:** Depression, akathisia (after 212 days of treatment, final dose unknown). This patient did not have Huntington's chorea.
- Patient 00759: **AE:** Depression (after 276 days of treatment, final dose unknown). This patient did have Huntington's chorea.
- Patient 00436: **AE:** Depression (after 1357 days of treatment, final dose 75 mg). This patient did have Huntington's chorea.
- Patient 00048: **AE:** Somnolence, headache (after 183 days of treatment, final dose unknown). This patient did have Huntington's chorea.
- Patient 00079: **AE:** Somnolence, nausea, tremor (after 21 days of treatment, final dose 75 mg). This patient did have Huntington's chorea.
- Patient 00083: **AE:** Somnolence, nervousness (after 22 days of treatment, final dose 75 mg). This pediatric patient (age 4 years) did not have Huntington's chorea.
- Patient 00410: **AE:** Somnolence, increased cough, dysphagia, tremor (after 203 days of treatment, final dose 37.5 mg). This patient did have Huntington's chorea.
- Patient 00787: **AE:** Somnolence (after 866 days of treatment, final dose 75 mg). This patient did not have Huntington's chorea.
- Patient 00803: **AE:** Somnolence (after 277 days of treatment, final dose 37.5 mg). This patient did not have Huntington's chorea.
- Patient 00093: **AE:** Parkinsonism (after 1218 days of treatment, final dose unknown). This patient did have Huntington's chorea.
- Patient 00267: **AE:** Parkinsonism (after 107 days of treatment, final dose 150 mg). This patient did have Huntington's chorea.
- Patient 00453: **AE:** Akathisia (after 203 days of treatment, final dose 25 mg). This pediatric patient (age 4 years) did not have Huntington's chorea.
- Patient 00984: **AE:** Akathisia (after 1169 days of treatment, final dose 37.5 mg). This patient did have Huntington's chorea.
- Patient 00868: **AE:** Insomnia (after 133 days of treatment, final dose unknown). This patient did have Huntington's chorea.
- Patient 00071: **AE:** Anxiety (after 98 days of treatment, final dose 75 mg). This patient did have Huntington's chorea.
- Patient 00151: **AE:** Headache (after 102 days of treatment, final dose 37.5 mg). This patient did have Huntington's chorea.
- Patient 00158: **AE:** Nervousness, emotional lability, hostility (after 722 days of treatment, final dose 75 mg). This patient did have Huntington's chorea.
- Patient 00284: **AE:** Dehydration (after 398 days of treatment, final dose 75 mg). This patient did have Huntington's chorea.
- Patient 00584: **AE:** Restlessness (after 568 days of treatment, final dose 62.5 mg). This patient did not have Huntington's chorea.
- Patient 00596: **AE:** Restlessness (after 568 days of treatment, final dose 62.5 mg). This patient did have Huntington's chorea.
- Patient 00856: **AE:** Dyspepsia (after 82 days of treatment, final dose unknown). This patient did have Huntington's chorea.
- Patient 00083: **AE:** Movement disorder (after 32 days of treatment, final dose 37.5 mg). This pediatric patient (age 3 years) did not have Huntington's chorea.

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- Patient 00927: AE: Sialorrhea (after 20 days of treatment, final dose 37.5 mg). This patient did not have Huntington's chorea.

#### Baylor non-chorea report

This is an analysis of the subset of patients who received tetrabenazine for movement disorders other than chorea (n=280) during the period from January 1 1997 through March 31 2002. Some to the patients may have started tetrabenazine therapy prior to January 1 1997.

Patients were financially responsible for getting to Houston Texas to be seen and for paying for their own medications. Since tetrabenazine is not approved for use in the US, it is not clear that they would have been eligible for insurance reimbursement.

The sponsor reports that "limited documentation of dates in the non-chorea database does not allow linkage of specific AEs to treatment discontinuation (ISS p.530)" So instead the sponsor provided information on all the AE reported by the 49 patients who discontinued:

- Death-4 patients (Suicide-1, Cardiovascular disease-3);
- Drowsiness/fatigue: n=20
- Parkinsonism: n=13
- Depression: n=10
- Nausea/vomiting: n=9
- Akathisia: n=6
- Dizziness: n=5
- Insomnia: n=4
- Headache: n=3
- Nervousness/anxiety: n=3
- Panic attacks: n=3
- Flu: n=2
- Mood swings: n=2
- Orthostatic hypotension: n=2
- Paresthesiae; n=2
- Sialorrhea: n=2
- Slurred speech: n=2
- Tremor: n=2
- Weakness: n=2
- Weight gain: n=2
- Rash : n=2
- Trance-like/zombie, Balance/gait difficulties, Dysphonia, hypertension, Memory problems/confusion, Drooling, Dry mouth, Rolling eyes, Agitation, alopecia, Blurred vision, Bradykinesia, Hallucinations, Increased movements, Jittery, lightheaded, low motivation, mental status changes, nocturea, dystonic reaction, foot drop, lithium tremor , MVA, feelings of rage were all noted in 1 patient/adverse event.

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Table 6: Reasons for discontinuation during the Baylor open label study

| Reason for Discontinuation               | 0 to <6 Months<br>(N=90)<br>N (%) | 6 to <12 Months<br>(N=37)<br>N (%) | 12 to <24 Months<br>(N=27)<br>N (%) | 24 Months to <5 Years<br>(N=46)<br>N (%) | 5 + Years<br>(N=47)<br>N (%) | Total<br>N (%)   |
|--|-----------------------------------|------------------------------------|-------------------------------------|--|------------------------------|------------------|
| Adverse events                           | 30 (11%)                          | 6 (2%)                             | 2 (1%)                              | 2 (1%)                                   | 9 (3%)                       | 49 (18%)         |
| Lack of efficacy                         | 23 (8%)                           | 0 (0%)                             | 1 (<1%)                             | 1 (<1%)                                  | 0 (0%)                       | 25 (9%)          |
| Movement disorder spontaneously resolved | 0 (0%)                            | 1 (<1%)                            | 0 (0%)                              | 1 (<1%)                                  | 0 (0%)                       | 2 (1%)           |
| Death (unrelated to tetrabenazine)       | 0 (0%)                            | 0 (0%)                             | 0 (0%)                              | 1 (<1%)                                  | 1 (<1%)                      | 2 (1%)           |
| Travel/financial reasons                 | 5 (2%)                            | 2 (1%)                             | 4 (1%)                              | 8 (3%)                                   | 4 (1%)                       | 23 (8%)          |
| Better results with BOTOX                | 1 (<1%)                           | 0 (0%)                             | 0 (0%)                              | 1 (<1%)                                  | 1 (<1%)                      | 3 (1%)           |
| Other                                    | 3 (1%)                            | 1 (<1%)                            | 1 (<1%)                             | 3 (1%)                                   | 3 (1%)                       | 11 (4%)          |
| Lost to follow-up                        | 4 (1%)                            | 1 (<1%)                            | 2 (1%)                              | 1 (<1%)                                  | 1 (<1%)                      | 9 (3%)           |
| <b>TOTAL</b>                             | <b>66 (24%)</b>                   | <b>11 (4%)</b>                     | <b>10 (4%)</b>                      | <b>18 (6%)</b>                           | <b>19 (7%)</b>               | <b>124 (44%)</b> |

(Table 7-18 from the ISS, note that duration data for 33 patients were missing)

### 7.1.3.2 Adverse events associated with dropouts

Table 7: Reason for discontinuation (excluding death) grouped by body system across studies.

|                              | 103,004<br>N=84 | 103,007<br>N=70 | 103,005<br>N=30 | 103,006<br>N=29 | Baylor            |                       |
|------------------------------|-----------------|-----------------|-----------------|-----------------|-------------------|-----------------------|
|                              |                 |                 |                 |                 | HD chorea<br>n=98 | Non HD chorea<br>n=47 |
| <b>Psychiatric Disorders</b> |                 |                 |                 |                 |                   |                       |
| Depression                   | 0               | 1               | 0               | 0               | 4                 | 4                     |
| Anxiety                      | 0               | 0               | 0               | 0               | 1                 | 0                     |
| Emotional lability           | 0               | 0               | 0               | 0               | 1                 | 0                     |
| Hostility                    | 0               | 0               | 0               | 0               | 1                 | 0                     |
| Insomnia                     | 0               | 0               | 0               | 0               | 1                 | 0                     |
| Paranoia                     | 1               | 0               | 0               | 0               | 0                 | 0                     |
| Suicidal ideation            | 0               | 1               | 0               | 0               | 0                 | 0                     |

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Table 7 (continued): Reason for discontinuation (excluding death) grouped by body system across studies.

|   | 103,004 | 103,007 | 103,005 | 103,006 | Baylor            |                       |
|---|---------|---------|---------|---------|-------------------|-----------------------|
|   | N=84    | N=70    | N=30    | N=29    | HD chorea<br>n=98 | Non HD chorea<br>n=47 |
| <b>Central Nervous System/Peripheral Nervous System disorders</b> |         |         |         |         |                   |                       |
| Somnolence  | 0       | 0       | 0       | 0       | 4                 | 4                     |
| Akathisia   | 1       | 2       | 0       | 0       | 1                 | 2                     |
| Parkinsonism  | 0       | 0       | 0       | 0       | 2                 | 1                     |
| Nervousness   | 0       | 0       | 0       | 0       | 1                 | 1                     |
| Sialorrhea  | 0       | 0       | 0       | 0       | 0                 | 1                     |
| Movement disorder   | 0       | 0       | 0       | 0       | 0                 | 1                     |
| Restlessness  | 0       | 0       | 0       | 0       | 1                 | 1                     |
| Tremor  | 0       | 0       | 0       | 0       | 2                 | 0                     |
| Fall  | 1       | 0       | 0       | 0       | 0                 | 0                     |
| Confusion   | 1       | 0       | 0       | 0       | 0                 | 0                     |
| Subarachnoid hemorrhage   | 1       | 0       | 0       | 0       | 0                 | 0                     |
| Vocal tics  | 0       | 1       | 0       | 0       | 0                 | 0                     |
| Abnormal coordination   | 0       | 1       | 0       | 0       | 0                 | 0                     |
| Unsteady gait   | 0       | 1       | 0       | 0       | 0                 | 0                     |
| Balance difficulties  | 0       | 1       | 0       | 0       | 0                 | 0                     |
| Headache  | 0       | 0       | 0       | 0       | 2                 | 0                     |
| <b>Gastrointestinal system disorders</b>                          |         |         |         |         |                   |                       |
| Dysphagia   | 0       | 0       | 0       | 0       | 1                 | 0                     |
| Nausea  | 0       | 0       | 0       | 0       | 1                 | 0                     |
| Dyspepsia   | 0       | 0       | 0       | 0       | 1                 | 0                     |
| <b>Respiratory system disorders</b>                               |         |         |         |         |                   |                       |
| Increased cough   | 0       | 0       | 0       | 0       | 1                 | 0                     |
| <b>Metabolic and nutritional disorders</b>                        |         |         |         |         |                   |                       |
| Dehydration   | 0       | 0       | 0       | 1       | 1                 | 0                     |
| <b>Malignancy</b>   |         |         |         |         |                   |                       |
| Breast cancer   | 1       | 0       | 0       | 0       | 0                 | 0                     |
| <b>Investigations</b>   |         |         |         |         |                   |                       |
| Abnormal liver function tests                                     | 0       | 1       | 0       | 0       | 0                 | 0                     |
| Abnormal bilirubin  | 0       | 1       | 0       | 0       | 0                 | 0                     |

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#### 7.1.3.3 Other significant adverse events

There were no other significant adverse events to be reported.

#### 7.1.4 Other Search Strategies

In light of the known monoamine depletion, the population and the frequency of certain adverse events reported in the literature, the sponsor was asked to compile data on the frequency of specific adverse events in the Prestwick sponsored studies/analyses.

##### Sedation

This category included adverse events coded as sedation, drowsiness, somnolence and asthenia. The latter term was included as the sponsor felt that it was “possibly equivalent to sedation.”

Sedation was reported in 15% (n=19) of the 125 subjects who participated in the clinical pharmacology studies. During the single dose studies, 11% of the subjects who received either 12.5 mg or 25 mg complained of this adverse event; 25% of the subjects who received 50 mg had the same complaint. In the repeat dose studies, over half of the subjects who received 25 mg QD complained of sedation; none of the subjects who received 25 mg BID complained of sedation. The reason for the apparent inverse correlation between dose and level of sedation is unclear.

While no patient withdrew from the study due to sedation during the randomized, placebo-controlled double-blind study in tetrabenazine-naïve patients, dose reduction or cessation of scheduled up-titration occurred in 28% (n=15) of the 54 participants due to sedation. In all but one patient, the sedation resolved after the dose was reduced. The 16 participants who complained of sedation were all receiving active drug. During the extension phase of this trial, during which everyone received active drug, 37% (n=28) complained of sedation over the 80 weeks of exposure.

In the staggered withdrawal study, which enrolled tetrabenazine-experienced patients, none of the patients complained of sedation. In the extension phase of this study, 10% (n=3) complained of sedation over the 48 weeks of exposure.

In the open-label Baylor study of patients with chorea who received tetrabenazine, 38% (n=37) of the patients with Huntington’s disease-related chorea complained of sedation. The majority of the patients who had chorea unrelated to Huntington’s disease (60%, n=28) complained of sedation. In the open-label Baylor study of patients with hyperkinetic movement disorders other than chorea who received tetrabenazine, 26% (n=74) complained of sedation.

Due to concerns that sedation might lead to an increased incidence of falls and/or worsen the cognitive impairment associated with Huntington’s disease, the data from the placebo controlled 12-weeks study (TBZ 103,004) was assessed. The only cognitive item affected on the Unified Huntington’s Disease Rating Scale (UHDRS) was the Stroop Interference test: Word reading. The tetrabenazine patients had a mean change of -4.74 (SD 13.03) while the placebo patients had a mean change of 0.97 (SD 10.55). While overall there was no significant difference in the

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incidence of falls between the active and the placebo group, 15% vs. 13%, it is notable that most falls in the active drug group occurred during the titration period (13%) as opposed to during the maintenance phase (6%). The sponsor postulated that decreases in chorea seen during the maintenance period were responsible for the decrease in the incidence of falls.

### Depression

Tetrabenazine depletes dopamine, norepinephrine and serotonin from nerve terminals in the central nervous system. Depletion of the latter two monoamines is thought to increase the risk of depressive symptoms. Depression is a common psychiatric disease amongst Huntington's disease patients. The prevalence of overt depression in Huntington's patients was estimated by the sponsor, on the basis of literature reports, to be 15-20%. The sponsor asserts that the prevalence of depressive symptoms would be higher. De Marchi and Mennella (2000) hypothesized that, based upon data from unaffected family members of patients with Huntington's chorea, major affective disorders and obsessive compulsive disorders may be part of the disease complex.

None of the subjects in the clinical pharmacology studies reported depression as an adverse event.

In the placebo-controlled randomized double-blind 12-week study, TBZ103004, depression was evaluated in the following ways:

- UHDRS Item 25 "Depressed mood, frequency and severity"
- UHDRS Item 28 "Suicidal thoughts, frequency and severity"
- UHDRS Item 38 "Does the examiner believe that the patient is depressed"
- Hamilton Depression Score (HAM-D) scoring
- Adverse event reporting

Over half (57%) of the 84 patients who entered the study had a past history of depression. In each treatment arm, over half of the patients were being treated with an anti-depressant at the time of study entry: tetrabenazine (56%, n=30), placebo (67%, n=20). In three women who were receiving tetrabenazine, the dose had to be reduced due to depression; the reduction relieved the depression in 2 of those women. Over the 12 weeks, three additional patients in the active drug group began anti-depressants and 1 person in the placebo group did so. During the study, there was a statistically significant difference ( $p=0.0031$ ) in the mean change from baseline in HAM-D scores between the two groups; the placebo group improved more (-2.55 vs. -0.48). The difference was not explained by effects on any particular item within the HAM-D. An analysis of individual HAM-D scores revealed that 2 patients in the active treatment group had scores  $\geq 15$  during the study; no patients in the placebo group had individual HAM-D scores  $\geq 15$ . One of the two patients experienced an increase in HAM-D score during an unsuccessful attempt to taper his anti-depressant. Overall 8 patients in the active group had depression reported as an adverse event, a report which was independent of the HAM-D scoring and the UHDRS; one of whom had an increase in HAM-D score to 19. The other seven had HAM-D scores which ranged from 7 – 11. None of the patients in the placebo group had depression reported as an AE.

When all submitted studies were reviewed, the incidence of depression reported as an adverse event in patients with chorea associated with Huntington's disease ranged from 15-30%. The

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incidence in patients who had chorea which was not associated with Huntington's was 21%. In a population of patients who had movement disorders other than chorea, including patients with schizophrenia and Tourette's syndrome, the incidence was 9%. While no patient with Huntington's chorea reported depression as an adverse event during study TBZ 103,005, this was a 5 day study which may not have been enough time for people to experience symptoms; the same cohort in the extension study had an incidence of 24%. During these studies, those persons who complained of depression were treated by decreasing the tetrabenazine dose, adjusting pre-existing antidepressant treatment or instituting new antidepressant therapy.

*[Reviewer's note: As acknowledged by the sponsor, use of an agent which potently and selectively depletes serotonin and norepinephrine may increase the risk of a depressive episode. The pharmacologic data indicates that this might be a dose related effect. The ED50 for depletion of dopamine in the rat striatum is approximately 0.4 mg/kg, while the ED50 for norepinephrine and serotonin depletion is approximately 2 mg/kg. Additionally, persons with Huntington's disease may have a genetic susceptibility to depression.]*

Suicide/suicidal ideation

The sponsor reports that a literature review determined that the rate of suicide in patients with Huntington's disease ranges from 3.6% to 12.7%; the rate in the general US population is reported to be 0.01% (ISS p.430).

There were no reports of suicide or suicidal ideation in the subjects who participated in the clinical pharmacology studies.

There were reports of both suicidal ideation and completed suicides in the patient studies.

Table 8: Reports of suicidal ideation/completed suicide

| Study/treatment duration           | Number of Patients enrolled | Indication                    | Suicidal ideation (n)                    | Completed suicide (n) |
|------------------------------------|-----------------------------|-------------------------------|--|-----------------------|
| TBZ 103,004<br>12 weeks            | 54                          | Chorea in HD                  | 1 (pt 447-213)                           | 1 (pt 447-271)        |
| TBZ 103,007<br>48 weeks            | 75                          | Chorea in HD                  | 1 (pt 747-262)                           | 0                     |
| TBZ 103,005<br>12 weeks            | 30                          | Chorea in HD                  | 0  | 0                     |
| TBZ 103,006<br>80 weeks            | 29                          | Chorea in HD                  | 1 (pt 646-430)                           | 0                     |
| TBZ 103,011<br>Up to several years | 98                          | Chorea in HD                  | 3 (pt 00057)<br>(pt 00089)<br>(pt 00558) | 0                     |
|                                    | 47                          | Chorea not associated with HD | 1 (pt 00878)                             | 1 (pt 00212)          |

Data from ISS tables 6-23 and 6-24

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The Division sent a letter to Prestwick, dated August 12 2005, in which Prestwick was instructed to examine its database for “possibly suicide-related adverse events (PSRAE)”. A draft guidance was provided with that letter: “advice for the pharmaceutical industry in exploring their placebo-controlled clinical trials databases for suicidality and preparing datasets for analysis by FDA.” The search was limited to events which occurred either within the double-blind treatment phase of placebo-controlled trials or within 24 hours of drug discontinuation.

The sponsor performed a search of the database using specified text strings in searches of preferred terms, verbatim terms and comment fields. Once false positives were excluded, 12 PRSAE remained. Narratives for these 12 patients were prepared. Three outside consultants classified the blinded narratives using the Columbia Group Classification System:

- Code 1 Completed Suicide
- Code 2 Suicide attempt
- Code 3 Preparatory acts towards self-injurious behavior
- Code 4 Suicidal ideation
- Code 5 Self-injurious behavior
- Code 6 Insufficient information
- Code 7 Self-injurious behavior, no suicide intent
- Code 8 Other: accident; psychiatric; medical

The panel reached independent agreement on all 12 cases. Patient 447-271 was Code 1. Patient 447-213 was Code 4. The remaining patients, 447-206, 447-207, 447-209, 447-220, 447-224, 447-238, 447-254, 447-297, 547-424, were all Code 8.

#### Insomnia

None of the 125 subjects who participated in the clinical pharmacology studies complained of this adverse event.

On Study TBZ 103, 004, insomnia was evaluated using the HAM-D scores for early, middle and late insomnia. No patient withdrew from the study due to sedation during the randomized, placebo-controlled double-blind study in tetrabenazine-naïve patients, dose reduction occurred in one of the 54 participants due to insomnia (Pt 447-264). The 12 participants who complained of insomnia were all receiving active drug. Seven people complained of insomnia during the upward titration phase of the study; the remainder complained during the maintenance period. All patients were taking 50 mg/day or more; 5 were at the maximal study-allowed dose of 100 mg /day. There were no associated complaints of depression while on study, but there was one patient who complained of depression the day after stopping treatment. During the 80-week extension phase of this study, 24% (n=18) patients complained of insomnia. Five of those patients had ongoing insomnia which had begun after week 6 in the initial study.

In the staggered withdrawal study, which enrolled tetrabenazine-experienced patients, one of the patients complained of insomnia. In the extension phase of this study, 10% (n=3) complained of insomnia over the 48 weeks of exposure.

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In the open-label Baylor study of patients with chorea who received tetrabenazine, 33% (n=32) of the patients with Huntington's disease-related chorea complained of insomnia. The minority of the patients who had chorea unrelated to Huntington's disease (19%, n=9) complained of insomnia. In the open-label Baylor study of patients with hyperkinetic movement disorders other than chorea who received tetrabenazine, 5% (n=15) complained of insomnia.

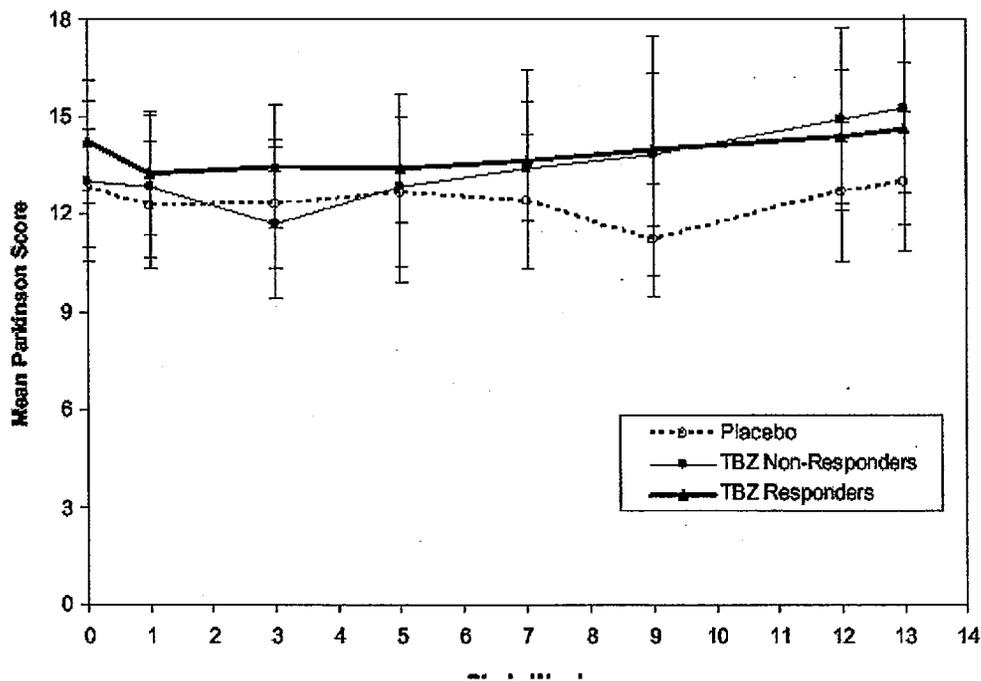
### Parkinsonism

Tetrabenazine depletes striatal dopamine. Depletion of striatal dopamine can cause parkinsonism. Parkinsonism has been described as an AE with tetrabenazine use.

None of the 125 subjects who participated in the clinical pharmacology studies complained of this adverse event.

During study TBZ 103, 004, parkinsonism was measured on the UHDRS and could also be reported as an AE. While no patient withdrew from the study due to parkinsonism during this randomized, placebo-controlled double-blind study in tetrabenazine-naïve patients, dose reduction or cessation of scheduled up-titration occurred in 6% (n=3) of the 54 participants. In all but one patient, the parkinsonism resolved after the dose was reduced. The participants who complained of sedation were all receiving active drug. During the extension phase of this trial, during which everyone received active drug, 3% (n=2) had parkinsonism over the 80 weeks of exposure. Of note the UHDRS parkinsonism scores were not significantly different in tetrabenazine responders as compared to non-responders.

Figure 1: UNDRS parkinsonism score



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In the staggered withdrawal study, which enrolled tetrabenazine-experienced patients, parkinsonism was not seen in any of the patients. No parkinsonism was seen nor did patients complain of parkinsonism over the 48 weeks of exposure.

In the open-label Baylor study of patients with chorea who received tetrabenazine, 11% (n=11) of the patients with Huntington's disease-related chorea complained of parkinsonism or had parkinsonism noted. The minority of the patients who had chorea unrelated to Huntington's disease (19%, n=9) complained of parkinsonism or had parkinsonism noted. In the open-label Baylor study of patients with hyperkinetic movement disorders other than chorea who received tetrabenazine, 19% (n=54) complained of parkinsonism or had parkinsonism noted.

Due to concerns that depletion of dopamine might lead to an increased incidence of akathisia, the data from the placebo controlled 12-week study (TBZ 103,004) was assessed using the Barnes score. There were no reports of akathisia as an AE in patients who received placebo. Five patients had akathisia reported as a dose-limiting effect during study TBZ103,004. The dose of study medication was decreased in all five with resolution of the akathisia in four; in two of these patients, a loss of efficacy occurred with the dose change. In the fifth patient, akathisia persisted despite dose reduction, leading to study withdrawal (pt 447-246). While akathisia was not reported as an AE during TBZ 103, 005 or its extension, it was reported in 9% (n=5) of the participants in TBZ 103 004 and 17% (n=13) of the participants in its extension. The incidence ranged from 8 to 15% in the Baylor studies. Overall akathisia was an uncommon reason for study withdrawal, ranging from 0% in Study TBZ 103,005 and its extension to 4% in the Baylor patients with chorea unassociated with Huntington's disease.

#### Dysphagia and pneumonia

These two adverse events have been associated with tetrabenazine use in the literature; the determination of causality is confounded by the fact that dysphagia and pneumonia are also symptoms of Huntington's disease.

Since dysphagia and dysarthria have been associated with dopamine depletion and the putative mechanism of tetrabenazine is dopamine depletion, the UPDRS swallowing and dysarthria were used to evaluate these adverse events during these studies.

None of the 125 subjects who participated in the clinical pharmacology studies reported these as adverse events.

During the randomized, placebo-controlled double-blind study in tetrabenazine-naïve patients, one patient reported dysphagia as an adverse event. During the extension phase of this trial, 3% (n=2) complained of dysphagia over the 80 weeks of exposure.

In the staggered withdrawal study, which enrolled tetrabenazine-experienced patients, 7% (n=2) of the patients complained of dysphagia. In the extension phase of this study, the same incidence was seen.

In the open-label Baylor study of patients with chorea who received tetrabenazine, 19% (n=19) of the patients with Huntington's disease-related chorea complained of dysphagia; 11 of these

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patients had dysphagia as a pre-existing condition. The minority of the patients who had chorea unrelated to Huntington's disease (6%, n=3) complained of dysphagia. In the open-label Baylor study of patients with hyperkinetic movement disorders other than chorea who received tetrabenazine, 1% (n=2) complained of dysphagia.

In the sponsor's analysis, the maximum daily dosage and the speed of titration may both be associated with the risk of dysphagia. The one study which used a maximum dose of 100 mg/day has a lower incidence of dysphagia, consistent with literature reports that suggest that doses higher than 100 mg may be associated with dysphagia. When a slower rate of titration was used, weekly, as opposed to every 3-5 days as in the Baylor protocol, the incidence appeared to be lower.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) comprises autonomic nervous system symptoms (hyperthermia, instability, diaphoresis); extrapyramidal system symptoms (dystonia and rigidity) and cognitive symptoms (confusion, agitation). The putative mechanism is decreased central nervous system dopamine activity, resultant from either dopamine receptor blockade or from dopamine depletion. This potentially fatal complication has been associated with neuroleptics, as well as all drugs which induce blockade of the dopamine D<sub>2</sub>type-receptor.

The Roche pharmacovigilance report describes 7 patients with NMS/hyperthermia: 3 had Huntington's disease; 2 had tardive dyskinesia and 1 each had chorea and dystonia. While 6 of the 7 patients had additional risk factors, it is impossible to state that there is no association between tetrabenazine and possible NMS. The sponsor has elected to list NMS in the warning section of the label for this product.

Table 9: Adverse events of special clinical interest

| Adverse Event<br>(COSTART and WHO preferred terms<br>together when possible) | TBZ<br>103,004             | TBZ<br>103,007             | TBZ<br>103,005             | TBZ<br>103,006             | TBZ<br>103,011              |
|--|----------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|
|  | 12.5-100<br>mg/day<br>n=54 | 12.5-150<br>mg/day<br>n=75 | 12.5-200<br>mg/day<br>n=30 | 12.5-200<br>mg/day<br>n=29 | 12.5-300<br>mg/day<br>n=145 |
| Somnolence+Sedation+drowsiness+stupor  | 15 (28%)                   | 35 (47%)                   | 0                          | 5 (17%)                    | 65 (45%)                    |
| Insomnia   | 12 (22%)                   | 16 (21%)                   | 1 (3%)                     | 0                          | 41 (28%)                    |
| Parkinsonism/extrapyramidal syndrome   | 1 (2%)                     | 2 (3%)                     | 0                          | 1 (4%)                     | 20 (14%)                    |
| Depression   | 8 (15%)                    | 18 (24%)                   | 0                          | 4 (15%)                    | 44 (30%)                    |
| Akathisia  | 5 (9%)                     | 11 (15%)                   | 0                          | 0                          | 17 (12%)                    |
| Dysphagia/swallowing difficult/choking                                       | 1 (2%)                     | 2 (7%)                     | 2 (7%)                     | 2 (6%)                     | 22 (15%)                    |
| Suicide  | 1 (2%)                     | 0                          | 0                          | 0                          | 1                           |

This is a modification of Table 2.7.4-29 in the summary of clinical safety

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## 7.1.5 Common Adverse Events

### 7.1.5.1 Eliciting adverse events data in the development program

In the Prestwick-sponsored studies, which include the clinical pharmacology studies, and the 2 double-blind studies as well as the open-label extensions of those studies, adverse events (AEs) were assessed by recording complaints provided in response to general open-ended questions regarding the patient's state of being. In studies 103,004, 103,005 and 103,007, telephone contacts were made providing an additional opportunity for assessing AEs.

During the Cambridge sponsored clinical pharmacology studies, AEs were assessed in a similar manner as the Prestwick studies.

During protocol H-721 conducted under Dr. Joseph Jankovic's IND 16,161 (which comprise study TBZ 103,011 and the Baylor non-chorea report), adverse events were assessed at follow-up visits (2-4 times/year) in addition to periodic telephone contacts. Patients were instructed to inform the study staff/PI of any adverse events. Since this protocol was initiated in 1979, no separate coding of SAEs was done at the original study visit. The study report states that the PI classified AEs "consistent with current information on the drug that require no intervention" as not severe and AEs "consistent with the current information on the drug which require intervention such as reduction of drug dosage" as severe (p. 36 of 233, in section 5.3.5.2).

*[Reviewer's note: While all AEs were supposed to be classified as either severe or not severe, it is not clear how adverse events which were not consistent with current information on the drug were coded given the definitions in the protocols.]*

*The recording of voluntary complaints in response to indirect questioning such as "How are you" or "Is anything bothering you?" and/or the dependence on spontaneous reports of AE may have under-ascertained complaints that occurred since patients may not recall a complaint that resolved or lessened in intensity by the time of contact.*

*It is not known which adverse events, experienced, other than dysphagia, were not incorporated into the database due to the PI's determination that these were disease related and not drug-related.]*

### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All studies used either COSTART, MedDRA or WHO classifications to code adverse events (see table below).

The COSTART dictionary codes "parkinsonism" as extrapyramidal syndrome but since this is a known idiosyncrasy of the system, it has been accounted for both in this review and in the submitted ISS.

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The sponsor's categorization of events appears to have been appropriate for the most part. There were instances where the AE WHO term was more or less specific than the actual reported AE term. This situation also arose when the AE preferred term was compared to the actual AE term. I have tried to impose logic on the categorization, choosing the more specific and accurate term when changes seemed appropriate. I have noted those changes when made.

Table 9: Classifications used to code adverse events

|   | Dictionary |        |     |
|---|------------|--------|-----|
|   | COSTART    | MedDRA | WHO |
| <b>Clinical Pharmacology Studies</b>              |            |        |     |
| TBZ 202,001                                       |            | X      |     |
| TBZ 103,003                                       | X          |        |     |
| TBZ 104,012                                       | X          |        |     |
| Cambridge Study 1700114 (both A and B)            | X          |        |     |
| TBZ 203,008                                       |            | X      |     |
| TBZ 203,009                                       |            | X      |     |
| TBZ 203,010                                       |            | X      |     |
| <b>Prestwick-Sponsored Studies in HD Patients</b> |            |        |     |
| TBZ 103,004                                       |            |        | X   |
| TBZ 103,005                                       |            |        | X   |
| TBZ 103,006                                       |            |        | X   |
| TBZ 103,007                                       |            |        | X   |
| <b>Baylor College of Medicine Analyses</b>        |            |        |     |
| TBZ 103,011                                       | X          |        |     |
| Baylor Non-Chorea Report                          |            |        | X   |

### 7.1.5.3 Incidence of common adverse events

Study TBZ 103,004 was the only pure placebo-controlled trial in tetrabenazine-naïve patients so it was used to develop the table seen below. This trial enrolled 84 people: 54 were treated with tetrabenazine; 30 were treated with placebo. Patients had a titration period of up to 7 weeks followed by a 5 week maintenance period on their "best dose."

*[Reviewer's note: On March 2, 2006 we were notified that a DSI investigation revealed that Dr. Jankovic did not report increased dysphagia in a number of patients due to his belief that the dysphagia was related to the underlying disease. It is not known which other adverse events experienced were not incorporated into the database due to the PI's determination that these were disease related and not drug-related. Dr. Jankovic did not enroll patients into Study 103, 004.]*

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Table 10: incidence of common adverse events in placebo-controlled trial TBZ103,004

| AE WHO term                             | Tetrabenazine<br>N=54 | Placebo<br>N=30 |
|---|-----------------------|-----------------|
| <b>Psychiatric disorders</b>            |                       |                 |
| Insomnia                                | 14 (26%)              | 0               |
| Agitation                               | 8 (15%)               | 0               |
| Anxiety                                 | 8 (15%)               | 1 (3%)          |
| Depression                              | 8 (15%)               | 0               |
| Irritability                            | 5 (9%)                | 1 (3%)          |
| Apathy                                  | 3 (6%)                | 0               |
| Anorexia                                | 3 (6%)                | 0               |
| Aggression                              | 2 (4%)                | 0               |
| Confusion                               | 2 (4%)                | 0               |
| Obsessive compulsive behavior           | 2 (4%)                | 1 (3%)          |
| Emotional lability                      | 1 (2%)                | 0               |
| Psychosis                               | 1 (2%)                | 0               |
| Suicidal ideation*                      | 1 (2%)                | 0               |
| Amnesia                                 | 1 (2%)                | 0               |
| Impaired concentration                  | 1 (2%)                | 0               |
| <b>Body as a whole disorders</b>        |                       |                 |
| Fatigue                                 | 13 (24%)              | 4               |
| Feeling of warmth                       | 1 (2%)                | 0               |
| Pain                                    | 1 (2%)                | 1 (3%)          |
| <b>Urinary system disorders</b>         |                       |                 |
| Dysuria                                 | 2 (4%)                | 0               |
| Hematuria                               | 1 (2%)                | 0               |
| Urinary tract infection                 | 1 (2%)                | 1 (3%)          |
| Urinary urgency                         | 1 (2%)                | 0               |
| <b>Respiratory system disorders</b>     |                       |                 |
| Upper respiratory tract infection       | 7 (13%)               | 2               |
| Cough                                   | 4 (7%)                | 3               |
| Bronchitis                              | 2 (4%)                | 0               |
| Dyspnea                                 | 2 (4%)                | 0               |
| Crackles (pulmonary edema)              | 1 (2%)                | 0               |
| Bilateral basilar pneumonia             | 1 (2%)                | 0               |
| Pharyngitis                             | 1 (2%)                | 1 (3%)          |
| <b>Musculoskeletal system disorders</b> |                       |                 |
| Back pain                               | 2 (4%)                | 0               |
| Bone fracture-spontaneous               | 1 (2%)                | 1 (3%)          |
| Pain neck/shoulder                      | 1 (2%)                | 0               |
| Myalgia                                 | 1 (2%)                | 0               |

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Table 10 (continued): incidence of common adverse events in trial TBZ103,004

| AE WHO term   | Tetrabenazine<br>N=54 | Placebo<br>N=30 |
|---|-----------------------|-----------------|
| <b>Central and peripheral nervous system disorders</b>                |                       |                 |
| Somnolence (including sedation, drowsiness, lethargy, and sleepiness) | 16 (30%)              | 2 (7%)          |
| Ataxia  | 5 (9%)                | 0               |
| Akathisia   | 5 (9%)                | 0               |
| Headache including migraine   | 3 (6%)                | 1 (3%)          |
| Bradykinesia  | 3 (6%)                | 0               |
| Abnormal gait   | 3 (6%)                | 0               |
| Dizziness   | 2 (4%)                | 1 (3%)          |
| Hypertonia  | 2 (4%)                | 0               |
| Chorea-increased  | 1 (2%)                | 0               |
| Subarachnoid hemorrhage**   | 1 (2%)                | 0               |
| Dysarthria  | 1 (2%)                | 1 (3%)          |
| Slowed speech***  | 1 (2%)                | 0               |
| Dystonia  | 1 (2%)                | 1 (3%)          |
| Abnormal coordination   | 1 (2%)                | 0               |
| Clumsiness  | 1 (2%)                | 0               |
| Parkinsonism  | 1 (2%)                | 0               |
| <b>Gastrointestinal system disorders</b>                              |                       |                 |
| Nausea  | 9 (17%)               | 0               |
| Diarrhea  | 4 (7%)                | 3 (10%)         |
| Vomiting  | 3 (6%)                | 1 (3%)          |
| Abdominal pain  | 2 (4%)                | 0               |
| Dyspepsia   | 1 (2%)                | 1 (3%)          |
| Dysphagia   | 1 (2%)                | 1 (3%)          |
| Gastroesophageal reflux   | 1 (2%)                | 0               |
| Constipation  | 1 (2%)                | 0               |
| Mouth ulcers (aphthous and NOS)                                       | 1 (2%)                | 1 (3%)          |
| Parotid duct obstruction  | 1 (2%)                | 0               |
| Salivation  | 1 (2%)                | 0               |
| Mouth dry   | 1 (2%)                | 0               |
| Melena  | 1 (2%)                | 0               |
| Diverticulitis  | 1 (2%)                | 0               |
| <b>Platelet, bleeding &amp; clotting disorders</b>                    |                       |                 |
| Epistaxis   | 1 (2%)                | 0               |
| <b>Skin and appendages disorders</b>                                  |                       |                 |
| Skin infection  | 1 (2%)                | 0               |
| Skin dryness  | 1 (2%)                | 0               |
| <b>Secondary terms</b>  |                       |                 |
| Fall  | 9 (17%)               | 4 (13%)         |
| Laceration  | 3 (6%)                | 0               |

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Table 10 (continued): incidence of common adverse events in trial TBZ103,004

| AE WHO term                          | Tetrabenazine N=54 | Placebo N=30 |
|--------------------------------------|--------------------|--------------|
| <b>Reproductive system disorders</b> |                    |              |
| Prostatitis                          | 1 (2%)             | 0            |
| <b>Vision disorders</b>              |                    |              |
| Burning sensation-eyes               | 1 (2%)             | 0            |
| Conjunctivitis                       | 1 (2%)             | 1 (3%)       |
| <b>Neoplasm</b>                      |                    |              |
| Infiltrating ductal carcinoma-female | 1 (2%)             | 0            |

\* The actual AE WHO term was "thought of self harm", I have replaced that with the reported AE as I felt it was a clearer representation of the issue.

\*\*This was categorized under vascular disorders/extracardiac. I have changed that as I think it would be more appropriately placed in this body system.

\*\*\*The actual WHO term was speech disorder. I have used the AE reported term for clarity.

There was no overlap between the people who reported restlessness and those who reported akathisia.

There were three people who complained of insomnia who also noted daytime somnolence and/or sedation (447-201, 447-236 and 447-240).

#### 7.1.5.4 Common adverse event tables

The sponsor submitted one long-term placebo controlled trial. The adverse event data from that 12-week trial is depicted in the table below. The data below describes all of the adverse events which were described in 2 or more patients.

Those adverse events which were only described in a single patient may be found in section 7.1.6.

The table showing the most frequent AE reported in patients treated across all clinical studies may be found in appendix 10.4

Table 11: Adverse events reported in more than 1 patient during a placebo-controlled trial

| Body System           | AE Preferred Term                             | Tetrabenazine N=54<br>n (%) | Placebo N=30<br>N (%) |
|-----------------------|---|-----------------------------|-----------------------|
| PSYCHIATRIC DISORDERS | Insomnia                                      | 14 (26%)                    | -                     |
|                       | Depression                                    | 8 (15%)                     | -                     |
|                       | Sedation/somnolence/drowsiness/<br>sleepiness | 17 (31%)                    | -                     |
|                       | Restlessness Aggravated                       | 7 (13%)                     | -                     |
|                       | Irritability                                  | 5 (9%)                      | 1 (3%)                |
|                       | Anxiety                                       | 8 (15%)                     | 1 (3%)                |
|                       | Appetite Decreased                            | 2 (4%)                      | -                     |
|                       | Obsessive Reaction                            | 2 (4%)                      | -                     |

Table 11: (continued) Adverse events reported in more than 1 patient during a placebo-controlled trial

| Body System                            | AE Preferred Term                 | Tetrabenazine N=54<br>n (%) | Placebo N=30<br>N (%) |
|--|-----------------------------------|-----------------------------|-----------------------|
| CENTRAL & PERIPHERAL<br>NERVOUS SYSTEM | Akathisia                         | 5 (9%)                      | -                     |
|  | Balance Difficulty                | 5 (9%)                      | -                     |
|  | Bradykinesia                      | 4 (8%)                      | -                     |
|  | Dizziness                         | 2 (4%)                      | -                     |
|  | Dysarthria                        | 2 (4%)                      | -                     |
|  | Gait Unsteady                     | 2 (4%)                      | -                     |
|  | Headache including migraine       | 3 (6%)                      | 1 (3%)                |
| GASTROINTESTINAL<br>SYSTEM DISORDERS   | Nausea                            | 7 (13%)                     | 2 (7%)                |
|  | Diarrhea                          | 4 (8%)                      | 3 (10%)               |
|  | Vomiting                          | 3 (6%)                      | 1 (3%)                |
| BODY AS A WHOLE –<br>GENERAL           | Fatigue                           | 12 (22%)                    | 4 (13%)               |
| SECONDARY TERMS                        | Fall                              | 8 (15%)                     | 4 (13%)               |
|  | Inflicted Injury                  | 3 (6%)                      | -                     |
| RESPIRATORY SYSTEM<br>DISORDERS        | Upper Respiratory Tract Infection | 6 (11%)                     | 2 (7%)                |
|  | Coughing                          | 3 (6%)                      | 3 (10%)               |
|  | Breath Shortness                  | 2 (4%)                      | -                     |
|  | Bronchitis                        | 2 (4%)                      | -                     |
| PLATELET,<br>BLEEDING & CLOTTING       | Bruise                            | 7 (13%)                     | 2 (7%)                |
| URINARY SYSTEM<br>DISORDERS            | Dysuria                           | 2 (4%)                      | -                     |

#### 7.1.5.5 Identifying common and drug-related adverse events

The adverse events that may be considered common and drug related are the following:

- Insomnia
- Sedation or somnolence
- Depression
- Fatigue
- Anxiety
- Aggravated restlessness

Although the small placebo-controlled study TBZ 103, 004 did not show evidence of parkinsonism as a frequently reported adverse event, the sponsor acknowledges that this is a drug associated adverse event and convened a committee to suggest a titration regimen to avoid this adverse event which appears to be related to the rate of upward dose titration.

#### 7.1.6 Less Common Adverse Events

The adverse events which occurred as isolated events in patients receiving active drug during placebo-controlled trial TBZ 103,004 are listed below:

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Psychiatric disorders

Aggressiveness, agitation, anger, anorexia, anxiety attack, apathy, bradyphrenia, compulsive reaction, impaired concentration, confusion, disorientation, abnormal dreaming, emotional lability, forgetfulness, lethargy, listlessness, nervousness, paranoid reaction, psychosis, thoughts of self-harm, withdrawal from social contacts

Central and Peripheral Nervous system

Chorea, clumsiness, abnormal coordination, dystonia, lightheaded feeling, muscle stiffness, muscle tone increased, speech disorder, walking difficulty

Gastrointestinal system disorders

Abdominal discomfort, blood in stool, constipation, abdominal cramp, diverticulitis, dysphagia, gastroesophageal reflux, dry mouth, obstructed parotid duct, salivation, upset stomach, oral aphthous ulcers

Body as a whole

Back pain, suicide, feeling of warmth, hot flushes, pain, sacro-iliac pain, temperature elevation

Secondary terms

Eye burns

Respiratory system disorders

Crackles, pneumonia, rhinitis, sinusitis, sore throat

Platelet, bleeding, clotting disorders

Epistaxis

Urinary system disorders

Bladder infection, blood in urine, urinary tract infection, urinary urgency

Skin and appendages disorders

Skin dry, skin infection

Musculoskeletal system disorders

Spontaneous bone fracture, muscle ache

Vision disorders

Conjunctivitis

Vascular (extracardiac disorders)

Subarachnoid hemorrhage

Reproductive system disorders

Prostatitis, female breast pain

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Neoplasms  
Carcinoma

While the placebo-controlled trial TBZ 103,004 enrolled fewer than 100 patients, the sponsor provided safety data from a staggered withdrawal trial, clinical pharmacology trials and open label trials as well as information from the literature. That data is presented in tabular form in appendix.

### 7.1.7 Laboratory Findings

#### 7.1.7.1 Overview of laboratory testing in the development program

Assessments of hematology values, and serum chemistry values were performed before and after dosing in all Prestwick-sponsored studies.

Assessments of urinalysis values were performed before and after dosing in all Prestwick-sponsored clinical pharmacology studies.

The scheduled laboratory testing from all studies is shown below in table form. This table, which was reproduced from the submission, divided the development plan into types of study.

Table 12: Schedule of laboratory testing

| Study   | Laboratory Collection Schedule  |
|---|---|
| <b>Double-blind, Placebo-controlled Clinical Pharmacology Studies</b>       |   |
| TBZ 202,001 (single-dose, crossover, 7-day washout)                         | Screening (Days -28 to -1)<br>For each dosing period: Prior to treatment (Day -1) and End of treatment (Day 2 = one day following dosing)   |
| TBZ 203,008 (4-day repeated-dose, 2 period crossover with 7-10 day washout) | Screening (Days -28 to -2)<br>For each dosing period: Prior to treatment (Day -1) and End of treatment (Day 5 = one day following dosing)<br>Follow-up (7-10 days following last dose in second treatment period) |
| <b>Open-label Clinical Pharmacology Studies</b>                             |   |
| TBZ 103,003 (2-period crossover single-dose study with 7-day washout)       | Screening (Days -21 to -1)<br>End of treatment (Day 9 = day following last dose in the second dosing period)  |
| TBZ 104,012 (2-period crossover single-dose study with 7-day washout)       | Screening (Days -21 to -1)<br>End of treatment (Day 9 = day following last dose in second dosing period)  |
| CL 170014A (2-period crossover single dose study with 7-day washout)        | Screening (Days -21 to -1)<br>Follow-up (5-7 days following the last dose in the second dosing period)  |
| CL 170014B (5-day repeated dose study)                                      | Screening (Days -21 to -1)<br>Follow-up (6-8 days following the last dose)  |

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Table 12 (continued): Schedule of laboratory testing

| Study  | Laboratory Collection Schedule  |
|--|---|
| TBZ 203,009 (4-day repeated dose with 6-day digoxin run-in phase)    | Screening (Days -28 to -2) Prior to treatment (Day -1 = day prior to initiation of digoxin and Day 6 = day prior to initiation of TBZ) End of treatment (Day 12 = 2 days following last dose of TBZ) Follow-up (9-12 days following last dose of TBZ) |
| TBZ 203-010 (single-dose, liver impairment study) Ongoing            | Screening (Days -21 to -2) Prior to treatment (Day -1) End of treatment (Day 3 = 2 days following last dose) Follow-up (8-16 days following last dose)  |
| <b>Double-blind Clinical Studies</b>                                 |   |
| TBZ 103,004 (randomized, placebo-controlled)                         | Screening (Days -14 to -1) On treatment (Weeks 9 and 12)  |
| TBZ 103,005 (placebo-controlled, staggered withdrawal)               | On treatment screening (up to 14 days prior to study drug withdrawal) End of Study (Study Day 5 = patients were withdrawn after their morning dose on Day 1, their evening dose on Day 2, or their evening dose on Day 4)                             |
| <b>Open-label Long-Term Clinical Studies</b>                         |   |
| TBZ 103,006 (follow-on to TBZ 103,005) <sup>a</sup>                  | Baseline enrollment (Day 5 of study TBZ 103,005 or within 2 weeks of completion of study TBZ 103,005) On treatment (Weeks 24 and 48)  |
| TBZ 103,007 (follow-on to TBZ 103,004) <sup>b</sup> Ongoing          | Day 0 (following ≥ 1 weeks washout from TBZ 103,004) On treatment (Weeks 24 and 48) Not yet completed (Months 12, 16, and 20) Interim Follow-up (Week 25 for those not continuing after Week 24)  |
| <b>Baylor Study</b>  |   |
| H-721 (which includes TBZ 103, 011 and the Baylor non-chorea report) | Laboratory data were not routinely collected  |

Table 1-27 from ISS

The variety of study designs led to a variety of definition of baseline and post treatment assessment as may be seen in the table below:

Table 13: definition for testing schedules

| Study Number | Protocol Title   | "Baseline" versus "Post-Treatment" Laboratory Values Selected for Mean Change Analysis                                    |
|--------------|--|---|
| TBZ 202,001  | Effect of a single administration of tetrabenazine on prolactin blood levels. A randomized, double-blind, placebo-controlled, cross-over study in healthy volunteers                       | Day -1 versus Day 2 laboratory values for each dosing period (first arm of the crossover and second arm of the crossover) |
| TBZ 103,003  | An Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period Study of the Effect of Food on the Absorption of Tetrabenazine in Healthy Adult Volunteers                              | Screening visit laboratory values versus end of study laboratory values (Day 9)   |
| TBZ 104,012  | An Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period Study of the Bioequivalence of 12.5 and 25 mg Tetrabenazine Tablets in Healthy Adult Volunteers Under Fasted Conditions | Screening visit laboratory values versus end of study laboratory values (Day 9)   |

Table 13 (continued): definition for testing schedules

| Study Number   | Protocol Title   | "Baseline" versus "Post-Treatment" Laboratory Values Selected for Mean Change Analysis                                     |
|----------------|--|--|
| CL 1700114 (A) | An Open Label Study to Establish the Bioavailability of Tetrabenazine and Dihydro-tetrabenazine Comprising a Single Dose Two-Way Cross-Over Study Comparing 12.5 and 50 mg Doses                         | Screening visit laboratory values versus Follow-up visit laboratory values   |
| TBZ 203,008    | Effect of Single and Repeated Doses of Tetrabenazine on Serum and Plasma Concentrations of Various Hormones. A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Male Volunteers | Day -1 versus Day 5 laboratory values for each dosing period (first arm of the crossover and second arm of the crossover)  |
| CL 1700114 (B) | An Open Label Study to Establish the Bioavailability of Tetrabenazine and Dihydro-tetrabenazine Comprising a Repeat Dose Study (25 mg) in Healthy Male and Female Subjects                               | Screening visit laboratory values versus Follow-up visit laboratory values   |
| TBZ 203,009    | Study of the Interaction of Tetrabenazine with P-Glycoprotein Based on Digoxin Bioavailability in Healthy Subjects   | Day 6 laboratory values (during digoxin dose) versus Day 12 laboratory values (post-dosing with digoxin and tetrabenazine) |
| TBZ 103,004    | A Randomized, Double-Blind, Placebo Controlled, Study of Tetrabenazine for the Treatment of Huntington's Chorea  | Screening visit laboratory values versus Week 12 visit laboratory values   |
| TBZ 103,005    | A Randomized, Double-Blind, Placebo-Controlled, Staggered Withdrawal Study in Patients with Huntington's Disease Treated with Tetrabenazine  | Screening visit laboratory values versus Day 5 laboratory values   |
| TBZ 103,006    | Open-Label, Up to 80-Week Extension Study of Tetrabenazine for the Treatment of Huntington's Chorea. Follow-On Protocol To Protocol TBZ 103,004  | Day 5 of study TBZ 103,005 or within 2 weeks of completion of study TBZ 103,005 versus Week 48 visit laboratory values     |
| TBZ 103,007    | An Open-Label, 24-Week (subsequently amended to 48 weeks) Treatment Study of Tetrabenazine in Patients with Huntington's Disease. Follow-On to Protocol TBZ 103,005                                      | Day 0 visit ( $\geq 1$ week washout from TBZ 103,004) versus Week 48 visit laboratory values                               |

Table 1-30 from the ISS

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The only placebo-controlled trial of more than 5 days was TBZ103, 004 so the comparisons of drug and control groups are based upon the results from that study.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

##### 7.1.7.3.1 Analyses focused on measures of central tendency

##### Hematology

There were no significant changes in the hematology values when the active study group was compared to the placebo group in the double-blind phase of the trial.

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Table 14: Mean change from baseline in patients treated for up to 12 weeks

| Laboratory Parameter        | Tetrabenazine<br>(N=54) | Placebo<br>(N=30) |
|-----------------------------|-------------------------|-------------------|
| Hemoglobin (g/dL)           | -0.17                   | 0.07              |
| WBC (x 10 <sup>3</sup> /μL) | -0.20                   | -0.41             |
| Neutrophils                 | -0.12                   | -0.27             |
| Lymphocytes                 | -0.31                   | -0.14             |
| Monocytes                   | -0.01                   | -0.03             |
| Eosinophils                 | 0.00                    | 0.02              |
| Basophils                   | 0.00                    | 0.00              |
| Platelets                   | 26.38                   | -3.76             |

Modification of table 11-14 from the ISS

There were no significant changes in the hematology values when the active study group was evaluated in the maintenance phase of the trial.

Table 15: Mean change from baseline in patients treated for up to 48 weeks

| Laboratory Parameter        | Week 24<br>(N=72) | Week 48<br>(N=54) |
|-----------------------------|-------------------|-------------------|
| Hemoglobin (g/dL)           | 0.13              | -0.18             |
| WBC (x 10 <sup>3</sup> /μL) | 0.18              | -0.12             |
| Neutrophils                 | 0.22              | 0.01              |
| Lymphocytes                 | -0.03             | -0.04             |
| Monocytes                   | 0.01              | -0.03             |
| Eosinophils                 | 0.03              | -0.04             |
| Basophils                   | 0.00              | -0.01             |
| Platelets                   | 17.4              | 14.0              |

Modification of table 11-14 from the ISS

### Chemistry

With the exception of the elevation in ALT value, there were no significant changes in the serum chemistries when the active study group was compared to the placebo group.

Table 16: Mean change from baseline in patients treated for up to 12 weeks

| Laboratory Parameter | Tetrabenazine<br>(N=54) | Placebo<br>(N=30) |
|----------------------|-------------------------|-------------------|
| Serum Sodium         | 0.41 (2.78)             | 0.25 (3.77)       |
| Serum Potassium      | 0.07 (0.42)             | -0.04 (0.36)      |
| Serum Chloride       | -0.76 (3.00)            | -0.49 (3.50)      |
| Serum Glucose        | 0.28 (14.62)            | -4.17 (14.02)     |
| Urea Nitrogen        | -0.64 (3.96)            | -0.17 (3.19)      |
| Creatinine           | 0.03 (0.11)             | -0.02 (0.14)      |
| AST                  | 2.04 (13.20)            | 1.32 (5.60)       |
| ALT                  | 12.18 (41.39)           | 1.97 (7.93)       |
| LDH                  | -6.96 (32.87)           | -5.49 (20.30)     |
| GGT                  | 2.32 (9.68)             | 1.10 (6.16)       |
| Total Bilirubin      | 0.00 (0.24)             | -0.00 (0.12)      |

Table 2.7.4-30, TBZ 103,004 study report

Table 16 (continued): Mean change from baseline in patients treated for up to 12 weeks

| Laboratory Parameter | Tetrabenazine<br>(N=54) | Placebo<br>(N=30) |
|----------------------|-------------------------|-------------------|
| Alkaline Phosphatase | -0.01 (26.91)           | -0.12 (10.90)     |
| Calcium (EDTA)       | -0.11 (0.42)            | -0.01 (0.41)      |
| Serum Uric Acid      | 0.06 (0.74)             | -0.11 (0.61)      |
| Total Protein        | -0.14 (0.43)            | -0.04 (0.48)      |
| Albumin              | -0.17 (0.30)            | -0.09 (0.30)      |
| Cholesterol          | 5.63 (35.24)            | 13.14 (29.90)     |
| HDL Cholesterol      | -3.49 (7.28)            | -2.17 (8.68)      |
| Triglycerides        | -18.48 (88.35)          | -26.83 (49.72)    |

Table 2.7.4-30, TBZ 103,004 study report

#### 7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

##### Hematology

Three subjects, all of whom were receiving tetrabenazine, were noted to have alterations in their leukocytes. These abnormalities resolved with continued treatment.

##### Chemistry

Three patients, all of whom had received tetrabenazine, had abnormal liver function tests:

- Patient 447-214 ALT 145 IU/L
- Patient 447-243 ALT 447 IU/L
- Patient 447-265 ALT 174 IU/L, AST 147 IU/L

With the exception of the ALT of 447 IU/L which was considered a Grade III abnormality ( 5.1 to 20 times normal ), the other findings were grade II abnormalities ( 2.5 to 5 times normal ) on a scale which ranged from Grade 0 (normal) to Grade IV (markedly abnormal).

#### 7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Patient 747-237, who was being treated for HD associated chorea, had tetrabenazine discontinued due to the finding of elevated ALT.

#### 7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were performed.

#### 7.1.7.5 Special assessments

During the preclinical studies, female rats were noted to have “vaginal mucification, increased incidence of proestrus and mammary gland hyperplasia” which was thought to be secondary to increased serum prolactin concentrations. Since prolactin levels were not measured in that study, it was not possible to make a more definitive comment.

The sponsor performed studies to assess the effect of tetrabenazine on prolactin and other hormones in humans: TBZ 202,001 and 203,008. No female volunteers were enrolled in these studies, “to avoid confounding of study results by the menstrual cycle (ISS, p.830)

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Study 202,001

Six healthy males were enrolled in this double-blind, randomized, placebo-controlled, single-dose crossover study. The dose administered was 12.5 mg of tetrabenazine with a 7 day washout period between drug dosing periods. Serum samples were obtained at 1 and 0.5 hours before the dose and at 1, 1.5, 4, 10 and 24 hours post-dosing.

There was a 2-3 fold increase in serum prolactin after administration of active drug as compared to placebo. The change in serum prolactin concentration remained statistically significant until 10 hours post-dosing.

#### Study 203,008

Twelve healthy males completed this double-blind, randomized, placebo-controlled, single-dose crossover study. Baseline serum samples were obtained on Study Days 1 and 4. Post dosing samples were drawn on Days 1, 3, and 4 at 1, 1.5, 2, 3, and 4 hours post-dosing.

The administration of 25 mg oral tetrabenazine as a single 25/mg/day dose (Days 1 and 4) or as 50mg/day divided b.i.d (days 2 and 3) resulted in increased prolactin levels in healthy male volunteers. No such statistically significant increases were seen in plasma concentrations of adreno-corticotrophic hormone, cortisol, growth hormone, testosterone, arginine vasopressin or thyroid stimulating hormone.

Figure 1: mean plasma concentration of prolactin after oral dosing of tetrabenazine

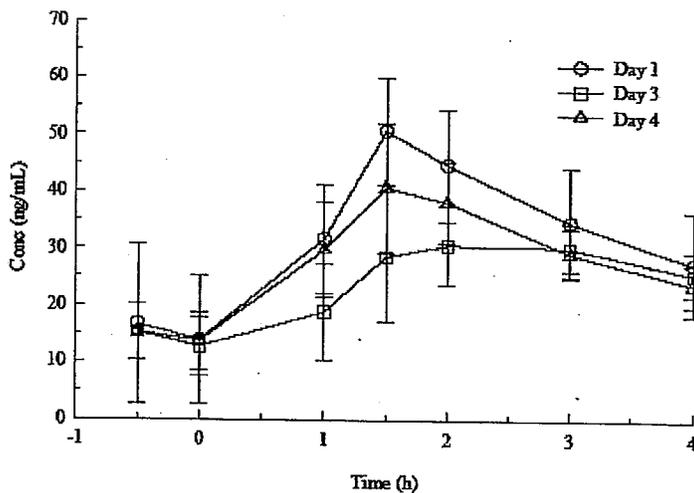


Figure 14-3 from the ISS

The FDA requested that Protocol TBZ 103,004 be amended to evaluate prolactin levels in the enrolled patients. Thirteen patients were enrolled subsequent to the amendment so data is available from only 15% of the patients enrolled in the study: 10 of whom received active drug; 3 of whom received placebo.

The submitted data comes from blood draws done at the beginning of the maintenance period that is week 9. Most of the doses were at the middle-high end of the maximally allowed 100 mg/day: 100 mg (4 patients); 87.5 mg (1 patient); 50 mg (4 patients). A single 56 year old woman was receiving 37.5 mg/day.

*[Reviewer’s note: It is difficult to make assessments based upon a small sample. As may be seen in the table below, in the placebo group we are presented with data from a 38 year old man, a 29 year old woman and a 59 year old woman; this constitutes an imbalance in gender and probable imbalance in menstrual status. In the active group, only 40% of the data comes from women and judging by the age range, it is probable that 3 were post- or peri-menopausal. We are not given baseline prolactin levels or other pertinent information such as menstrual status, and/or oral contraceptive use making the information presented almost uninterpretable.]*

Table 17: Serum prolactin concentrations in Study TBZ 103,004

| Treatment     | Patient ID | Gender | Age | Tetrabenazine Dose at Week 9 (mg/day) | Prolactin Serum Concentration (ng/ml) |
|---------------|------------|--------|-----|---------------------------------------|---------------------------------------|
| Tetrabenazine | 447-223    | Male   | 62  | 100                                   |                                       |
|               | 447-224    | Male   | 63  | 50                                    |                                       |
|               | 447-228    | Male   | 38  | 50                                    |                                       |
|               | 447-258    | Female | 49  | 100                                   |                                       |
|               | 447-267    | Female | 32  | 50                                    |                                       |
|               | 447-268    | Male   | 51  | 100                                   |                                       |
|               | 447-274    | Male   | 68  | 87.5                                  |                                       |
|               | 447-275    | Male   | 74  | 100                                   |                                       |
|               | 447-279    | Female | 56  | 37.5                                  |                                       |
|               | 447-316    | Female | 44  | 50                                    |                                       |
| Placebo       | 447-247    | Male   | 38  | 0                                     |                                       |
|               | 447-259    | Female | 59  | 0                                     |                                       |
|               | 447-307    | Female | 29  | 0                                     |                                       |

(Table 14-1 from the ISS)

7.1.7.6 Reviewer’s summary

The only laboratory values of note are the liver function tests. While only one patient was discontinued due to an elevation in ALT, elevations were noted in multiple patients. We may wish to consider routine monitoring of liver function tests at least during the first 12 weeks of therapy.

The prolactin results indicate that elevations in prolactin may occur but we are unable to say more than that based upon the scanty data presented in males only.

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 7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Measures of systolic and diastolic blood pressure as well as heart rate were incorporated into all of the Phase I clinical pharmacology studies: TBZ 202,001; TBZ 103,003; TBZ 104, 012; CL1700114; TBZ 203,008; TBZ 203,009.

In four of these studies, patients were evaluated for evidence of orthostatic hypotension (defined as a  $\geq 20$  mm Hg decrease in systolic blood pressure after arising from a supine position and standing for 2 minutes). Body temperature (oral) was measured in all but one of these studies.

In each study a pre-dose time point was used as baseline, in the case of multiple pre-dose measurements the baseline was the measurement which was temporally closest to dosing. In each study a post-dose time point was used for comparison, in the case of multiple post-dose measurements the measurement which was temporally closest to the Cmax was used as the comparison.

Table 18: Schedule for vital sign testing during the clinical pharmacology studies

| Study                   | Day -1 | Pre-dose | Hours post-dose |                |                |   |   |   |   |    |                |
|-------------------------|--------|----------|-----------------|----------------|----------------|---|---|---|---|----|----------------|
|                         |        |          | 0.5             | 1 <sub>a</sub> | 2 <sub>a</sub> | 3 | 4 | 5 | 8 | 12 | 24             |
| TBZ 104,012             |        | X        |                 |                |                |   | X |   | X |    | X              |
| CL 1700114 <sub>b</sub> | X      | X        |                 | X              |                | X |   |   |   |    | X              |
| TBZ 203,008             | X      | X        | X               | X              | X              | X |   | X |   | X  | X <sub>c</sub> |
| TBZ 203,009             | X      | X        |                 |                |                |   |   |   |   | X  |                |
| TBZ 202,001             | X      | X        |                 |                |                |   |   |   |   |    | X              |
| TBZ 103,003             |        | X        |                 |                |                |   |   |   |   |    | X              |

(table 10-2 from the ISS)

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During the Prestwick Phase II-III studies in patients with chorea, vital signs were measured as screening, baseline and during treatment, as shown in the table below:

Table 19: Testing done during the Phase III studies

| Study Number         | Systolic and Diastolic Blood Pressure                |   | Radial Pulse  |   | Body Weight                  |
|----------------------|--|---|---|---|------------------------------|
|                      | Measurement  | Timing  | Measurement   | Timing  |                              |
| TBZ 103,004<br>N=84  | Sitting (n=84)<br>Supine and standing (subset of 19) | Screening;<br>Baseline; Week 1; Week 3; Week 5; Week 7; Week 9; Week 12; Week 13                              | Sitting (n=84)<br>Supine and standing (subset of 19), radial artery | Screening;<br>Baseline; Week 1; Week 3; Week 5; Week 7; Week 9; Week 12; Week 13                              | At baseline and end-of-study |
| TBZ 103,005<br>N=30  | Supine and standing                                  | Screening;<br>Baseline; Day 3; Day 5  | Sitting, radial artery  | Screening;<br>Baseline; Day 3; Day 5  | At baseline and end-of-study |
| TBZ 103,006<br>N=29  | Supine and standing                                  | Baseline; Week 12; Week 24; Week 48   | Sitting, radial artery  | Baseline; Week 12; Week 24; Week 48   | At baseline and end-of-study |
| TBZ 103,007<br>N=75  | Supine and standing                                  | Baseline, Week 2, Week 6, Week 12, Week 24, Week 25, Week 36, Week 48, Week 49, Week 64, Week 80, and Week 81 | Supine and standing, radial artery                                  | Baseline, Week 2, Week 6, Week 12, Week 24, Week 25, Week 36, Week 48, Week 49, Week 64, Week 80, and Week 81 | At baseline and end-of-study |
| TBZ 103,011<br>N=145 | Sitting  | Baseline and return clinic visits   | Sitting, site not specified   | Baseline and return clinic visits   | At baseline and end-of-study |

(Table 1-24 in the ISS)

#### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The sponsor performed analyses of the data from all of the clinical pharmacology studies with the exception of the study done in hepatic impaired patients and controls: study TBZ 203, 010. The sponsor presented mean change values from baseline. The number and percentage of patients with clinically significant abnormal vital signs were calculated (BP systolic  $\geq 180$  or  $\leq 85$  mmHg, BP diastolic  $\geq 115$ , pulse  $\geq 150$  (phase I) or  $\leq 50$  bpm). Additional analyses of measured episodes of orthostatic hypotension were also performed.

The sponsor performed analyses of the data from all of the Phase III studies. The sponsor presented mean change values from baseline. The number and percentage of patients with clinically significant abnormal vital signs were calculated (BP systolic  $\geq 180$  mmHg; BP systolic  $\leq 85$  mmHg; BP diastolic  $\geq 115$  mmHg; heart rate  $\leq 50$  bpm; heart rate  $\geq 120$  bpm).

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The risk for orthostatic hypotension, defined as a  $\geq 20$  mmHg decrease in systolic BP, was evaluated in one of the placebo-controlled studies: Study TBZ 103,004. The effect of abrupt withdrawal of tetrabenazine) on vital sign assessments was evaluated in Study TBZ 103,005.

### 7.1.8.3 Standard analyses and explorations of vital signs data

#### 7.1.8.3.1 *Analyses focused on measures of central tendencies*

##### Phase I trials

The mean changes in systolic blood pressure, diastolic blood pressure and heart rate seen after doses of 12.5 mg to 50 mg of tetrabenazine were minimal with no apparent dose-related trends towards increase or decrease.

##### Phase III trials including open-label extension studies

The mean changes in systolic blood pressure, diastolic blood pressure and heart rate seen were minimal with no apparent dose-related trends towards increase or decrease. No effects on vital signs were seen after abrupt drug discontinuation as occurred in study TBZ 103, 005.

#### 7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

##### Phase I trials

Two patients who were receiving tetrabenazine and digoxin simultaneously (study TBZ 203,009) had systolic blood pressures  $\leq 85$  mmHg. Two subjects on tetrabenazine alone had systolic blood pressures  $\leq 85$  mmHG as compared to a single patient on placebo. No patients in the active group had a diastolic blood pressure reading  $\geq 115$  mmHg though one person receiving placebo did.

Sixteen subjects (14%) of the subjects on tetrabenazine alone and 7 (39%) of the subjects who received placebo had heart rates below 50 beats/minute; the lowest rate was 42 beats/minute. In the digoxin/tetrabenazine combination study, two patients on tetrabenazine alone and three on the combination of medications had heart beats below 50 beats/minute.

One subject on tetrabenazine alone, one subject on digoxin alone and one subject on the combination had heart rates of 120 beats/minute or more.

The only abnormal body temperature which was truly of note was a temperature of 102.3F in subject 1247-123. This subject was found to have an abscess of the right buttock.

*[Reviewer's note: While the vital signs given above met the pre-specified criteria for outliers, for the most part they were not accompanied by clinical symptoms. The abnormal signs resolved without intervention in all patients except the gentleman with the buttock abscess. He received antipyretic treatment. His abscess was probably not related to his use of study drug.]*

Phase III trials including open-label extension studies: TBZ 103,004; 103, 005; 103,006; 103,007

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Two patients, both of whom were receiving placebo, had systolic blood pressures  $\geq 180$  mmHg. Three patients on tetrabenazine had systolic blood pressures  $\leq 85$  mmHG as compared to a single patient on placebo.

Two subjects on tetrabenazine and one subject who received placebo had heart rates equal to 50 beats/minute.

*[Reviewer's note: While the vital signs given above met the pre-specified criteria for outliers, they were not accompanied by clinical symptoms.]*

#### 7.1.8.4 Additional analyses and explorations

During three clinical pharmacology studies, subjects were evaluated for orthostatic hypotension. Of the participants, 7/54 (13%) tetrabenazine treated subjects were found to have orthostatic hypotension as compared to 2/12 (17%) placebo-treated subjects. Six of these subjects had a single episode of orthostatic hypotension at 4 to 24 hours post-dose. One subject (ID 1247-128) had two episodes: 4 hours and 8 hours post-dose.

During Prestwick-sponsored Phase III trial TBZ 103,005, patients were evaluated for changes in vital signs following abrupt drug withdrawal. There was no adverse effect on vital signs noted after drug discontinuation.

A subset of patients (n=23) were evaluated for orthostatic hypotension during Prestwick-sponsored Phase III trial TBZ 103,004. While there were no changes overall, two patients did have evidence of orthostatic hypotension: one who had received tetrabenazine; one who had received placebo. In neither case was the hypotension symptomatic.

#### 7.1.8.5 Literature/postmarketing data

Huang (1976) reported 3 Huntington's disease patients with postural hypotension while on doses ranging from 100-200 mg/day. This finding led to treatment discontinuation in 2 of those patients. The overall reported incidence of postural hypotension in association with tetrabenazine is 1%.

The sponsor provided post-marketing reports from Roche Pharmaceuticals as well as Cambridge laboratories which cover the time period from 1963 to 2004. There were 14 adverse drug reactions reported as cardiovascular during that time:

- Myocardial infarction-6 cases
- Hypotension/postural hypotension-5 cases
- Syncope-2 cases
- Hypertension-1 case
- Congestive heart failure-1 case

The sponsor also provided data from the Cambridge laboratories 2004 PSUR and the UK MCA website (<http://www.yellowcard.gov.uk/daps.html>). The latter contained 2 new cardiovascular ADRs: one myocardial infarction; one instance of cardiomegaly (accessed January 24, 2006).

There is no clear evidence that the use of tetrabenazine is associated with predictable changes in vital sign parameters.

### 7.1.9 Electrocardiograms (ECGs)

#### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were obtained in seven clinical pharmacology trials as well as two double-blind, placebo-controlled efficacy trials (TBZ 103,004 and 103,005).

Qualitative analysis examining the incidence of "normal", "abnormal but not clinically significant" and "abnormal, clinically significant" ECGs was done at the time by the investigators during the trials. A blinded independent cardiologist did a retrospective review of this incidence for two of the Clinical Pharmacology trials: TBZ 203,008 and CL 1700114.

A blinded retrospective quantitative analysis of QTc was done by the investigators on the ECGs performed in Phase I studies TBZ 104, 012 and TBZ 203, 008 and in the Phase III studies TBZ103,004 and TBZ 103, 005.

- Study TBZ 104,012: The analysis was restricted to the ECGs performed immediately pre- and post-dosing, excluding the baseline and end-of-study ECGs. 103 pre- and post-dose ECGs were reviewed by a blinded independent consultant who was responsible for manually measuring the RR and QT intervals. The interval data were further analyzed by the sponsor who calculated corrected QT intervals as well as summary statistics. The pre-dose intervals were averaged to determine a baseline for each period. Change from baseline was averaged for each correction formula.
- Study TBZ 203,008: The analysis was restricted to the ECGs performed immediately pre- and post-dosing, excluding the screening and end-of-study ECGs. 333 pre- and post-dose ECGs were reviewed by a blinded independent consultant who was responsible for manually measuring the RR and QT intervals. The interval data were further analyzed by the sponsor who calculated corrected QT intervals as well as summary statistics. The two pre-dose QT intervals were averaged to determine a baseline for each period. Eleven post-dose ECGs were averaged for comparison to baseline.
- Study TBZ 103,004 and extension study TBZ 103, 007: A single 12-lead ECG was recorded at screening/baseline as well as Weeks 12 and 48. Any clinically significant findings were to be reported as adverse events. 96 pre- and post-dose ECGs were reviewed by a blinded independent consultant who was responsible for manually measuring the RR and QT intervals. The interval data were further analyzed by the sponsor who calculated corrected QT intervals as well as summary statistics. The pre-dose intervals were averaged to determine a baseline for each period. Categorical analyses included listings of patients who had QTc values > 450 ms, and changes from baseline which were greater than or equal to 30 or 60 ms. Individual and summary data were returned to the independent consultant for interpretation.

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- Study TBZ 103,005 and extension study TBZ 103, 006: A single 12-lead ECG was recorded at screening/baseline as well as day 5 and week 24. Any clinically significant findings were to be reported as adverse events. 58 pre- and post-dose ECGs were reviewed by a blinded independent consultant who was responsible for manually measuring the RR and QT intervals. The interval data were further analyzed by the sponsor who calculated corrected QT intervals as well as summary statistics. The pre-dose intervals were averaged to determine a baseline for each period. Categorical analyses included listings of patients who had QTc values > 450 ms, and changes from baseline which were greater than or equal to 30 or 60 ms. Individual and summary data were returned to the independent consultant for interpretation. This was a staggered withdrawal study; on Day 5 13 of the 30 participants had no measurable levels of tetrabenazine and were considered off treatment. Central tendency and categorical analyses were performed for those patients. For the patients with measurable levels of tetrabenazine or its metabolites, descriptive statistics of the pooled data was provided in addition to a categorical analysis of QTc > 450 msec.

#### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Studies TBZ103,004 and TBZ 103, 005 were both placebo-controlled randomized studies in Huntington disease patients so they are the Phase III trials that I have chosen to detail in the results below.

#### 7.1.9.3 Standard analyses and explorations of ECG data

##### Clinical Pharmacology studies (n=7)

Most (84%) of the pre-dose ECGs were interpreted by the investigator as normal; none were deemed abnormal to a clinically significant degree. The interpretation was unchanged following drug exposure; 84% of the pre-dose ECGs were interpreted by the investigator as normal and none were abnormal to a clinically significant degree.

An independent cardiologist reviewed the ECG findings from TBZ 203,008 (a study of repeat dosing in healthy volunteers) and CL 1700114 (which evaluated single oral doses of 50 mg-the highest dose in Phase I studies).

- TBZ 203,008

He found an increase in the number of ECGs which were abnormal but not clinically significant after dosing (5% to 9%); the investigator had reported 6% in this category both pre and post dosing. None of the ECGs were deemed abnormal to a clinically significant degree.

- CL 1700114

He agreed with the investigator; both reported 0% in this category both pre and post dosing. For Part B of the latter study, he found a decrease in the number of ECGs which were abnormal but not clinically significant after dosing (16% to 12%); the investigator had reported 0% in this category both pre and post dosing. None of the ECGs were deemed abnormal to a clinically significant degree.