1. Background

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2. Current application

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

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

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

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

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

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

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

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

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

2.1 Evaluation of akathisia, depression, dysphagia and parkinsonism

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

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

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

	004 N= 54			007 N= 75			006 N= 29			All N=158
	Original NDA	4/10/07 CR		Original NDA	4/10/07 CR		Original NDA	4/10/07 CR		4/10/07 CR
	Sp	Sp	**FDA**	Sp	Sp	**FDA**	Sp	Sp	**FDA**	**FDA**
Akathisia	5	5	**7**[1,2]	11	15	**15**	-	-	**0**[2]	**20***
Parkinsonism	3	5	**8**[3]	2	2	**2**	1	3	**3**	**13**
Depression	8	8	**10**[4]	18	24	**26**[5]	4	9	**10**[5]	**44***
Dysphagia[6]	1	1	**2**[7]	2	3	**6**[8]	2	3	**3**	**11**

N= number of patients randomized to TBZ. Sp= sponsor analysis. [1] Two additional cases of akathisia in 004. [2] Additionally, 3 cases of restlessness in 004 and 2 in 006 are potential cases of akathisia. [3] Includes one case of "stiffness when walking", one "coordination abnormal, balance difficulty" that improved with dose reduction and one case of bradykinesia that was not in the AE listing. [4]Includes one patient who was depressed before committing suicide but did not report the AE to the investigator and one patient who was not listed in the AE dataset but started mirtazapine for depression (as per dataset of concomitant medications). [5] Includes patients not listed in AE dataset whose antidepressant medication was initiated or changed for an indication of depression (2 in 007 and 1 in 006). [6] One case of dysphagia occurred on placebo in study 004. [7] Includes 1 case of choking. [8] Includes 3 cases of choking. *Some patients had more than one event. Source: Table 9 of Dr. McNeil's March 15, 2006 review of original NDA application; AE listings and datasets in the February 2007 Complete Response; UH file for study 004 submitted September 2005.

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

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

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

2.1.1. Akathisia

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

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

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

Of note, a case coded as restlessness in the adverse event listings of study 004, was listed as akathisia among the comments in the UH file (a file that includes UHDRS scores) submitted with the original application in September 2005 (subject 447-236). The event reappeared in study 007 and this time it was coded as akathisia. Another patient who was reported to have sedation and depression in the adverse event listings, was reported to have mild akathisia in the UH file of September 2005 (447-267). Additionally, one

patient with restlessness/agitation had a BARNES score of 4 (consistent with significant akathisia). On the other hand, several patients with an AE of akathisia had a BARNES score of 0 (see Appendix 2).

> *Comment: As per the August 1, 2007 response to an FDA informational request, the sponsor clarified that the neurologist's conclusions were based on the AE listings. The sponsor reported that they are confident that adverse event information in the CRFs is accurately reflected in the databases and AE listings, and that no verbatim terms were miscoded for studies 004, 006 and 007. However, if akathisia was incorrectly recorded as restlessness in the CRF, it would appear as restlessness in the listings.*
>
> *In the absence of a more specific description of the adverse event, based solely on the listings and the analysis of BARNES scores, it is challenging to differentiate pure motor restlessness from true akathisia. In my opinion all cases that include the term restlessness should be considered potential cases of drug-induced akathisia.*
>
> *On December 4, 2007, in response to the FDA request of additional information on the patients with restlessness, the sponsor acknowledged that based on the BARNES scores, all cases of restlessness were in fact consistent with akathisia. Therefore, a total of 5+2+3= 10 patients had akathisia in study 004, as compared to zero in the placebo group.*

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

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

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

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

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

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

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

As per the sponsor analysis presented in the Complete Response, twenty patients taking TBZ developed akathisia (5 in 004 and 15 in 007); none on placebo and none in study 006 developed akathisia. As per my analysis - that includes the two cases of akathisia listed in the UH file - a total of 20 patients had akathisia in studies 004, 007 and 006, including two patients who had events in both, 004 and 007 (ID# 236 and ID# 248). Four of these AEs were severe. As per the December 4, 2007 sponsor's communication, there would be three additional cases of restlessness that should have been accounted as akathisia.

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

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

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

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

ID	AE onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])					
	Rel day	Dose		Base line	After AE	At week 12	At week 24	At week 48	At week 80
747-239	25	150	Dose reduced / None / Recovered on Relative Day 89	20	8 (125)	9 (62.5)	9 (62.5)	13 (62.5)	13 (50)
747-245	142	75	Dose reduced [5]/ multiple meds[6] / Ongoing at study end. Pat d/c Day 153 due to consent withdrawal. Akathisia resolved after 4 mo. (also had depression)	17	NA[7]	14 (62.5)	14 (62.5)	NA[7]	NA
747-247	113	37.5	Drug discontinued on Day 114 / None / Ongoing at study end. Pat d/c due to depression and akathisia. Patient was lost to follow up after 1 week in 007.	14	10 (37.5)	7 (62.5)	7 (62.5)	10 (37.5)	NA
747-248	163	50	Drug discontinued on Day 175/ Seroquel 25 mg started Day 175/ Ongoing at study end. Pat d/c on Day 175 due to akathisia and exclusionary med. Final BARNES scores= 3.	15	16 (50)	10 (50)	16 (50)	NA	NA
747-267	8	37.5	None / None /Recovered on Relative Day 39.. Pat d/c on Day 459 due to obsessive reaction and depression.	21	17 (37.5)	13 (62.5)	7 (50)	12 (50)	NA
747-272	267	137.5	Drug stopped for akathisia on Day 280/ None/ Pt d/c due to moving out of state (last dose: Day 280)5, 7 (This patient also had depression) Recovered on Relative Day 332.	16	11 (137.5)	10 (125)	18 (125)	11 (137) (Day 280)	NA
747-273	32	87.5	Dose reduced/Alprazolam 0.25 mg PRN added/ Intensity reduced to mild on Day 60	15	18 (100)	14 (112)	13 (87.5)	13 (87.5)	NA
	80	125	Dose reduced/none/recovered on day 88. Pt d/c due to site unable to continue protocol past week 48.						
747-287	62	87.5	None/none/recovered on rel day 69	10	10 (175)	4 (200)	1 (150)	18 (150)	25 (75)

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

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

Not included in Table 4 is one case of restlessness/agitation (ID# 747-263) coincident with worsening chorea and insomnia on day 563 & 564 while on the 12.5 mg /day dose during the washout period. This was clearly not a case of drug-induced akathisia.

As per the AE listings of study 006, there were two cases of restlessness and no cases of akathisia in this study. It is unclear whether they underwent dose reduction or not; one resolved within 2 months (647-429), and one did not resolve (647-242). It is somewhat interesting that no cases of akathisia were reported in this single center study. Based on the rate of akathisia/restlessness in studies 004 and 007, one would expect to see at least four cases of akathisia in 006.

- Analysis of response of akathisia/restlessness to dose reduction

A summary of the course of the 27 cases of akathisia and restlessness (10 in 004, 15 in 007 and 2 in 006) (in 25 patients) is presented in Table 5.

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

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

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

In this table, patients who had an event that resolved in 004 and relapsed in 007 are counted twice. The asterisk indicates patients initially coded as having restlessness, and later acknowledged by the sponsor to have akathisia.

Summary of akathisia:

Akathisia is a known AE associated with the use of dopamine antagonists. There were seven cases of akathisia in study 004 (13%) (including one patient mentioned to have akathisia in one file [called "UH" file, submitted on September 2005] but listed as having restlessness in the AEs file, and one patient noted to have mild akathisia in the UH file but not listed in the AEs file). Including the term restlessness, there would be 10 cases of akathisia/ restlessness in 004 (19%). Altogether, there were 22 cases of akathisia in 20 out of 111 patients (20 %) enrolled in the Prestwick-sponsored studies (7 in 004, 15 in 007 and none in 006). Four of these cases were severe. Including the cases of restlessness that the sponsor acknowledged that were akathisia, there would be 27 cases of akathisia in 25 patients.

- **Was akathisia dose related?**

The data suggest that akathisia was dose related but was not easily controlled with dose reduction. The median dose at onset of the first event of akathisia/restlessness in 004 was 75 mg/day (range 50 to 100). The median time to onset was 48 days (range 19 to 59). No cases of akathisia/restlessness were seen at doses < 50 mg/day in study 004, however, there were three cases at doses < 50 mg/day in study 007 (one of whom had been on placebo in study 004). The median dose at onset in 007 was 87.5 mg/day (range 37.5 to 200) mg daily. The final dose among patients who had developed akathisia in study 004 was 12.5 to 87.5 mg daily and in study 007 was 12.5 to 125 mg daily.

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

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

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

Not always. There appears to have been a problem either in terms of deciding whether the observed AEs were treatment-emergent akathisia, or in the coding process. One case of akathisia was coded as restlessness in the AE listing and as akathisia in another file; one case was recorded in the UH file but not transferred to the AE listing). Some cases recorded under the verbatim term of "restlessness" were coded in the AE listings under the WHO term "akathisia" and others were not. Akathisia and restlessness were generally considered probably or possibly related to study drug. However, several cases did not undergo dose reduction. It could be that the investigators did not think of the possibility that the adverse event could get better with dose reduction or that they chose to tolerate some degree of akathisia in order to improve chorea.

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

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

> *Comment: The sponsor has proposed a RiskMAP to ensure appropriate titration to reduce the risk of "restlessness." Restlessness is not an AE that is usually associated with a RisMAP. Whether in a RiskMAP or in labeling, I believe it is important to make clear that akathisia is an expected adverse event (known to occur with dopamine antagonists) that might be controlled with dose reduction but sometimes requires discontinuation.*

2.1.2. Depression/worsening depression and suicidality

Depression and suicidality stand out as the most concerning adverse events associated with TBZ use. A total of 51 events of depression/worsening depression occurred in 44 patients enrolled in the Prestwick sponsored studies (44/111, 40%). Most cases were mild to moderate. Six of the 51 cases of depression/worsening depression were severe.

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

placebo (0/30). In addition to the patient who committed suicide (447-271), one had suicidal ideation (474-213). The sponsor has acknowledged that these two cases should have been included in their analyses of depression.

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

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

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

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

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

ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])			
	Rel. Day	Dose		Base line[1]	After AE	At week 7	At week 12
447-206[2]	4	25	None / Continued Celexa 20 mg from entry/ Ongoing when patient prematurely d/c due to subarachnoid hemorrhage. HAM-D one week after last dose was 5. Depression resolved one month after drug d/c.	14	8 (25)	NA	NA
447-228	62	50	None/ Re-start Paxil 40 mg on Day 65 (unclear why had been d/c) / recovered on day 85.[3]	11	6 (50)	8 (50)	8 (50)
447-229	82	100	None/ None / Recovered after washout on Day 92. (No prior hx of depression.)	14	15 (100)	14 (87.5)	15 (100)
447-231	24	62.5	Dose reduced (also had bradykinesia)/Continued Prozac 20 mg from entry/ Recovered on Day 40	19	7 (50)	9 (50)	12 12.5)[4]
447-244	50	37.5	None / Started Paxil 12.5 mg / Recovered after washout on Day 91	12	11 (37.5)	11 37,5)	10 37.5)
447-251	31	75	Dose Reduced / Increased Paxil from 20 to 40 mg on Day 36 / Recovered Day 62	10	3 (75)	2 (50)	2 (12.5)[3]
447-267	51	62.5	Dose reduced / Continued Paxil 40 mg from entry/ Recovered on Relative Day 58. Patient also had mild akathisia.[3] He later attempted suicide during extension study 007.	19	14 (50)	14 (50)	8 (50)
447-274[4]	7	37.5	None / Stopped Trazadone 200 mg on Day 16, restarted Trazadone (100 → 250) on Day 20 / Recovered on Relative Day 33	12	12 (37.5)	8 (87.5)	8 (62.5)
447-271	*50*	*87.5*	*None/No hx of depression but Hx of suicidal ideation. Patient committed suicide. Retrospective diagnosis of depression.*	*22*	*NA*	*16 (87.5)*	*NA*
447-213	*69*	*12.5*	*None/ No hx of depression. Suicidal ideation listed in AE dataset. Dose had been reduced due to akathisia and later d/c due to paranoid reaction & thoughts of self harm. As per concomitant medication dataset, mirtazapine dose was started for depression on day 69, and increased on day 78 Outcome of depression is unknown.*	*19*	*?*	*10 (100)*	*NA*

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

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

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

Tables of the cases of depression/worsening depression in studies 007 and 006 (with a format similar to Table 6) are presented in Appendix 3 and 4 respectively, of this review. Summaries of the findings are as follows:

- In study 007, 26 out of 75 (35%) patients had depression/worsening depression (seven of whom had no prior history of depression). One patient who had presented an AE of depression that resolved in study 004, attempted suicide in study 007 (ID# 747-267).

  Of the 26 cases of depression, 24 had a reported AE of depression/worsening depression and two had a change in antidepressant regimen (antidepressant started, added, dose increased, or switched) for an indication of depression (n=2, ID# 747-314 [Trazodone on day 399] and ID# 747-225 [Zoloft on day 586 for OCD/depression]) even though there was no report of depression in the AE listing.

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

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

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

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

2.1.2.1 Discussion about depression and suicidality

In addition to one patient who committed suicide (271) and one with suicidal ideation in 004 (213), one patient who had depression in 004 attempted suicide in 007 (747-267) and two had suicidal ideation (647-430 and 747-262). Additionally, a suicidal gesture (00058

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

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

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

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

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

The FDA reviewer conducted additional analyses at baseline for the following Behavioral Assessment questions within the UHDRS:

- Question 25 A: Frequency of Depressed mood

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

- Question 26 A: Low self steem/guilt

The possible choices for these two questions are 0= never; 1= seldom, < once a week; 2= sometimes, at least once a week; 3= frequently, several times a week; 4= very frequently, all the time.

Thirteen patients in the TBZ group (24%) and 5 in the placebo group (17%), responded had a score of ≥ 1 for question 25A. Twelve patients in the TBZ group (22%) and 5 in the placebo group (17%) had a score ≥ 1 for question 26A.

- Question 28 A: Suicidal thoughts. The possible choices to this question are:

0= not thinking about suicide or self harm
1= seldom thinking about sucide, 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 sucide, sometimes for days and weeks on end

All patients in study 004 scored 0 in this question at entry.

-Question 39: "Does the participant require pharmacotherapy for depression?"

The response to this question was "yes" for 50% of TBZ patients and 47% of placebo patients. It is unclear why there is a discrepancy between this response and the number of patients taking antidepressant therapy as per the concomitant medication listings.

Table 7. Baseline measures of depression in Study 004

Baseline measure of depression	TBZ (N=54)	Placebo (N=30)
HAM-D score[1] Mean (SD), range	4.5 (3.4), 0-14	5.1 (3.9), 0-14
Patients treated with antidepressants at study entry[2]	30 (56%)	20 (67%)
Patients with past history of depression	34 (63%)	14 (47%)
Patients with Yes on UHDRS 38 at study entry[3]	8 (15%)	2 (7%)
Patients with Yes on UHDRS 39 at study entry[4]	27 (50%)	14 (47%)
Question 25A: depressed mood	13 (24%)	12 (22%)
Question 28 A & B: suicidal thoughts	0%	0%

[1]HAM-D: 17-item Hamilton Depression Scale; [2]Participants taking more than one medication are counted for each medication in the table. [3]UHDRS: Unified Huntington's Disease Rating Scale: "Does the examiner believe that the patient is depressed?." [4]Question 39 of UHDRS: "Does the participant require pharmacotherapy for depression?" Source: UH file submitted 9/05.

The baseline characteristics regarding the risk of depression do not appear to be different enough to explain the dramatic difference in the incidence of depression and suicidality between the TBZ and placebo groups in study 004. In this study, seven of the 34 patients with prior history of depression developed worsening depression (21%), as compared to none of the 14 patients with history of depression randomized to placebo (0%).

Given the known pharmacologic effect of TBZ (serotonin/norepinephrine depletion, although to a lesser degree than dopamine depletion), an increase in the rate of depression in patients taking TBZ as compared to placebo is not unexpected.

- Dose and time at which patient developed depression

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

The median time at onset of the first event of depression/worsening depression in study 004 was 50 days (4 to 82 days). The median time to onset in study 007 was approximately 2 ½ months; however, some of these patients had been on TBZ and some had been on placebo in study 004. In study 006, the median time to onset of first event was 158 days. Therefore, the risk of depression may go beyond the first 12 weeks of treatment.

- Response to dose reduction/medical treatment

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

Table 8.a. Course of cases of depression in studies 004, 007 and 006 (n=51[1]) in 44 patients (all on TBZ)

TBZ Dose reduction alone	**7 (14 %)**	
Resolved while on TBZ (1-2 weeks to 3 months)	7	*447*-231[3], 267[4], *747*- 231[3], 237[5], 239, 266[3], 291[3]
Change in antidepressant regimen[2] alone	**25 (49%)**	
Resolved while on TBZ treatment (within 1 week to 5 months after AE onset)	**10**	*447*-228, 274, *747*-217, 230, 252[3,4], 272[5], 288[3], 316, 647-441
Resolved after study completion (after washout)	**1**	*447*-244
Ongoing at study completion or early withdrawal (no data on recovery)	**10**	*747*-203, 207, 208, 209[3], 210, 266[3], 279, *647*-426, 428, 430
Unknown course[6]	**4**	*447*-213, *747*-225, 314 & *647*-403
TBZ dose reduction + change in antidepressant regimen	**11 (22%)**	
Resolved while on TBZ [2] (1 week-7 months)	**4**	*474*-251, *747*-243[7], 209[3] & 288[3]
Ongoing at study completion or early withdrawal (no data on recovery)	7	474-213, *747*-223, 245, 247 262, 267, 313, *647*-402
Neither TBZ dose reduction nor change in regimen	**8 (16 %)**	
Resolved while on TBZ treatment (3-5 months after AE onset)	**3**	*647*-401, 418 & 419
Resolved after study completion (after washout)	**3**	*447*-229, 206, *747*-291[3,8],
Ongoing at study completion or early withdrawal (no data on recovery)	**2**	*447*-271, *647*-414

[1] In 45 patients. Events from patients who recovered and relapsed are counted as separate cases. [2] Antidepressant regimen change: increase dose, start, add or switch to new antidepressant. [3]Subjects 447-231,747-209, 266, 288, 291 and 747-252 had events that resolved within 1 to 7 months and reappeared 3 to 7 months later, receiving more than one treatment approach. [4] 747-252 had to separate episodes, both treated with antidepressant dose change. [5] Later withdrew because of moving out of state. [6]Change in antidepressant regimen recorded in medication file but not in AE dataset. Duration and outcome for these events are unknown. [7] Later this patient withdrew early withdrawal because of increased transaminases. [8]Onset on day 210, recovery was on day 596; unclear if still on treatment or not.

Of the 51 cases of depression/ worsening depression evaluated in this review, 14 % underwent TBZ dose reduction alone, 49 % underwent change in antidepressant regimen alone, 22 % underwent both and 16 % neither (numbers rounded, no decimal). Approximately half of the cases (24/51) resolved with dose reduction and or medical treatment, and the time to resolution was 1 to 7 months.

Seven patients with depression/worsening depression that resolved with either dose reduction or medical treatment, relapsed 3 to 7 months later. Only two of these patients recovered while on TBZ. The onset, duration, treatment approach and outcome are presented in the following table:

Table 8.b. Patients with recurrent depression in studies 004 & 007

ID	1st episode			2nd episode		
	Onset (day/dose)	Action	Resol (day)	Onset (day/dose)	Action	Resol (day)
447-231*	24 (62.5)	DR	40	24 (62.5)	DR	32
447-267*	51 (62.5)	DR	58	125 (62.5)	DR+AD	WD[1]
747-209	145 (62.5)	DR+AD	359	535 (25)	AD	Ongoing
747-252	2 (12.5)	AD	44	183 (25)	AD	237
747-266	56 (75)	AD	169	337 (50)	AD	Ongoing
747-288	50 (50)	DR+AD	182	355 (50)	AD	580[2]
747-291	42 (87.5)	DR	71	210 (75)	None	596[2]

DR= Dose reduction. AD= change in antidepressant regimen. WD= withdrawal. * Second episode occurred in study 007. [1]TBZ WD on D 463 because of worsening depression. Psychosis with depressive features started on D 466. Event resolved on day 473. [2] Resolved after Week 80 (2-3 weeks after study completion date).

Approximately half of the patients who developed depression/worsening depression (23/45) had an ongoing AE of depression at the end of the studies and one fourth had withdrawn for various reasons (mostly adverse event of depression). Of the patients who withdrew early (n=11),[7] all but two (447-271 and 447-213, the patient who committed suicide and the patient with suicidal ideation, respectively) had a prior history of depression before entering the studies.

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

Comment: TBZ dose reduction and/or change in antidepressant regimen appeared to be useful in the management of TBZ-associated depression. However, less than 50%

[7] Reasons for withdrawal among patients who had depression were as follows (one of each): Depression + suicidal thoughts (7-262); depression + psychosis/suicide attempt (7-267); paranoid reaction + suicidal ideation (4-213); delusional suicidal ideation (6-430); depression + akathisia (7-247); exclusionary medication + chorea (7-203); consent withdrawal (7-245), caregiver preference (7-223); fall and subarachnoid hemorrhage (4-206); Suicide (4-271); elevated transaminases (7-243).

resolved with dose reduction/treatment/ discontinuation. This analysis includes patients in the open label studies. Without a control arm it is impossible to distinguish whether these cases are part of the underlying disease or are drug related.

In my opinion, the most appropriate approach to managing these patients is stopping TBZ. That would be the only way to determine whether the depression/worsening depression is drug related or not. Stopping TBZ should be particularly done if the patient is going to start a new antidepressant treatment that is a CYP2D6 inhibitor.

Some experts recommend concomitant use of an antidepressant for prevention of depression/worsening depression in patients taking TBZ. However, the efficacy and safety of this approach has not been adequately studied.

- Evaluation of HAM-D SCORES over time

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

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

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

Source: Table 62, study 004 CSR.

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

- Comparison of the rates of depression in patients with HD

I estimated the rate of depression in the Prestwick development program using the number of events found in my review as the numerator, and exposure data provided by the sponsor as the denominator (See Table 10) and compared these rates to the rate of depression in the CARE HD study. CARE-HD is a non-Prestwick study in 347 patients with HD followed for up to 3 years, with the following treatment arms: Remacemide, Co Q_{10}, placebo, Remacemide+ Co Q_{10}. (The sponsor has used the CARE HD study to estimate the natural course of the functional outcomes and the rate of dysphagia in a

population of HD patients with similar clinical characteristics to those enrolled in the Prestwick's studies). The rate of depression among HD patients treated with TBZ across studies was 2-7 fold higher than that of HD patients not treated with TBZ in the CARE HD study.

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

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

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

Summary about depression/worsening depression:

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

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

Altogether, 51 events of depression/worsening depression occurred in 44 out of the 111 patients enrolled in Prestwick-sponsored TBZ studies (40%). Six of these cases were severe. The reporting rate of depression in the Prestwick-sponsored studies was 2 to 7-fold higher than in the CARE-HD study, a large study in patients with HD, receiving treatments other than TBZ.

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

In general, depression was recognized by the investigators as potential TBZ-related AE. TBZ dose reduction was done in less than half of the cases and medical treatment was instituted in approximately 75% of cases. Six patients with a reported AE of depression/worsening depression had neither dose reduction nor medical treatment. Investigators may have preferred to tolerate mild depression over to decreasing the dose of TBZ and losing therapeutic benefit. However, in four of 51 cases, investigators initiated or increased doses of antidepressants for an indication of depression, without recording depression as an AE (one case in 004, three in 007 and one in 006). Occasionally, depression was considered by the investigator to be unlikely to be related to study drug (e.g. 447-228 and 244).

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

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

Of the 51 cases identified in studies 004, 006 and 007, approximately 14% underwent dose reduction alone, 49% underwent medical treatment alone and 22% underwent both. Overall, 47% had resolution of the event with either dose reduction/change in antidepressant regimen or no intervention. The outcome is unknown for four patients who were recorded to have a change in antidepressant regimen for an indication of depression but not recorded to have an AE of depression.

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

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

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

Upon development of an adverse event of depression with or without dose reduction, chorea scores varied. Some patients had a small increase in chorea scores but others stayed the same as before the event or continued to improve. Of the 3 patients with depression who underwent dose reduction in 004, all three recovered and had a drop in

TCS of ≥ 3 points; however, one relapsed and attempted suicide in 007. Of the 12 patients with dose reduction because of depression in study 007, seven recovered and only two achieved a drop in TCS ≥ 3 by week 80.

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

The current proposal does not adequately address this issue, as the risk of depression might increase earlier than 4 weeks and extend beyond 12 weeks. Additionally, it is difficult to assess depression over the phone, and it is unclear who will be deciding whether titration should be continued or not. Further discussions with the sponsor about an amended RiskMAP is warranted.

2.1.3. Dysphagia

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

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

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

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

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

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

APPEARS THIS WAY
ON ORIGINAL

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

Pat ID	AE Onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])					
				Base line	After AE	At week			
	Rel. Day	Dose				12	24	48	80
747-241	32	100	Dose reduced /None/ Recovered on Day 32. Patient completed chose to discontinue because of mild lethargy.	10	4 (87.5)	2 (87.5)	4 (87.5)	4 (50)	NA
747-249	335	75	Dose reduced /None/ Recovered on Day 358 (Week 48 visit).	10	6 (37.5)	3 (87.5)	2 87.5)	6 (37.5)	4 (25)
747-257	198	50	None / None / Ongoing. Hospitalized, feeding tube, pneumonia.	21	13 (50)	18 (50)	8 (50)	9 (50)	7 (50)
747-242	*?*	*150*	*None (single episode of choking)*	?	*?*	? (150)	? (150)	? (100)	? (150)
747-265	*210*	*87.5*	*None. Choking started 7 months into TBZ treatment; no resolution patient also had worsening chorea*	?	*?*	? (87.5)	? (87.5)	? (87.5)	? (75)
747-273	*?*	*87.5*	*None/ This patient had several episodes of choking and saliva increased, starting on day 6. Dose was titrated down and up for other AEs (akathisia) (up to 125 mg at some point)*	*?*	*?*	*? (112.5)*	*? (87.5)*	? (87.5)	? NA[1]

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

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

Table 13. Patients who developed Dysphagia in study 006

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

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

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

- Review of Dysphagia in study 011

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

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

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

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

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

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

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

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

- Evaluation of Dysphagia Scores in study 004

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

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

Table 14. Dysphagia scores in study 004

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

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

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

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

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

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

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

- Reporting rate of dysphagia with TBZ

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

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

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

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

As per the sponsor's analysis, in study 004 the rate of dysphagia was higher in the placebo group as compared to the TBZ-treated group. As per my analysis, including the case of choking, the rates of dysphagia are about the same for TBZ and placebo groups. The rate of dysphagia in patients taking TBZ in all Prestwick sponsored studies was higher than in the CARE HD study.

Summary of dysphagia:

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

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

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

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

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

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

Not always. A total of 11 cases of dysphagia/choking were identified by the FDA reviewer in the Prestwick sponsored studies (2 on TBZ, one on placebo in study 004; 6 in 007 and 3 in 006). Three cases of choking in 007 were not included in the sponsor's analyses of dysphagia. None of the cases of choking underwent dose reduction. Four of the cases of dysphagia underwent dose reduction and resolved (although it took up to 6 months to resolve for one case). Because of the concern raised in the AE letter of March 2004, I specifically evaluated potential AEs of dysphagia in 011. Dysphagia was rarely considered to be a drug related AE in study 011. Only 2 out of 21 cases of dysphagia/choking were considered to be possibly or probably related to study drug and only 3 underwent dose reduction. Moreover, there were four cases of aspiration pneumonia likely related to dysphagia without recorded dysphagia as an AE in these patients.

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

> *Comment: The sponsor acknowledges that dysphagia is a component of HD that it can also be caused by medications that reduce dopaminergic activity. However, the sponsor concludes that TBZ is not associated with an increased rate of dysphagia, and even suggests that it could improve it. Overall, it appears that dysphagia was not consistently recognized as a potential TBZ-related event by the investigators in this development program. There appears to be an under-ascertainment of this adverse event in this application. The data in this application do not rule out an increased risk of dysphagia in patients treated with TBZ. Moreover, the rate of dysphagia in the Prestwick program is higher than among patients with HD not receiving TBZ.*

2.1.4. Parkinsonism

By using an expanded definition of parkinsonism that included bradykinesia, parkinsonism and extrapyramidal disorder, the sponsor identified a total of five cases in study 004, two in 007 and three in 006. By reviewing the datasets for study 004, I identified three more cases, making a total of 8 cases of parkinsonism in study 004 (ID#

447-231, 447-233 and 447-240). I did not identify new cases from studies 006 and 007. Tables 17, 18 and 19 summarize the cases of parkinsonism in study 004, 007 and 006, respectively. The cases that I identified are presented in *Italics.*

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

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

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

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

The sponsor does not acknowledge the three cases identified by the FDA as cases of parkinsonism. Their position is that these were cases of worsening of the

underlying disease. This discrepancy points to the difficulty in distinguishing parkinsonism and other abnormal movements from an underlying disease in which one of the major manifestations – and in this case, the primary endpoint- is an abnormal movement.

Not included in Table 17, are three cases that presented balance difficulties that could have been symptoms of parkinsonism, however, they could also be symptoms of worsening chorea. Without other AE terms that suggest parkinsonism or response to dose reduction, I am not including these patients in my analyses:

- Patient 447-223 developed "balance unsteady" and "gait unsteady" on day 38 of TBZ treatment, at the 75 mg dose. The gait/balance unsteady is listed as lasting one and a half months and resolving without dose reduction. These terms are consistent with but not specific of parkinsonism. This patient showed improvement in chorea scores at the end of the study, therefore the balance difficulty was unlikely to be due to worsening chorea. He had been recently started on carbamazepine for "agitation/anger." Unsteadiness is listed under the ADVERSE REACTIONS section of the carbamazepine labeling. Since the events resolved without dose reduction it may be incorrect to attribute to TBZ.
- Patient 447-237 presented "unsteady feet/balance difficulty" (listed as "ataxia" in the study dataset), on day # 45 of TBZ treatment, along with impaired concentration, insomnia, fatigue and "eyes burn". It is unclear if the AE resolved. This patient showed improvement in chorea scores at the end of the study (day #80), therefore the balance difficulty on day #45 is unlikely to be due to worsening chorea.
- Patient 447-313 reported prominent incoordination and balance loss while on TBZ on 1/8/04 (as per UHDRS file submitted September 2005). This AE is not listed in the Adverse Event listing. Listed AEs include akathisia, paranoid reaction and suicidal ideation.

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

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

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

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

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

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

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

Table 19. Patients who developed parkinsonism in study 006

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

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

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

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

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

- Response of parkinsonism to dose reduction

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

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

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

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

Summary about parkinsonism:

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

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

In general, investigators considered parkinsonism-related events as probably or possibly related to study drug, however, they often chose not to reduce dosing in order to decrease

chorea scores. As per the sponsor response of December 4, 2007, the three additional cases of parkinsonism identified by the FDA in study 004 had been considered by the investigator as worsening of the underlying disease. This observation points to the difficulty in identifying parkinsonism from the underlying disease. Dose was reduced in 9 out of 13 cases, however, in three of the cases dose reduction was made not because of parkinsonism, but because of other AEs. In other cases, despite the lack of resolution of the AE with dose reduction, some investigators preferred not to reduce the dose further (ID# 447-203).

- **Was parkinsonism dose-related?**

Yes. The mean and median time to onset of the first event in study 004 was 29 days (range 17 to 50 days). Mean and median dose at the onset of the first event in study 004 was 66 and 62.5 mg/day, respectively. All cases occurred at doses of 50 mg/day or above (except for a couple of patients who had recurrence of the event at doses of 25 and 37.5 mg/day). Parkinsonism also occurred in the long term open label studies, at doses of 25 to 200 mg daily.

Of the nine cases that underwent dose reduction, four cases resolved (1 day to 3 months later), one resolved without dose reduction (within 4 weeks) and four cases did not resolve. Two cases resolved after stopping TBZ during washout. The outcome of the patient who did not enter 007 and the one who was lost to FU in 007 is unknown. The final dose among patients who had presented parkinsonism in study 004 was 25-50 mg daily.

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

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

2.1.5 Analysis of Extrapyramidal Symptoms (EPS)

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

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

	TBZ (25-100 mg/day) N=54 n (%)	Placebo N=30 n (%)
Akathisia/restlessness[1]	10	-
Akathisia	7	
Restlessness	3	
Bradykinesia[2]	4	-
Clumsiness/balance difficulty[3]	1	-
Dystonia[4]	1	1 (3.3)
Gait unsteady/balance difficulty[5]	2	-
Parkinsonism	1	-
Stiffness when walking[6]	1	-
Unsteady feet/Balance difficulty[7]	1	-
Incoordination/balance loss[8]	1	-
All	21 (38.8)	1 (3.3)

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

All four cases of balance difficulty occurred in the TBZ-treated group. If we do not take into account the cases of "balance difficulty", we still have 17 cases (31.5 %) of potential EPS in study 004.

Comment: EPS is a common adverse reaction observed with dopamine antagonist therapy, and therefore, not unexpected to occur with TBZ. Approximately one third of patients developed abnormal movements consistent with EPS in the TBZ group, as compared to 3% on placebo. EPS appeared to be dose-related (most cases occurred at doses >50 mg) and to respond (partially or completely) to dose reduction or discontinuation (although it might have taken several months).

HD patients have an impaired subjective experience of chorea.[8] I share the concerns of one expert who states "It would seem inappropriate to treat an aspect of motor disorder of which the patient is unaware with agents that may worsen those aspects of motor dysfunction for which the patient does have awareness and are associated with greater functional disability [bradykinesia]".[9] This

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

application lacks the patient's perspective on the beneficial effects of TBZ. Some patients may prefer to have "mild akathisia" or "mild bradykinesia" in lieu of severe chorea, but others may not.

2.1.6 Other safety issues

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

2.1.6.1 Sedation

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

Sedation was clearly dose-related and resolved in all cases with dose reduction. Most of these patients maintained a drop in TCS of ≥ 3 despite dose reduction to doses ≤ 50 mg/day.

Sedation may in part explain why patients appeared to have a small worsening in functional and cognitive assessments despite the improvement in Total Chorea Scores.

Impairment of cognition is a recognized AE of dopamine antagonists and should be included in the WARNINGS & PRECAUTIONS section of the label. ——

2.1.6.2 Falls/traumatic injury

Chorea of the trunk and legs along with poor postural control cause gait instability and increases the risk of falls and serious injury; however, many patients with HD may have a gait abnormality that is separate from chorea. Unexplained falling is common even early in the illness[10] By controlling chorea, TBZ could potentially reduce the incidence of falls and serious injuries. On the other hand, since TBZ is associated with sedation, parkinsonism and akathisia, it could potentially increase the risk of falls and injury by these mechanisms. Evaluation of Gait Scores in study 004 (which was one of the secondary efficacy endpoints) showed no benefit on gait for TBZ as compared to placebo.

[10] Cudkowicz M. et al. Chapter 23, The Neurology of Huntington's Disease. Movement Disorders in Neurology and Psychiatry. Second Edition. Blackwell Science Inc., 1999.

Evaluation of the adverse event listing in study 004 shows that the total number of traumatic injuries in the TBZ group is 10 (18.5 %) as compared to 4 (13%) in the placebo group. (This analysis includes two patients in the TBZ group who had adverse events consistent with traumatic injuries, without a reported fall.) Moreover, three patients in the TBZ group reported several separate fall episodes throughout the study (up to five separate falls in one of these patients). No patients on placebo reported multiple falls. Falls and traumatic injuries did not appear to be dose-related (see Table 22).

Table 22. Patients with adverse events suggestive of traumatic injury in study 004[1]

Tetrabenazine (N=54) n=10 (18.5 %)[1]			Placebo (N=30) n= 4 (13%)[2]	
ID# Adverse event	Onset (day #)	TBZ dose (mg/day)	ID# Adverse event	Onset (day#)
206- Fall & subarachnoid hemorrhage	13	25	209- Fall & wrist sprain	15
224- Fall & head & face injury[3]	38 & 85	50	241- Fall & chipped bone left ankle	42
228- Fall & knee & arm bruises[4]	8 & 29	25-37.5	273- Fall	17
229- Fall[5]	13	37.5	298- Fall & facial bruise	30
238- Fall & scalp laceration	82	75		
251- Fall & black eye	17	50		
258 - Fall & eye ecchymosis	8	37.5		
274- Fall & sacral pain[6]	6 & 96	25-87.5		
207- Laceration of head[7]	35	25		
264- Ankle fracture	81	50		

[1]In addition one patient who had a traumatic injury because he was assaulted is not included in this table. [2]In addition one patient on placebo who fell off his bike is not included in this table. [3]Reported three different fall episodes at this dose. Dose had been reduced from 62.5 for parkinsonism. [4]Reported two different fall episodes. [5] Increased chorea and truncal dystonia. [6]Reported five different fall episodes throughout study 004. He had depression and apathy. [7] Dose had been recently reduced from 62.5 mg/day for parkinsonism.

Therefore, in the small placebo-controlled study, TBZ did not reduce the risk of traumatic injuries as compared to placebo. They did not seem to be dose related, as several events occurred at the 25 mg/day dose. In study 007, 22 out of the 75 subjects had one or more falls. Most of these falls occurred in patients with reported AE of sedation, akathisia or depression and two were associated with worsening chorea. I tried to correlate the AE of falls with changes in blood pressure, but this analysis was not possible

2.1.6.3 Tardive dyskinesia (TD)

TD is characterized by involuntary movements of the tongue, jaw, trunk, or extremities in association with the long term use of neuroleptic medications. No cases of TD were reported in studies 004, 006 and 007, however, one patient was reported to have "uncontrollable movements of the mouth and tongue" in study 011 (103-011-529). TD is most commonly associated with long-term, cumulative doses of dopamine antagonists. I see no reason why TBZ should be spared from been associated with TD. The most likely explanation for the lack of clear cases of TD is the small size of the available database. In

my opinion, ——————————— , this AE should be included in the ——— section of labeling.[11]

2.1.6.4 Hyperprolactinemia

TBZ is associated with increased prolactin levels as compared to placebo. This issue was raised in Dr. McNeil's first cycle review. She was concerned about the risk of osteoporosis. Hyperprolactinemia is known to occur with most antipsychotics and not unexpected to occur with a dopamine depleting agent. This AE should be included in labeling.

2.1.6.5 Neuroleptic Malignant Syndrome (NMS)

NMS, characterized by hyperpyrexia, muscle rigidity, altered mental status and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia), sometimes with rhabdomyolysis and acute renal failure in association with TBZ, has been reported in the literature [12] and as postmarketing reports to non-US regulatory agencies. This information should be included in the WARNINGS & PRECAUTIONS section of labeling.

2.1.6.6 Lack of data on concomitant use of antipsychotic medications

HD is known to be associated with behavioral and psychiatric disorders. None of the Prestwick sponsored studies allowed use of antipsychotic medications. A few patients used antipsychotics concomitantly with TBZ in the Baylor Chorea studies. However, because data on AE were collected retrospectively and at least 10% of patients were lost to follow up, this database is not as reliable as the Prestwick-sponsored studies. ———

2.1.6.7 QTc prolongation

A prolongation of the QTc interval (study 015, a Thorough QTc study) was identified by the Clinical Pharmacology reviewer (Sally Yasuda, Ph.D.). Her findings are summarized as follows:

"The maximum time-matched placebo-adjusted change from baseline in the QTcI was 3.6 and 7.7 msec with an upper confidence interval of 6.2 and 10.4 msec for TBZ 25 mg and TBZ 50 mg, respectively," however, the study had not reached the maximum possible exposure to TBZ or its metabolites.

The positive TQT study indicates that tetrabenazine has a *possible* proarrhythmic effect.

[11] There were two cases of TD in the Nitoman postmarketing database (submitted 11/27/07)
[12] Ossemann et al. tetrabenazine as a cause of neuroleptic malignant syndrome Mov Disord 1996;11(1).

The magnitude of QT prolongation is at the threshold of regulatory concern. In general, there is a qualitative relationship between QT prolongation and the risk of TdP. Data on drugs that prolong the mean QT/QTc interval by 5-20 ms are inconclusive. We have no information on the effects of the 100 mg dose, with or without concomitant CYP2D6 inhibition, on the QT interval. Thus, the dose-response relationship is not fully explored (nor has there been an exploration in patients with risk factors).

The safety database is too small to be very elucidating regarding tetrabenazine's proarrhythmic potential. There has been a report of sudden death and three reports of cardiac arrest in the postmarketing database, but information from these cases is limited, and the denominator is unknown.

The QTc Review Team recommends full disclosure of the QTc effects of TBZ. The executive summary from the review conducted by the QTc Review Team is presented in Appendix 7 of this review. I recommend that these effects be prominently presented such as in [redacted]

2.1.6.8 Drug Interaction issue

Study 107,018 evaluated the effect of CYP2D6 inhibition in the presence of paroxetine, a strong CYP2D6 inhibitor. For α-HTBZ there was an approximate 1.3x increase in Cmax and an approximate 3.2x increase in AUCinf after administration of repeated doses of paroxetine. In addition, there was an approximate 2x increase in the elimination half-life (from approximately 7 to approximately 14 hours) in the presence of a strong CYP2D6 inhibitor. For β-HTBZ the Cmax was approximately 2.4x greater and the AUCinf was approximately 9x greater after administration of paroxetine compared to no CYP2D6 inhibitor. The β-HTBZ elimination half-life was approximately 3x greater after CYP2D6 inhibition than when TBZ was given alone (approximately 4.5 vs. approximately 13.5 hrs). In addition, in the absence of CYP2D6 inhibition, exposure to α-HTBZ is generally greater than to β-HTBZ (median ratio of 3). Following CYP2D6 inhibition with paroxetine, the median ratio is 1.

These observations raise concerns as patients taking strong CYP2D6 inhibitors or patients who are CYP2D6 poor metabolizers will have substantially increased exposure to α- and β-HTBZ. This issue should be addressed in labeling.

2.1.7 Postmarketing safety

The latest PSUR submitted to non-US regulatory authorities on December 19, 2005, covers the period form June 2000 to October 2005. The adverse event profile of TBZ in this PSUR is consistent to what have been observed in the clinical studies reviewed as part of this NDA application. However, data submitted as part of the background package to the AC held on December 6, 2007, included additional information (Appendix

8 of this review). Of note, the table of postmarketing reports includes 12 deaths, three cardiac arrests, seven cases of Neuroleptic Malignant Syndrome (NMS), and 10 reports of hypotension/orthostatic hypotension. Unfortunately the sponsor has not been able to provide an estimate of the exposure of TBZ over the last 40 years. At the FDA request, the sponsor submitted the listings that support the table included in their AC package. A summary of the findings is presented in Appendix 9

Comment: Overall, the safety profile of TBZ looks very similar to those of the antipsychotics, with associated adverse events such as EPS, NMS, hyperprolactinemia, etc.

Of note, TBZ was initially developed as an antipsychotic but development for this indication stopped when other dopamine antagonists with a better safety profile were developed for the indication. The current database has comparative efficacy or safety data with newer antipsychotics. It is possible that TBZ may have a worse safety profile than newer antipsychotics currently used off-label for the treatment of chorea. In fact, there is an old abstract comparing the efficacy and safety of TBZ and haloperidol in patients with HD. In this study TBZ was associated with superior efficacy than haloperidol, but more patients developed depression and parkinsonism.

Major concerns associated with the use of TBZ are EPS, depression/suicidality, and potential arrhythmogenic effects. The association with dysphagia at the doses proposed for approval (up to 100 mg/day) is unclear. A significant issue is that some of the events associated with TBZ may be difficult to distinguish from the underlying disease.

2.2 Evaluation of dose-response relationship and benefit/risk assessment

An extensive review of the efficacy and safety of TBZ was conducted by Drs. Carole Davis and Elizabeth McNeil during the first review cycle. As mentioned in previous reviews, evaluation of the safety of TBZ is hampered by the following factors:

1. There is only one placebo-controlled study of 12 weeks duration (study 004); the other placebo-controlled study was a five day withdrawal study and contributes little to the evaluation of safety.
2. Some of the adverse reactions associated with TBZ are also symptoms of or difficult to distinguish from the underlying disease (e.g. depression, dysphagia, bradykinesia)

The sponsor recommends starting TBZ at the 12.5 mg twice a day dose with slow titration up over 12 weeks – which is a different schedule than the one used in the clinical program-, to a maximum effect or to a maximum dose of 100 mg day.

Published literature over the past 40 years of TBZ use reports wide inter individual differences in the doses that cause dose-limiting side effects, as well as the "best dose", with a narrow difference between the dose that is effective and the dose associated with intolerable toxicity. Prior to study initiation, the sponsor had determined from a review of the literature that the common AEs related to monoamine depletion were thought to be dose-related and could be remedied by judicious dose titration. Events which were

thought to fall in this category were sedation, depression, parkinsonism, akathisia, anxiety, nervousness, insomnia, irritability, confusion, increased salivation, nausea, vomiting, dizziness an diaphoresis. As per the sponsor's assessment, the risk for dysphagia was increased with doses greater than 100 mg/day. [13]

The studies in this application used a flexible dose design with dose titration to maximum drug effect or presence of adverse events (to a maximum dose of 100 mg/day in study 004, and 200 mg/day in 006 and 007). The flexible study design and the lack of a systematic approach in the presence of AEs makes very difficult to interpret the dose-response relationship, particularly in terms of toxicity in this NDA. Despite these difficulties, there seems to be evidence for a dose-response in terms of both, efficacy and toxicity (see sections 2.1.1 to 2.1.3).

2.2.1 Exploratory analyses of efficacy

An analysis by the FDA Office of Biometrics indicates a significant dose-response relationship in terms of efficacy. For details about the methodology of this analysis the reader is referred to Dr. Gubburu's review of March 20, 2006. Additional analyses suggest that patients with the highest TCS at entry were the ones to benefit the most from TBZ (Table 23). This finding was corroborated in Dr. Bhattaram's review of November, 2007.

Table 23. Adjusted mean (±SD) in Change from baseline in Total Chorea Scores (TCS) by baseline TCS.[1]

Total Chorea Score at baseline	TBZ (N=54)		Placebo (N=30)	
	N (%)	Adjusted mean change	N (%)	Adjusted mean change
>14	22 (41)	-7.35 ±0.98	13 (43)	-2.99 ± 1.25
≤ 14	32 (59)	-2.98 ± 0.67	17 (57)	-0.73 ± 0.86

[1]Nominal p value <0.05 for both analyses. Source: Table 19, study 004, Sponsor's Complete Study Report.

On the other hand, patients with the lowest functional impairment appeared to have less deleterious effects on the Functional Assessment score (See Table 23, also provided by the sponsor, but with a different format/analysis).

[13] Dr. Elizabeth McNeil's first cycle review of NDA 21-894, March 3, 2006.

Table 24. Mean Change in Functional Assessment Score from baseline to week 12, by baseline FA severity.[1]

	TBZ (N=54)		Placebo (N=30)		Unadjusted effect size
Baseline FA	N	Mean change	N	Mean change	
Tertile 1 (≤17)	19	-0.26	7	1	-1.26
Tertile 2 (18-21)	15	-0.47	11	0.27	-0.74
Tertile 3 (≥ 22)	13	-0.54	11	0	-0.54

Note: higher scores on FA are associated with better function. Source: Table 35., Vol 48, Complete Response (February 9, 2007). Overall baseline score for FA was 18.8 ± 4.4 for TBZ and 19.6 ± 3.8 for placebo (Source Table 12, study 004 Complete Study Report).

TBZ treated patients who experienced an AE of sedation (including the terms sedation, drowsiness, sleepiness and lethargy) had a greater decline in Functional Assessment (-0.82 points) as compared to those who did not experience sedation-related events (-0.17), and compared to patients on placebo (0 to +0.36). The data suggest that sedation may be contributing to the small decline in Functional Assessment.

Table 25. Changes in Functional Assessment scores by presence of sedation[1]

	TBZ (N=54)		Placebo (N=30)	
Patients with	Sedation N=17	No sedation N=37	Sedation N=1	No sedation N=29
Mean (SD) change in FA	-0.82 (2.3)	-0.17 (2.04)	0 (0)	0.36 (1.13)

Source: July 18, 2007 response to June 14, 2007 FDA informational request. [1] Includes sedation, somnolence, sleepiness, drowsiness, lethargy, for patients with baseline and Week 12 data. FA: Functional Assessment (Domain 4 of the UHDRS, includes 25 questions)

A similar exploratory analysis of changes in Total Chorea Scores by the presence of sedation showed a greater reduction in chorea score (by approximately 2.1 points) among TBZ-treated patients with sedation related AEs (See Table below).

Table 26. Changes in Total Chorea Scores by presence of sedation[1]

	TBZ (N=54)		Placebo (N=30)	
Patients with	Sedation N=17	No sedation N=37	Sedation N=1	No sedation N=29
Mean (SD) change in Total chorea score	-6.65 (5.20)	-4.55 (4.11)	-3.00 (0)	-1.00 (3.8)

Source: July 18, 2007 response to June 14, 2007 FDA informational request. [1] Includes sedation, somnolence, sleepiness, drowsiness, lethargy, for patients with baseline and Week 12 data. FA: Functional Assessment (Domain 4 of the UHDRS, includes 25 questions)

2.2.2 Exploration of dose response in terms of toxicity

Dose toxicity response for akathisia, depression, dysphagia and parkinsonism have been discussed in detail under sections 2.1.1 to 2.1.4 of this review. Sedation is briefly discussed under section 2.1.6.1. These analyses are very suggestive of a dose response relationship in terms of toxicity. In study 004 the median dose at onset of the first event of akathisia, depression and parkinsonism was > 50 mg/day (75 mg/day for akathisia and 62.5 mg/day for parkinsonism and depression [although some cases of depression occurred at doses <50 mg/day]). No cases of dysphagia were reported at doses <50 mg/day. Sedation appeared at doses <50 mg doses but it clearly responded to dose reduction.

A formal assessment of the dose-response relationship is confounded by time (because of the flexible dose design) and hampered by the fact that not all patients with an AE underwent dose reduction. Modeling analyses of dose response conducted by the FDA Office of Pharmacometrics showed a trend for a greater decrease in Functional Assessment scores with higher doses of TBZ, but there did not seem to be evidence of a dose response for parkinsonism scores, sedation scores and cognitive scores. For details the reader is referred to Dr. Bhattaram's review.

2.2.3 Exploratory analyses of dose response relationship in terms of both, efficacy and safety

An exploratory analysis of the dose achieved at week 12 in study 004 indicates that 21 of 54 patients (39%) were on 100 mg/day and 11 (20%) were on 50 mg/day. Fifteen percent were on doses <50 mg/day and another 15% were at doses in between 50 and 100 mg/day (See Appendix 6 of this review). (Source: Listing 1.2, App 4, February 9, 2007 CR). Overall, 54% achieved 62.5 to 100 mg/day dose, 35% achieved doses up to 50 mg/day and 6 patients had no data at the end of the study.

A slightly higher percentage of patients responded with a TCS drop of at least 3 points within the ≤ 50 mg/day dose (79%), as compared to those within the >50 mg/day dose (66%). Patients with a drop in TCS ≥3 are referred to as "responders" because this change was pre-defined as a clinically meaningful effect in chorea by HD experts in the study Steering Committee.

These findings are summarized in the following table:

Table 27. Study 004. Final dose at week 12.[1]

Final dose (mg/day)	All (N=54) n (%)	Responders TCS drop ≥ 3 n (%)	% of patients on dose group who achieved TCS drop ≥ 3
>50 – 100	29 (54)	19 (35)	19/29 (66%)
Up to 50	19 (35)	15 (28)	15/19 (79%)

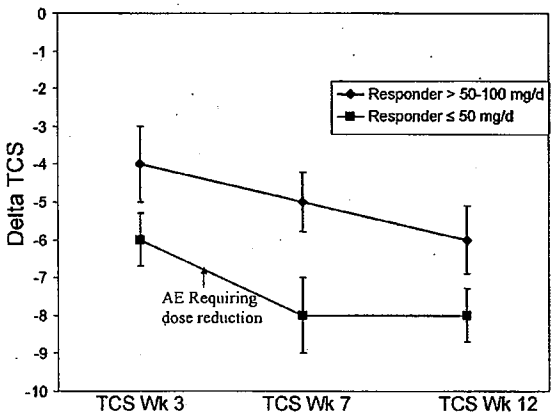
[1] Source: Appendix 4, Listing 1.2 of Complete Response. Data on TCS at week 12 were not available for 6 patients (five who discontinued because of AE, and one for unknown reasons [474-313]).

A listing of TCS over time in study 004 as submitted by the sponsor is included in Appendix 9. A table of responders who were on doses > 62.5-100 mg/day at week 12 along with the adverse events presented by these patients is presented in Appendix 10. Responders who achieved doses up to 50 mg/day at week 12 are shown in Appendix 11.

Fourteen of the 19 patients who responded and completed the study at doses of 62.5 to 100 mg/day and 13 of the 15 patients who responded and completed the study at doses ≤ 50 mg/day had already responded with a drop of ≥3 at week 3 (altogether, 27 out of 34 patients). All but 2 of the 34 patients who completed the study and achieved a TCS ≥3 at week 12, already had a drop in TCS ≥3 at week 7, regardless of the dose that they were taking.

Figure 1 shows the median change in TCS over time among patients who achieved a drop in TCS ≥ 3 points at the end of the study.

Figure 1. Median Change from baseline (± SE) in TCS over time in patients who completed the study and achieved a drop in TCS ≥ 3.



TCS= Total chorea score. Wk= week. At week 3 most patients were on 50 mg/day. At week 7, patients were supposed to be on 100 mg/day, unless not tolerated.

This figure shows that most responders at week 12 had already responded by week 3. Some patients continued to improve through week 7, and others through week 12.

A table summarizing TCS over time in patients who did not achieve a responder status at week 12 is presented in Appendix 11, along with the AE presented by these patients. The table includes both those patients who completed and did not achieve the 3 point drop in TCS, and patients who did not complete the study. The data show that all five patients who withdrew because of AE had been responders in previous visits. Of the 14 patients who completed 12 weeks but did not achieve a responder status at week 12, 11 were non-responders at week 7. Four of these 14 patients developed akathisia, two developed parkinsonism and two developed depression at doses above 50 mg/day.

The data suggest that some patients are more sensitive to the beneficial and adverse effects of TBZ, while others need higher doses in order to get the desired effects on chorea. However, titration needs to be careful as some patients who had responded at lower doses will require discontinuation after developing AEs. The data also suggest that if a patient has not responded at the maximum tolerated dose (usually by week 7) it is unlikely that he/she will respond later.

These post-hoc analyses of TCS and doses over time were done as an attempt to evaluate whether the benefit to risk profile for the 50 mg/day dose is more favorable as compared to the 100 mg/day dose and whether there was a group of patients who could prospectively be identified as more likely or less likely to respond to TBZ therapy. Unfortunately, the small database and the flexible study design do not allow drawing definitive conclusions regarding dose response in terms of toxicity. These analyses do not substitute for a well designed parallel study comparing a maximum dose of 50 mg/day vs. a maximum dose of 100 mg/day.

2.2.4 Discussion of benefits and risks

Efficacy analyses demonstrate a strong dose-response in terms of Total Chorea Scores (See modeling analyses by Pharmacometrics' team). However, based on the percentage of patients who achieved improvements in chorea scores among patients who were on the 100 and 50 mg/day dose at the end of 12 weeks (52 vs. 91% respectively) and the observation that most cases of parkinsonism, akathisia, balance difficulty, depression and dysphagia were observed at doses >50 mg/day, the 50 mg dose appears to have a more favorable benefit/risk profile than the 100 mg dose.

TBZ is clearly effective to treat the chorea component of Huntington's Disease, but because of the way the drug is prescribed (to maximum effect on chorea unless AEs develop), most patients will present adverse events at some point. Some of the AEs associated with TBZ are easily recognizable and manageable by dose reduction (sedation, parkinsonism) but others are not (akathisia) or may be difficult to separate from the underlying disease (depression, dysphagia). Sedation responded rapidly to dose

reduction, however, for some the other adverse events, resolution took days to months after dose reduction and data on resolution after withdrawal are missing for most patients.

The question was raised whether TBZ's benefit of decreasing chorea scores by 50% in 38% of patients outweighs the risk evident in the placebo-controlled study of developing akathisia (13%), parkinsonism (11%) and depression (19%), as compared to 0% on placebo - particularly in patients who may not appreciate the extent of their abnormal movements-, and whether it is worth pushing the dose up to improve TCS further when some of the AEs will be difficult to manage or difficult to distinguish from the underlying disease.

When evaluating benefits and risks, one takes into consideration the effect size of the efficacy outcomes as well as the frequency, severity, reversibility and time to resolution of the AEs, among other factors. One very important factor that is missing in this application is the patients' perspective. As per Carole Davis' review, patients' perception/ appreciation of TBZ effects were not adequately evaluated in this study. A patient's global assessment was collected but it was done at the end of week 13 (after the washout) and was not consistently done by the patient (sometimes it was done by the caregiver).

In my opinion, notwithstanding the limitations of the available database, the data suggest that the sponsor may not have found the optimal dose or patient population for which the improvement in chorea outweighs the rate/severity of adverse events. I believe that a study comparing the efficacy and safety of the 50 mg dose vs. the 100 mg dose with an adequate assessment of the patient's global impression would be helpful in establishing the optimal dosing for this drug.

The safety profile of TBZ, a monoamine depleting agent, appears to be qualitatively similar to that of other dopamine antagonists used off-label for the treatment of chorea of HD (e.g. haloperidol, risperidone, olanzapine). Head to head comparisons between TBZ and other dopamine antagonists are not a regulatory requirement for approval. However, it would be helpful for the HD community to have such a study conducted in the postmarketing setting.

An additional factor that needs to be taken into consideration when discussing the approvability of this drug is the fact that once approved, it will likely be used off-label for conditions for which the risk and benefits have not been adequately established, such as non-HD chorea and Tourette's syndrome. This is of concern particularly in the pediatric population.

The use of a RiskMAP offers a potential approach to reducing some of the safety concerns associated with TBZ. The sponsor's proposed RiskMAP is unlikely to reduce the rate of depression for reasons described earlier. Further collaboration between the sponsor and the Agency to develop a more acceptable RiskMAP is warranted.

A FDA Peripheral and Nervous System Advisory Committee was held on December 6, 2007 to discuss this application. The panel unanimously voted in favor of approving TBZ for the treatment of chorea of HD despite the "panoply" of adverse events associated with this drug and the fact that there was mild worsening in some cognitive and functional assessments. The panel considered that the benefits associated with TBZ outweigh the risks associated with its use, and that the adverse events might be reduced with adequate labeling and a more appropriate RiskMAP. The panel recommended that the goal of treatment should be reduction rather than suppression of chorea, and that the minimum dose effective in reducing targeted motor symptoms should be used, instead of titrating up to maximum dose or intolerable toxicity, differently from what was done in the development program.

I agree with the panel that TBZ may help reducing involuntary movements associated with chorea of HD in some patients with this devastating disease. Patients deserve to have a choice but should not have unrealistic expectations about the efficacy of this drug. They should also be well informed about the potential risks associated with its use, in particular the risk of depression/suicidality and potential pro-arrhythmogenic effect.

APPEARS THIS WAY
ON ORIGINAL

Appendix 1. Study 007. Patients in 007 who had been on placebo during study 004.

Study ID: 447202, 447209, 447211, 447215, 447220, 447222, 447226, 447230, 447232 447239, 447241, 447245, 447247, 447250, 447253, 447256, 447259, 447262, 447266 447272, 447273, 447281, 447287, 447291, 447298, 447307, 447314

Appendix 2. Sponsor's analysis of BARNES scores in patients with AE potentially related to akathisia.

Table 61. Highest BARNES Global Clinical Score in Patients With Akathisia, Anxiety, or Restlessness/Agitation Events in Studies 004, 007 and 006

Study AE	Cases	Highest BARNES Global Clinical Score					
		0	1	2	3	4	5
Study 004							
Akathisia	5	0	2	2	0	1	0
Anxiety	4[1]	4	0	0	0	0	0
Restlessness/Agitation	13[2]	8	3	1	0	1	0
Study 007							
Akathisia	15	6[5]	1	4	3	1	0
Anxiety	14[3]	10	3[6]	1[7]	0	0	0
Restlessness/Agitation	5[4]	2	1	2[8,9]	0	0	0
Study 006							
Akathisia	0	0	0	0	0	0	0
Anxiety	6	6	0	0	0	0	0
Restlessness/Agitation	4[10]	4	0	0	0	0	0

Source: CSR TBZ 103,004: 16.2.7.1, 16.4.14; Amended CSR TBZ 103,006: 16.2.7.1, 16.4.14; Amended CSR TBZ 103,007: 16.2.7.1, 16.4.1.4

Note: Patients who had an AE of akathisia are counted as akathisia only; patients who had an AE of restlessness or agitation are counted in that category even if they also had an AE of anxiety.

1. Patients 238 (maximum score of 0), 251 (maximum score of 0), and 313 (maximum score of 0) had anxiety-like events as an AE and were excluded from anxiety. In addition, Patient 299 (maximum score of 1) had restlessness, irritability and anxiety as an AE and was counted only in anxiety-like events.
2. One patient (ID 299) had AE of restlessness and irritability (maximum score of 1) and was only counted once in anxiety-like events. Patient 279 (maximum score of 1) had AE of akathisia and was excluded from anxiety-like events.
3. Patient 207 (maximum score of 2) and Patient 245 (maximum score of 0) also had akathisia as AE and were excluded from anxiety. Patient 202 (maximum score of 0) had akathisia, anxiety and anxiety-like event as an AE and is counted only in akathisia.
4. Patients 250 (maximum score of 2), 263 (maximum score of 2) and 266 (maximum score of 0) had anxiety-like events as an AE and were excluded from anxiety. Patient 223 (maximum score of 0) had AE of akathisia and was excluded from anxiety-like events. In addition, Patients 202 (maximum score of 0) and 245 (maximum score of 0) had an anxiety-like event, anxiety and akathisia as AEs and was counted only in akathisia.
5. Two (ID 202 and ID 219) of six patients had mild akathisia.
6. Baseline score of 2 for one patient (ID 279), therefore this is a decrease.
7. One patient (ID 262) was direct rollover from Study 004 and akathisia was a pre-existing condition.
8. Baseline score of 1 for one patient (ID 263), therefore a 1 point increase.
9. AE of restlessness (moderate) began after discontinuation from tetrabenazine.
10. One patient (ID 424) had AE of anxiety, agitation and restlessness (maximum score of 0) and was counted in anxiety-like events.

Appendix 3. Cases of depression in study 007 (n=26)

Pat ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome		Total Chorea Score (dose [mg/day])				
	Rel. Day	Dose		Base line[1]	After AE	At week 12	24	48	80
747-203	220	25	None/Started Fluoxetine 20 mg on D 232, ↑to 30 mg on D 243/ Ongoing at study end. Final HAM-D was 4. D/c due to need for exclusionary med and AE of chorea	15	8 (25)	9 (25)	17 (25)	4 (25)	N/A
747-207	172	25	None/Continued Amitriptyline 50-150 mg from study entry; ↑Paxil from 20 mg to 40 mg on D 172/Ongoing at W80. Total HAM-D of 13 at W80, down from 20 at W48.	16	12 (25)	12 (12.5)	12 (25)	5 (12.5)	7 (12.5)[2]
747-208	253	137.5	None/ Continued Imipramine 150 mg from study entry; Zoloft dose ↓ to 100 mg on Day 6 and Neurontin stopped on D 253; Mirtazapine on Day 547-564/ Ongoing. HAM-D score at W80 was 6, down from 11 when AE reported.	23	9 (137)	19 (112.5)	15 (112.)	24 (137.5)	12 (112.5)
747-209	145	62.5	Dose ↓on Day 166 to 37.5 mg and to 25 mg on D 170 when depression called severe / Switched Effexor 75mg to Paxil 12.5 mg on D 263, switch back to Effexor 75 mg D 266, Effexor increased to 150 mg one day after severe depression stopped (D 360) /Recovered on rel D 359.	11	9 (62.5)	7 (62.5)	9 (62.5)	5 (50)	9 (37.5)[3]
	535	25	None/Continued Amitriptyline 50-150 mg from study entry; Increased Paxil from 20 mg to 40 mg on Day 172/Ongoing at W80. HAM-D of 13 at W80, down from 20 at W24.	11	5 (25)				
747-210	80	87.5	None/ ↑ Prozac from 40 to 120 mg on D81, added Trazodone 100 mg D 160-220; Switched Prozac to Celexa 40 mg on D 448 /Ongoing at W80 but HAM-D score of 5 to 6 during last 28 weeks of study	17	3 (87.5)	3 (87.5)	2 (87.5)	5 (87.5)	10 (87.5)
747-217	157	87.5	None/Switched from Citalopram to Zoloft 50 mg on Day 261 /Recovered Day 267	15	8 (87.5)	6 (87.5)	8 (87.5)	7 (87.5)[4]	NA

Appendix 3. (cont) Cases of depression in study 007 (n=26)

ID	AE Onset		Study Drug Action/ Medical Rx/ AE Outcome	Total Chorea Score (dose [mg/day])					
	Rel day	Dose		Base line	11 (62.5)	At week 12	24	48	80
747-223	89	100	None indicated for depression, but pt had numerous dose ↓ for sedation or akathisia / Increased Citalopram to 30 mg on Day 55, then ↓ to 20 on Day 174; added Buspar Day 55-62. Did not complete study due to caregiver preference/ Ongoing at end of study, but HAM-D was 9 (down from max of 18)	15	13 (50)	11 (62.5)	11 (75)	15[5] (50)	
747-230	428	50	None/↑ Effexor from 75 mg to 150 mg on Day 428 & later↓to 75 mg (Day 460) /Recovered on Relative Day 460	17	10 (50 mg)	10 (75)	10 (50)	10 (50)	13 (25)
747-231	24	62.5	Dose reduced/Continued Prozac 20 mg from study entry /Recovered on Day 32	15	9 (62.5)	10 (50 mg)	12 (50 mg)	7 (50 mg)	10 (50 mg)
747-237	31	75	Dose reduced/ None/ Recov D 37. Patient d/c due to abnormal LFT's on Day 87	15	9 (62.5)	10 (50)[6]	NA	NA	NA
747-239	76	75	Dose reduced/Continued Paroxetine 40 mg from study entry/Recovered on Day 89	20	12 (50)	9 (62.5)	13 (62.5)	13 (50)	11 (62.5)
747-243	31	50	Dose reduced/Started Paxil 20 mg D 31, ↑ to 30 mg on D 44/ Recovered D 83. D/C due to request of caregiver on D 176	14	21 (0)	4 (62.5	8 (50)	NA	NA
747-245	142	75	Dose reduced, then stopped D 153 /Zoloft 25 mg started Day 149-153/ Ongoing at study end, final HAM-D score= 12 with 'Depressed Mood' =0 (range 0-4). D/C TBZ on Day 149[7], restarted x 3 days, but then withdrew consent D 153	17	7 (62.5)	14 (62.5)	NA	NA	NA
747-247	57	62.5	Dose reduced/Started Citalopram 10 mg on Day 85, ↑ to 20 mg on Day 107/ Ongoing at study end. D/C on Day 113 due to depression and akathisia. Patient had HAM-D of 16 (down from max of 23), but HAM-D 'Depressed Mood' score was 1 (range 0-4)	14	11 (62.5)	7 62.5)	10 (37.5)	NA	NA

Appendix 3. (cont.) Cases of depression in study 007 (n=26)

ID	AE onset		Study Drug Action/ Medical Rx/AE Outcome	Total Chorea Score (dose [mg/day])					
	Rel day	Dose		Base line	At After visit	At week 12	24	48	80
747-252	2	12.5	None/Started Zoloft 25 mg on Day 16, to 50 mg on Day 23/Recovered on Day 44	11	9 (12.5)	9 (25)	6 (25)	9 (37.5)	8 (12.5)
	183	25	None/increased Zoloft to 75 mg, D 213, Recovered D 237.	11	9 (25)				
747-262	69	75	Dose reduced 5x / ↑Zoloft to 100 mg on Day 86, further to 150 mg on Day 117/ D/C Day 145 for suicidal ideation. Depression ongoing at study end (Week 25), but 1 week later mood improved with no suicidal thoughts.	10	7 (50)	7 (50)	15 (12.5)	NA	NA
747-266	56	75	Dose reduced/Continued Citalopram 20 mg from study entry /Recovered on Day 169	9	3 (50 mg)	3 (50 mg)	0 (50 mg)	6 (50 mg)	1 (37.5 mg)
	337	50	None/Switched Citalopram to Wellbutrin 150 mg on Day 357 /Ongoing at Week 80, but HAM-D of 1 at study end	9	6 (50)				
747-267	125	62.5	Dose reduced/Increased Paxil to 50 mg on Day 162/ Intensity reduced from mod to mild on Day 233 but increased to mod on Day 438. TBZ d/c Day 463. Psychosis with depressive features began Day 466, Recovered on Day 473.	21	7 (50)	13 (62.5)	7 (50)	12 (50)	NA
747-272	46	100	None/None/ Intensity increased to mod on Day 86	16	10 (100)	10 (125)	18 (125)	11 (137.5)	NA
	87	125	None/None/ Intensity reduced to mild on Day 174	16	10 (125)			(Day 280) [8]	
	175	125	None / Zoloft 50 mg started (Day 189-194) and Celexa 10 mg for insomnia (Day 255-267) / Recovered on Day 266. D/C moved out of state D 280.	16	18 (125)				
747-279	-225[9]	50	None/Continued Mirtazapine; Paxil increased to 40 mg ~Day 225[9]/Ongoing at study end, but last HAM-D was 6		5 (50)	9 (50)	7 (50)	5 (50)	NA
747-288	50	50	Dose reduced / Continued Zoloft 150 mg. Amitriptyline 20 mg started D 43, to 50 mg Day 77 / Recovered D 182	13	9 (50)	5 (50)	7 (50)	7 (50)	2 (50)

Appendix 3. (cont) Cases of depression in study 007 (n=26)

ID	AE onset		**Study Drug Action/ Medical Rx/AE Outcome**	Total Chorea Score (dose [mg/day])					
	Rel day	Dose		Base line	After AE	At week 12	24	48	80
Same Pt. (288)	355	50	None / Continued Zoloft to D9 358, Wellbutrin 100-200 mg (Day 344-study end) and Amitriptyline / Recov D 580	13	7 (50)				
747-291	42	87.5	Dose reduced/ None/ Recovered on Relative Day 71	11	5 (100)	4 (75)	4 (75)	8 (75)	6 (75)
	210	75	None/None/Recovered on Day 596. HAM-D scores from Day 176 to 596 ranged from 0 to 5	11	6 (75)				
747-313	145	200	Dose reduced /Started Citalopram 10 mg on D 247, increase to 20 mg Day 473, Started prn Xanax / Intensity ↑ to severe on Day 479	13	9 (150)	7 (200)	9 (150)	5 (150) 11 (Wk 64)	
	480	150	None / Added Amitriptyline 100 mg on Day 547 / Ongoing at study end, with final HAM-D score of 23.	13	11 (150)				
747-316	19	37.5	None / Continued Zoloft 200 mg, Wellbutrin 150 mg Day 16-27; Started Pamelor 50 mg on Day 31 and prn Klonopin on Day 33 / Recovered on Day 171. HAM-D scores ranged from 7-10 during depression and were 5-8 thereafter	16	5 (37.5)	7 (37.5)	4 (37.5)	1 (37.5)	0 (37.5)
747-225	*586*	*?*	*Not listed as AE. Zoloft increased from 100 to 220 for indication of depression.*	*?*	*?*	*?*	*?*	*?*	*?*
747-314	*399*	*?*	*Not listed as AE. Trazodone added on day 399 and amitriptyline dose increased on day 455 for indication of OCD/depression.*	*?*	*?*	*?*	*?*	*?*	*?*

[1]Baseline = 0 mg. [2] Patient 747-207 stopped taking study drug one day before the Week 80 visit. [3] Patient 747-209 stopped taking study drug one day before the Week 80 visit. [4] Patient 747-217 withdrew 11 days before the Week 80 visit. Had TCS=6 at Week 64 visit. [5] Patient had a TCS score =9 at Week 64 visit. [6] Patient 747-237 had last dose on Day 87 (withdrawn for abnormal labs).[7] Patient 747-245 stopped taking study medication 16 days before the Week 24 visit and was withdrawn from the study, with akathisia, agitation, anxiety and ongoing depression. [8] Patient 747-272 withdrew between the Week 36 and Week 48 visit due to a move out of state and inability to continue participation in the study.[9] Patient 747-279: Month and year but specific start date for adverse event not specified. Source: July 18 and 31, 2007 response to June 14, 2007 informational request. *Cases found by FDA from review of concomitant medications listings are in Italics.* ?= No data was available on chorea scores for these patients.

Appendix 4. Cases of depression in study 006 (N=10)

Patient ID	AE onset Rel. Day	Dose	Study drug action/medical Rx/AE outcome	Total Chorea Score (dose [mg/day])				
				Baseline		At Week		
				005[1]	006[2]	12	24	48
647-401	270	87.5	None/ None / Recovered on Relative Day 361. HAM-D ranged between 5 and 8 during study.	13	13 Off TBZ 16 hr	15 (75 mg)	3 (87.5 mg)	6 (87.5 mg)
647-402	11	100	Dose reduced / Continued Zoloft 100 from entry. Started mirtazapine 7.5 mg QD on Day 14 / Intensity decreased to Moderate on Day 182	25	27 Off TBZ 2.5 days	25 (75 mg)	8 (125 mg)	2 (150 mg)
	182	125	None / None / Intensity increased to severe on Day 252					
	252	150	None / Change from Sertraline 100 mg QHS to Paxil 20 mg QD on Day 321 /Ongoing; HAM-D scores improving from W12 visit, and final HAM-D was 7.					
647-411	105	50	None / Zoloft increased from 100 mg to 150 mg on Day 106/ Recovered on Day 112	10	12 Off TBZ 2.5 days	7 (62.5)	11 (62.5)	9 (62.5)
647-414[3]	236	50	None / Continued Prozac 20 mg from entry/ Ongoing. HAM-D scores were 3 from Wk 12 to Study end.	8	9 Off TBZ 4 days	14 (37.5)	5 (50)	5 (50)
647-418	169	87.5	None / None / Recovered on Day 340. HAM-D scores ranged from 3-6 between Wk 12 and Study end.	10	154 Off TBZ 4 days	16 (87.5)	16 (87.5	15 (87.5)
647-419	158	100	None / None / Recovered on Relative Day 330.	5	12 Off TBZ 4 days	11 (100)	6 (100)	8 (100)
647-426	95	37.5	None / Paxil 12.5 mg started Day 95; increased to 25 mg Day 110, then switched to Paxil CR 20 mg on Day 201 / Ongoing. Final HAM-D score 16.	7	125 Off TBZ 4 days	6 (37.5)	5 (37.5)	4 (62.5)
647-428	282	75	None / Continued Lexapro 30 mg from entry; Added Wellbutrin 150 mg on Day 41 for smoking cessation / Ongoing. Final HAM-D 13.	3	126 Off TBZ 2.5 days	6 (75 mg)	6 (75 mg)	3 (75 mg)
647-430	1	37.5	None/Paxil 12.5 started and later switched to Paxil CR. Had 2 day suspension of TBZ for delutional suicidal ideation on day 75.	5	15 Off TBZ 4 days	3 (37.5)	15 (0)	NA

Appendix 4. (cont) Cases of depression in study 006 (n=10)

Patient ID	AE onset Rel. Day	Dose	Study drug action/medical Rx/AE outcome	Total Chorea Score (dose [mg/day])				
				Baseline		At Week		
				005[1]	006[2]	12	24	48
647-403	*2*	*?*	*None/ amitriptyline dose increased for depression.*	*?*	*?*	*?*	*?*	*?*

Rel. Day = Day relative to dosing d/c: discontinuation [1] Baseline Chorea scores from Study 005 are on Tetrabenazine [2] The baseline Chorea score for Study 006 was the Day 5 Chorea score from Study 005. As this was a staggered withdrawal study, patients were off TBZ from 1 to 4 days. [3] Patient 647-414 experienced depression and anxiety on same start date and remained ongoing at study end. Both AEs were attributed to legal issues. [4] Patient 647-418: The listing for the Baseline UHDRS chorea score for TBZ 103,006 states '13,' but it should state '15', as per protocol, the measurements made during the end-of study visit of TBZ 103,005 will serve as Screening/Enrollment/Baseline values for TBZ 103,006. [5] Patient 647-426 experienced anxiety approximately 1 month prior to start of depression–[6] Patient 647-428: The listing for the Baseline UHDRS chorea score for TBZ 103,006 states '14,' but it should state '12', as per protocol, the measurements made during the end-of study visit of TBZ 103,005 will serve as Screening/Enrollment/Baseline values for TBZ 103,006. Source: July 18 and July 31, 2007 response to FDA informational request of June 14, 2007. *Cases found by FDA from review of concomitant medications listings are in Italics.* No data was available on chorea scores for these patients.

Appendix 5. Antidepressant and benzodiazepine medications prior to and on study entry in study 004

Medications at entry	TBZ (N=54)	Placebo (N=30)
Antidepressants	30 (56%)*	20 (67%)*
Amitriptyline	3	2
Bupropion	1	0
Citalopram	7	2
Fluoxetine	3	2
Imipramine	1	0
Mirtazapine	2	1
Nefazodone	1	0
Nortriptyline	0	1
Paroxetine	6	5
Sertraline	10	3
Trazodone	3	1
Venlafaxine	0	4
Benzodiazepines	9 (17%)*	5 (17%)*
Aprazolam	1	2
Clonazepam	5	2
Diazepam	2	1
Temazepam	1	0

*Patients taking more than one medication are counted only once in the table. Source Table 13, 004 CSR

Appendix 6. Patients with a response of "yes" to questions 38 and 39 of the UHDRS at visit 0 (baseline).[1]

TBZ			Placebo		
USUBJID	UH38	UH39	USUBJID	UH38	UH39
447206	0	Y	447209	0	Y
447207	Y	Y	447211	Y	Y
447208	0	Y	447215	Y	Y
447210	Y	Y	447220	0	Y
447217	0	Y	447230	0	Y
447219	Y	0	447232	0	Y
447223	Y	Y	447234	0	Y
447225	0	Y	447239	0	Y
447228	0	Y	447256	0	Y
447231	0	Y	447259	0	Y
447235	Y	Y	447262	0	Y
447236	0	Y	447266	0	Y
447240	0	Y	447269	0	0
447246	0	Y	447287	0	Y
447251	0	Y	447314	0	Y
447255	0	Y			
447258	0	Y			
447261	0	Y			
447264	0	Y			
447265	0	Y			
447267	0	Y			
447274	Y	Y			
447279	0	Y			
447285	0	Y			
447286	0	Y			
447288	Y	Y			
447297	0	Y			
447313	0	Y			
447316	Y	0			
Total	8 (14.8%)	27 (50%)	Total	2 (6.6 %)	14 (46.6%)

[1] UHDRS: Unified Huntington's Disease Research Score.
Question 38: Does the investigator believe the patient is depressed?
Question 39: Does the patient need medical treatment for depression?

Appendix 7. QTc Review Team. Executive Summary. (Christine Garnett and Atul Bhattaram, Division of Pharmacometrics, December 7, 2007)

1.1 OVERALL SUMMARY OF FINDINGS

Administration of tetrabenazine (TBZ) was shown to prolong the QT interval in a dose dependent manner at alpha- and beta-HTBZ concentrations lower than what is expected when TBZ in co-administered with a CYP2D6 inhibitor. The maximum mean change in baseline and placebo corrected QTcI was 3.6 ms (90% CI: 1.0, 6.2 ms) and 7.7 ms (90% CI: 5.0, 10.4 ms) following administration of single doses of 25-mg and 50-mg TBZ (Table 1). The upper limit of the maximum mean change for the 50-mg dose group exceeded the 10 ms threshold for regulatory concern indicating that this study is positive by ICH E14 guidelines.

The limitation of the study is the plasma alpha- and beta-HTBZ concentrations achieved with the 50 mg dose do not cover the expected increases in concentrations when 100 mg/day is co-administered with a CYP2D6 inhibitor, such as paroxetine. The predicted mean Cmax based on pharmacokinetic simulation is 285 ng/mL which is ~70 ng/mL higher than the observed mean Cmax (212 ng/mL) in paroxetine-interaction study (TBZ 107,018, Figure 11). A combined pharmacokinetic and pharmacodynamic model was used to analyze the relationship between ΔΔQTcF and total HTBZ (alpha- and beta-HTBZ) plasma concentrations. The effect of total HTBZ on the QTcF interval could be explained by a linear pharmacodynamic model with a 2-h delay. One possible explanation for the observed delay is the existence of another metabolite that prolongs QT. The sponsor's mass balance study showed that alpha- and beta-HTBZ are converted to secondary metabolites. Exposure-response analysis was not conducted using the data obtained from the paroxetine interaction study (TBZ 107,018) due to the lack of placebo group.

A single dose of 400 mg moxifloxacin administered unblinded in the last period, increased the QT interval by 13 ms (lower 95% confidence bound 10 ms) at 2.5 hour after dosing. The study was adequately designed and conducted to detect an effect on the QT interval.

2 PROPOSED LABEL

The sponsor did not propose any QT labeling.

We recommend that a full disclosure of the QT prolonging effects of TBZ be included in the label. Caution is warranted when prescribing TBZ to patients taking drugs known to prolong the QT interval, taking CYP2D6 inhibitors, with Long QT syndrome or [redacted] with risk factors for QT interval prolongation such as hypokalemia, hypomagnesemia, left ventricular dysfunction or with QT interval prolongation.

Appendix 8. Postmarketing reports with Tetrabenazine (as per package submitted to AC meeting of December 6, 2007).

BODY SYSTEM	ADR TERM	No. of Events
Body as a Whole - General Disorders	Death	12
	Asthenia	10
	Fever	6
	Efficacy, Lack of	5
	Falling	3
Central & Peripheral Nervous System Disorders	Somnolence	34
	Extrapyramidal Disorder	29
	Dystonia	7
	Neuroleptic Malignant Syndrome	7
	Tremor	7
	Akathisia	4
	Condition Aggravated	4
	Speech Disorder	4
	Dyskinesia	3
	Headache	3
	Parathesia	3
	Rigidity	3
Gastro-Intestinal System Disorders	Hypersalivation	12
	Dysphagia	11
	Diarrhea	4
	Gastrointestinal Discomfort	4
	Nausea	3
	Vomiting	3
Heart Rate and Rhythm Disorders	ECG Abnormal	4
	Cardiac Arrest	3
	Tachycardia	3
Metabolic and Nutritional Disorders	Dehydration	3
Myo Endo Pericardial & Valve Disorders	Myocardial Infarction	6
Psychiatric Disorders	Depression	12
	Confusion	6
	Agitation	4
	Apathy	4
	Suicide Attempt	4
	Hallucination	3
	Irritability	3
Respiratory System Disorders	Pneumonia	9
	Aspiration	3
Skin and Appendages Disorders	Rash Erythematous	4
Urinary System Disorders	Urinary Tract Infection	3
Vascular Disorders	Hypotension	6
	Hypotension Postural	4
	CVA	3
Vision Disorders	Vision Disturbance	3

* In addition, other significant AEs such as sudden death (N=1), suicide (N=2), attempted suicide (N=1), suicidal ideation (N=1), and coma (N=1) were reported.

Appendix 9. Death in listings of postmarketing adverse event reports submitted by the sponsor on November 27, 2007.

– Nitoman Database: January 1960 to November 1994 (n=29) Pneumonia/aspiration pneumonia: 8 Myocardial infarction: 4 Unknown: 3 Cardiac arrest: 3 Sudden death: 2 Dehydration: 2 Progressive disease: 2 Congestive heart failure: 1 Cerebrovascular accident: 1 Gastrointestinal bleeding: 1 Suicide: 1 Swallowing impaired: 1
– Nitoman Database December 1994- November 1998 (n=7): Pneumonia/aspiration pneumonia/sepsis: 2 Respiratory disorder/infection: 1 Myocardial infarction: 1 Sudden death: 1 Extrapyramidal disorder: 1 Therapeutic response increased (multiple drug involved): 1
– From list of serious adverse reactions received from Cambridge Laboratories (n=5).[1] Unknown: 2 Sudden death: 1 Cardiomegaly: 1 Suicide: 1

[1]Some of the reports of serious AE are dated back to 1986, and some as recent as June 2007. The date of the event is unknown for several reports.

Although TBZ has been marketed for over 40 years, the postmarketing spontaneous reporting data are extremely limited. Some of these cases may have been unrelated to TBZ or due to progression of the underlying disease, however, the listings are just listings and they do not contain any clinical information on the cases to further elaborate on the potential relationship to study drug. Moreover, the sponsor has not been able to provide an estimate of the number of patients exposed to TBZ over these years.

Of note, there were two cases of Tardive Dyskinesia in the Nitoman database. Also of note, there were 19 pediatric cases (ages 2-16 years), two of them serious (hallucination and seizures). Fifteen of the 17 non-serious reports come from a recently published study (Jain et al., 2006), mostly sedation, agitation and depression, and one oculogyria. All of them were reported to have improved.

Appendix 10. Patients who achieved drop in TCS ≥ 3 at doses >50 mg/day at Week 12.

ID	Base	Week 3		Week 7		Week 12		Onset at ≤ 50 mg/d	Onset > 50 mg/d
	TCS	Dose	Delta TCS	Dose	Delta TCS	Dose	Delta TCS		
210	15	50	-	100		100		Somnolence (50)	-
223	16	50		100		100		Agitation (37.5)	Balance difficulty (75)
227	15	50		87.5		100		Nausea (25)	Sedation (75) Obsessive reaction (100)
235								xxxxx	xxxxx
237	13	50		87.5		100			Concentration impaired, balance difficulty, insomnia (100)
242	17	50		100		100		-	-
243	14	50		100		100		-	-
249	11	62.5		100		100		-	-
265	21	50		87.5		100		Fatigue (37.5)	-
268	20	62.5		100		100		-	Upper resp infection (75)
275	15	50		100		100		Restlessness (37.5)	Sedation, fatigue (75)
297	14	62.5		100		100		Anger outburst (25)	-
286	14	62.5		NA		100		Upper resp inf (25)	-
217	13	50		100		87.5		Nausea (37.5)	Akathisia (100)
225	13	50		100		87.5		Cough (37.5)	Sedation (100)
238	14	50		100		75		-	Fall (75), akathisia (100)
274	12	37.5		87.5		87.5		Fall, apathy (37.5)	Loose stools (87.5)
285	18	50		37.5		75		-	Withdrawn from social contacts (100)
288	12	50		62.5		62.5		-	Fatigue, insomnia, irritability, anorexia (62.5)

Source: Sponsor listing 1.2 and 1.16 of Appendix 4 of Complete Response submitted February 9, 2007).

Appendix 11. Patients who achieved drop in TCS ≥ 3 at doses up to 50 mg/day at Week 12.

ID	Base	Week 3		Week 7		Week 12		Onset at ≤ 50 mg/d	Onset > 50 mg/d
	TCS	Dose	Delta TCS	Dose	Delta TCS	Dose	Delta TCS		
214	20	37.5		50		50		Drowsiness	↑drowsiness (62.5)
224	10	50		50		50		Fall	Parkinsonism (62.5)
228	11	37.5		50		50		Dizziness, fall,	
								Depression	Sedation (62.5)
231	19	50		50		50		-	Depression (62.5)
251	10	50		75		50		Fall	Depression, forgetfulness,
									obsessive reaction (75)
257	22	62.5		50		50		-	Drowsiness (75)
263	10	50		100		50		-	Fatigue (75)
									parkinsonism 87.5mg/d
264	11	50		75		50		Fatigue (25), insomnia (50)	Anxiety (87.5)
267	19	62.5		62.5		50		Sedation (50)	Depression (62.5)
316		50		50		50		Fatigue, nausea (37.5)	-
201		37.5		37.5		37.5		Insomnia (37.5)	-
203		50		50		37.5		Bradykinesia (50)	Bradykinesia, slow speech (62.5), sedation (75)
207		50		25		25		Drowsiness (25)	Parkinsonism, head injury (62.5)
236		50		50		37.5		Hypertonia, bradykinesia, akathisia (50)	Sedation, disorientation (62.5)
252		50		37.5		37.5		Fatigue (25) Insomnia (50)	-

Source: Sponsor listing 1.2 and 1.16 of Appendix 4 of Complete Response submitted February 9, 2007).

Appendix 12. Study 004- Patients who did not achieve "responder" status at week 12.

ID	Base	Week 3		Week 7		Week 12		Onset at ≤ 50 mg/d (dose in mg/day)	Onset > 50 mg/d (dose in mg/day)
	TCS	Dose	Delta TCS	Dose	Delta TCS	Dose	Delta TCS		
Patients who Completed study									
208	13	62.5		100		100		-	Anxiety, akathisia (100)
219	10	50		100		100		-	-
221	10	62.5		100		100		Nausea (50)	-
229	14	50		87.5		100		Fall (37.5) akathisia (50)	Sleep disturbed (75), depression (100)
233	20	50		100		87.5		-	Sedation (75), stiffness when walking (87.5)
240	15	62.5		50		50		Sedation (50)	Dysphagia, dysarthria, clumsiness, balance difficulty (75)
244	12	50		37.5		37.5		Nausea (50)	Sedation, depression (62.5)
248	11	50		75		37.5		Nausea,vomiting (50)	Sedation, akathisia (75)
255	19	50		100		100		-	-
258	19	62.5		100		100		Fatigue (25), fall (37.5)	Insomnia (100)
260	14	62.5		100		100		-	-
261	14	50		75		62.5		Fatigue (37.5)	Diarrhea, anxiety (75)
279	11	50		37.5		37.5		-	Akathisia (75)
299	10	50		100		100		-	Insomnia, anxiety akathisia (100)
Patients with Early withdrawal									
206	14	na		na	na	na	na	Depression, fall subarachnoid hemor. (25)	
213	19	50		100		na	na	-	Akathisia, insomnia, anorexia (100)
246	13	50		100		na	na	-	Akathisia (100)
254	11	62.5		na	na	na	na	-	Breast CA (87.5)
271	22	62.5		87.5		na	na	-	Suicide (87.5)

Na= Not available. Source: Sponsor listing 1.2 and 1.16 of Appendix 4 of Complete Response submitted February 9, 2007). TCS scores were not available in one patient who completed wek 12 and entered stud 007 (447-313).

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

/s/

Maria Villalba
12/13/2007 10:19:03 AM
MEDICAL OFFICER

Alice T. Hughes
12/13/2007 10:30:11 AM
MEDICAL OFFICER

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	21894
Brand Name	Tetrabenazine
Generic Name	Xenazine
Sponsor	Prestwick Pharmaceuticals Inc
Indication	Treatment of Chorea associated with Huntington's Disease
Dosage Form	Tablets
Drug Class	Monoamine Depletor
Therapeutic Dose	12.5-100 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Up to 200 mg
Application Submission Date	October 12, 2007
Review Classification	Standard NDA
Date Consult Received	October 24, 2007
Clinical Division	Division of Neuropharmacological Drug Products
PDUFA Date	January 6, 2008

1 SUMMARY

1.1 Overall Summary of Findings

Administration of tetrabenazine (TBZ) was shown to prolong the QT interval in a dose-dependent manner at alpha- and beta-HTBZ concentrations lower than what is expected when TBZ in co-administered with a CYP2D6 inhibitor. The maximum mean change in baseline and placebo corrected QTcI was 3.6 ms (90% CI: 1.0, 6.2 ms) and 7.7 ms (90% CI: 5.0, 10.4 ms) following administration of single doses of 25-mg and 50-mg TBZ (Table 1). The upper limit of the maximum mean change for the 50-mg dose group exceeded the 10 ms threshold for regulatory concern indicating that this study is positive by ICH E14 guidelines.

The limitation of the study is the plasma alpha- and beta-HTBZ concentrations achieved with the 50 mg dose do not cover the expected increases in concentrations when 100 mg/day is co-administered with a CYP2D6 inhibitor, such as paroxetine. The predicted mean C_{max} based on pharmacokinetic simulation is 285 ng/mL which is ~70 ng/mL higher than the observed mean C_{max} (212 ng/mL) in paroxetine-interaction study (TBZ 107,018, Figure 11).

A combined pharmacokinetic and pharmacodynamic model was used to analyze the relationship between ΔΔQTcF and total HTBZ (alpha- and beta-HTBZ) plasma

concentrations. The effect of total HTBZ on the QTcF interval could be explained by a linear pharmacodynamic model with a 2-h delay. One possible explanation for the observed delay is the existence of another metabolite that prolongs QT. The sponsor's mass balance study showed that alpha- and beta-HTBZ are converted to secondary metabolites. Exposure-response analysis was not conducted using the data obtained from the paroxetine interaction study (TBZ 107,018) due to the lack of placebo group.

A single dose of 400 mg moxifloxacin administered unblinded in the last period, increased the QT interval by 13 ms (lower 95% confidence bound 10 ms) at 2.5 hour after dosing. The study was adequately designed and conducted to detect an effect on the QT interval.

2 PROPOSED LABEL

The sponsor [redacted]

We recommend that a full disclosure of the QT prolonging effects of TBZ be included in the label. Caution is warranted when prescribing TBZ to patients taking drugs known to prolong the QT interval, taking CYP2D6 inhibitors, with Long QT syndrome or [redacted] and with risk factors for QT interval prolongation such as hypokalemia, hypomagnesemia, left ventricular dysfunction or with QT interval prolongation.

3 BACKGROUND

3.1 PREVIOUS CLINICAL EXPERIENCE

TBZ was initially developed by Hoffmann-La Roche in the mid-1950s as an antipsychotic drug. TBZ has been marketed in several European countries for over 30 years for the treatment of Huntington's chorea in doses ranging from 25 to 200 mg per day. The most common adverse events associated with the use of TBZ consist of sedation, depression, parkinsonism, akathisia, anxiety, nervousness, insomnia, irritability, confusion, increased salivation, nausea, vomiting, dizziness, and increased sweating. There is no mention in the current product insert of TBZ's effect on the QT interval.

Reviewer's comment: Since the product has been marketed for several years, an evaluation of TBZ's effect on the QT interval should include an examination of the AERS database to see if any signal of QT prolongation or predisposition to serious ventricular arrhythmias is reported.

3.2 CLINICAL PHARMACOLOGY

The following description of the PK was obtained from the proposed label.

> **Absorption and Bioavailability in Adults:** Following oral administration of TBZ in doses ranging from 12.5 to 50 mg, plasma concentrations of tetrabenazine are generally below the limit of detection. This is explained by the rapid first-pass metabolism of tetrabenazine with the consequent formation of α-HTBZ and β-HTBZ. Peak plasma concentrations (Cmax) of α-HTBZ (active metabolite) and β-HTBZ are reached within 1 to 1½ hours post-dosing. The average terminal elimination half-life of α-HTBZ ranges from 3 hours to 5 hours and that of β-HTBZ from 2 hours to 4 hours. Steady-state plasma concentrations with α-HTBZ

and β-HTBZ should be achieved after approximately 1 to 2 days of dosing. Following administration of single doses of 12.5 mg, 25 mg, and 50 mg oral doses of tetrabenazine, mean plasma concentrations, Cmax, and area under the plasma concentration time curve (AUC) of total HTBZ (α-HTBZ plus β-HTBZ) increased in proportion to the increase in dose. Consistent with the short terminal elimination half-life, at steady state there is an approximate 50% increase (accumulation) in plasma concentrations of α-HTBZ and β-HTBZ.

Metabolism:Tetrabenazine, α-HTBZ, and β-HTBZ appear to be substrates for CYP2D6 but not for any other CYP450 subtypes.

Excretion: After oral administration, tetrabenazine has not been found in human urine. Urinary excretion of dihydrotetrabenazine accounted for less than 10% of the administered dose.

Protein Binding: The in vitro protein binding of tetrabenazine, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%; and β-HTBZ binding ranged from 59% to 63%.

Food Effect: The single dose bioavailability of two 12.5 mg tablets is equivalent to that of one 25 mg tablets with respect to the rate and extent of absorption. The effects of food on the bioavailability of tetrabenazine were studied in subjects administered a single-dose with and without food. Taking tetrabenazine with food has no effect on either mean plasma concentrations, Cmax, or AUC of α-HTBZ or β-HTBZ.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The Sponsor assessed the effects of administering TBZ on QT interval in studies TBZ 104,015 and TBZ 107,018. TBZ 104,015 is a thorough QT study while TBZ 107,018 is a drug inaction study with paroxetine (Appendix 6.2).

The focus of this review is on the TQT study.

4.2 TQT STUDY

4.2.1 Title

Effect of Tetrabenazine on QT and QTc Intervals: A Randomized, Double-Blind, Placebo-Controlled, Active Comparator, Crossover Study in Healthy Adult Volunteers

4.2.2 Protocol Number

TBZ 104,015

4.2.3 Objectives

Primary

- To assess of a single dose of TBZ (25 or 50 mg) has the potential to cause QT prolongation in healthy adults.

Secondary

- To characterize the pharmacokinetics of TBZ and its metabolites, α- and β-dihydrotetrabenazine (α-HTBZ and β-HTBZ) after administration of a single dose of 25 mg or 50 mg.

4.2.4 Study Description

4.2.4.1 Design

A single-site, restricted randomized, 4-treatment, 4-period, double-blind (for placebo and TBZ), placebo- and active-controlled crossover design. Because of a restricted randomization, the TBZ 25 mg dose was always administered prior to the TBZ 50 mg dose, and moxifloxacin was always administered the last treatment period. Each treatment period was separated by at least 2 days washout.

Subjects were randomized at one of ABCD, BACD, and BCAD sequences. A, B, C, and D are defined at 4.2.5.1 Treatment Arms.

Reviewer's comments:
Treatment arms are not randomized through all periods. Moxifloxacin was always administered at the last period. TBZ 25 mg always preceded TBZ 50 mg.

4.2.4.2 Blinding

The investigator and subjects were blinded to treatment during the first 3 treatment periods, and administration of moxifloxacin (positive control) was open-label.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

Subjects were randomized to one of four treatment groups:

- A: Placebo (tablets identical in appearance to the TBZ tablets)
- B: tetrabenazine (TBZ) 25 mg (25 mg dose was administrated as a 1 x 25 mg TBZ tablet and 1 x placebo)
- C: tetrabenazine (TBZ) 50 mg (the 50 mg dose was administrated as 2 x 25 mg TBZ tablets)
- D: moxifloxacin (MOX) 400 mg

4.2.5.2 Sponsor's Justification for Doses

"Most patients with HD respond to doses of tetrabenazine lower than 100 mg/day given in 2 to 3 divided doses, and patients will typically respond to 3 x 12.5 mg/day or 3 x 25 mg/day.

Accordingly, the therapeutic dose of tetrabenazine chosen for Study TBZ 104,015 was 25 mg. Based on prior clinical experience in healthy volunteers, there was concern that single doses higher doses higher than 50 mg would be poorly tolerated and, consequently, 50 mg was selected as the supratherapeutic dose for this trial.

The concern regarding the tolerability of doses above 50 mg came largely from Healthy Volunteer Study CL 1700114 (A), where somnolence was

reported in 52% (13 of 25) of subjects. Tetrabenazine was administered as 25 mg daily for 5 consecutive days, and based on a half-life of approximately 5 hours minimal residual exposure to tetrabenazine or its metabolites was expected at the end of the dosing interval. Furthermore, asthenia was reported in 16% of subjects and asthenia was observed in 25% (3 of 12) of subjects who received 50 mg in the single-dose portion of the study, CL 1700114 (B)."

Reviewer's Comments: The sponsor's choice of a single 25 and 50 mg dose of tetrabenazine in healthy subjects is reasonable based on the tolerability profile. However, it will not be reflective of the likely worst case scenario where patients will be taking CYP2D6 inhibitors resulting in greater accumulation of α and β-tetrabenazine. The doses studied will not cover the expected increases in TBZ exposure in patients with hepatic impairment. TBZ is contraindicated in subjects with hepatic impairment.

4.2.5.3 Instructions with Regard to Meals

On both Baseline (Day 0) and Treatment (Day 1) days, subjects were not allowed to consume food for 10 hours prior to starting any study-related procedures. No fluids were allowed on Treatment (Day 1) from 2 hours prior to dosing until 2 hours after dosing, other than the 240 mL of water with drug administration.

4.2.5.4 ECG and PK Assessments

The ECG and PK assessments are shown in Appendix 6.1

4.2.5.5 Baseline

Triplicate ECGs were extracted from the flash card at 3 2-minute intervals, with the last replicate being extracted at least 1-minute prior to the actual time of the PK draw at the following time-points: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 23 hours post-dose at day 0. Baseline was defined as the average of the triplicate ECGs at each time point on day 0.

4.2.6 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained prior to blood draws for PK but no mention is made in the study report or protocol of restricting subject activity at the time of ECG acquisition.

The ECGs were stored on a flash card continuously for 24 hours and not available for review until the data is received by the central ECG laboratory. The central ECG reader was blinded to the subject's treatment, sequence and the time of recording. For each subject in each treatment period, ECGs were measured in triplicate (downloaded at 2-minute intervals immediately prior to the scheduled times of the PK draws).

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

A total of 51 healthy subjects (29 female, 22 male) ages 18 to 50 years of age were randomized. Ten subjects withdrew; 3 withdrawals were due to adverse events and the

other 7 withdrawals were voluntary. The remaining 41 subjects (20 female, 21 male) completed the study. Dropouts were to be replaced on a case-by-case basis at the discretion of the Sponsor. It is not clear if dropouts were replaced due to adverse events.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The time-matched differences in QTcI between TBZ/moxifloxacin and placebo after baseline adjustment were estimated based on an ANOVA model with treatment, period and sequence as fixed effects, and subject within sequence as a random effect. Baseline was included in the model to account for regression to the mean effect contained in the maximum change based on statistical significance at 10% level.

The upper bound of the 2-sided 90% CI for the mean difference between the 50-mg TBZ and placebo in the maximum time-matched (at 2.5 hours post-dose) QTcI interval changes from baseline was 10.4. The difference in treatment means was 7.7 ms (Table 1).

The sensitivity analysis for QTcI measurement was conducted using the positive control (moxifloxacin) compared to placebo. The lower bound of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo at a maximum time-matched (2.5 hour post-dose) was greater than 5 ms (Table 1).

Table 1: Maximum Time-matched, Placebo-adjusted Mean Change from Baseline in QTcI

Treatment	Time of maximum change	LS Mean	Pairwise comparison	Difference	90% CI
Placebo	-	0.7	-	-	-
TBZ 25 mg	2.5 hours	4.3	TBZ 25 mg-Placebo	3.6	(1.0, 6.2)
TBZ 50 mg	2.5 hours	8.4	TBZ 50 mg-Placebo	7.7	(5.0, 10.4)
MOX 400 mg	2.5 hours	13.2	MOX 400 mg-Placebo	12.5	(9.7, 15.3)

TBZ=tetrabenazine; MOX=moxifloxacin
Source Data: *Table 9*

(Sponsor's Panel 11.12 on page 72 of study-tbz-104-015)

Table 2 presents the subgroup analyses by gender. In females, the upper bound of the 2-sided 90% CI for the mean difference between the 50-mg TBZ and placebo in the maximum time-matched (at 2.5 hours post-dose) QTcI interval changes from baseline was 13.3 ms. The mean difference was 9.5 ms. Figures 1-3 presented the time-course of the time-matched, placebo-adjusted mean change from baseline for TBZ 25 mg, TBZ 50 mg, and moxifloxacin 400 mg, respectively, by gender.

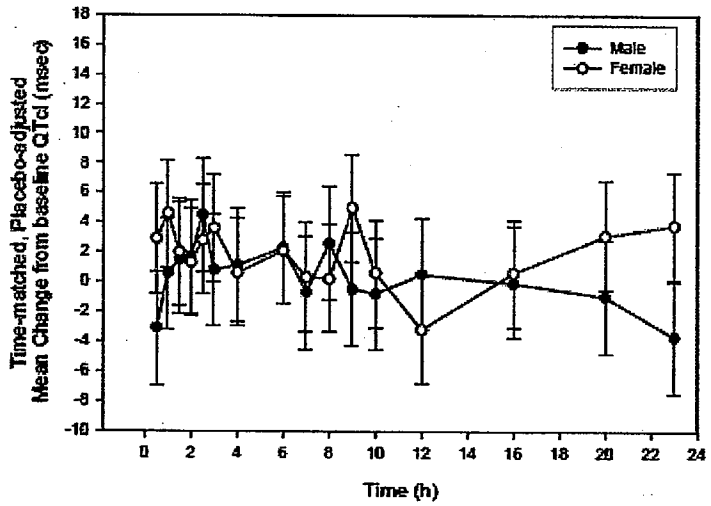
Table 2: Maximum Time-matched, placebo-adjusted Mean Change from Baseline in QTcI by Gender

Treatment	Gender	Time of maximum change	Pairwise comparison	Difference (msec)	90% CI
TBZ 25 mg	Male	2.5 hours	TBZ 25 mg-Placebo	4.5	(0.7, 8.3)
	Female	9.0 hours	TBZ 25 mg-Placebo	5.0	(1.3, 8.6)
TBZ 50 mg	Male	2.5 hours	TBZ 50 mg-Placebo	6.0	(2.1, 9.8)
	Female	2.5 hours	TBZ 50 mg-Placebo	9.5	(5.7, 13.3)
MOX 400 mg	Male	2.5 hours	MOX 400 mg-Placebo	12.1	(8.2, 15.9)
	Female	2.5 hours	MOX 400 mg-Placebo	13.0	(9.0, 17.0)

TBZ=tetrabenazine; MOX=moxifloxacin
Source Data: *Table 9.2*

(Sponsor's Panel 11.12 on page 77 of study-tbz-104-015)

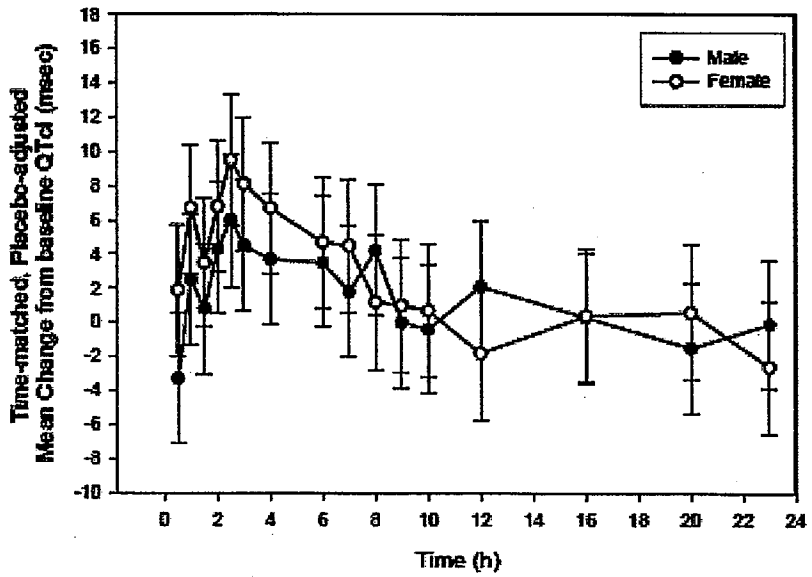
Figure 1: Time-matched, placebo-adjusted mean change from baseline in QTcI by gender



(Sponsor's Figure 11.14 on page 76 of study-tbz-104-015)

Figure 2: Time-matched, placebo-adjusted mean change from baseline in QTcI by gender

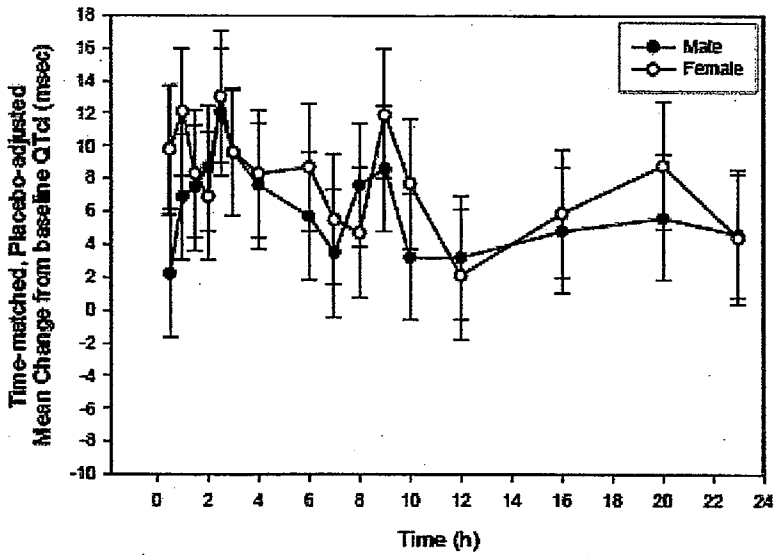
TBZ 50 MG



(Sponsor's Figure 11.14 on page 76 of study-tbz-104-015)

Figure 3: Time-matched, placebo-adjusted mean change from baseline in QTcI by gender

MOX 400 mg



(Sponsor's Figure 11.14 on page 76 of study-tbz-104-015)

Reviewer's comments:
The maximum upper bound of the 2-sided 90% CI for QTcI between the mean difference of TBZ 50-mg and placebo after time-matched baseline adjustment was 10.4 ms. The difference in treatment means was 7.7 ms. In addition, results based on subgroup analyses also show signals of QTc prolongation (Table 2) in female, the upper bound of the 2-sided 90% CI was 13.3 ms and the mean difference was 9.5 ms.

4.2.7.2.2 Categorical Analysis

Categorical analysis of QTcI was conducted in the following groups: absolute QTcI > 500 ms, > 480 ms, and >450 ms; and changes from baseline QTcI ≥ 30 ms and < 60 ms, and ≥ 60 ms. No subject had QTcI > 480 ms, QTcI > 500 ms and a change from baseline QTcI ≥ 60 ms. Five subjects (11.4%) in the 50-mg TBZ, 4 subjects (9.8%) in the Moxifloxacin, and 3 subjects (6%) in 25-mg TBZ groups showed changes of QTcI ≥ 30 and < 60 ms from baseline (see Table 3).

Table 3: Absolute Values and Change from Baseline on Treatment

Category	Placebo N (%)	TBZ 25 mg N (%)	TBZ 50 mg N (%)	MOX 400 mg N (%)
Absolute QTcI new >500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Absolute QTcI new >480 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Absolute QTcI new >450 msec	2 (4.4)	4 (8.0)	4 (9.1)	4 (9.8)
Change from Baseline QTcI ≥30 and <60 msec	1 (2.2)	3 (6.0)	5 (11.4)	4 (9.8)
Change from Baseline QTcI ≥60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

(Sponsor's Panel 11.14 on page 77 of study-tbz-104-015)

4.2.7.2.3 Additional Analyses

The sponsor also performed analyses based on the endpoints QTcF and QTcB.

4.2.7.3 Safety Analysis

There were no deaths or serious adverse events reported during the study. Three subjects were withdrawn from the study because of adverse events (accelerated junctional rhythm, positive fecal hemoccult, and restlessness). One subject (# 1547-0186) had syncope 2 hours following administration of TBZ 25 mg. No action was taken and the AE resolved within 1 minute. The subject's SBP and DBP were 102 and 59 mmHg, respectively, at the time of the event and pulse rate was 58 bpm. The subject also had postural dizziness following administration of TBZ 50 mg. No seizures or ventricular arrhythmias are reported.

The number of subjects who experienced at least one treatment-emergent AE (TEAE) while receiving TBZ 25 mg; 63.6% (28 of 44) subjects experienced at least one TEAE while receiving TBZ 50 mg; 43.9% (18 of 41) subjects experienced at least one TEAE while receiving MOX 400 mg; and 35.6% (16 of 45) subjects experienced at least one TEAE while receiving placebo. The majority of TEAEs reported by subjects were mild in severity, with 82.4% (42 of 51) of subjects reporting an AE of mild severity, and 21.6% (11 of 51) reporting an AE of moderate severity. Six subjects receiving TBZ experienced postural dizziness of moderate intensity. The most commonly reported TEAEs in subjects

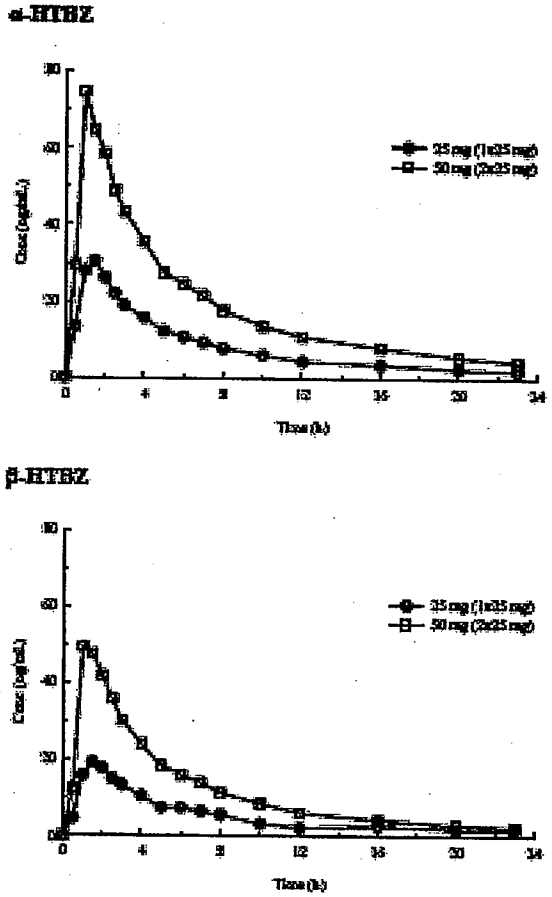
receiving TBZ were somnolence, dizziness (postural), nausea (50 mg dose only), headache, and contact dermatitis.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

Figure 4 shows the mean plasma concentrations of alpha and beta-tetrabenazine after oral administration of 25 and 50 mg dose of tetrabenazine.

Figure 4: Mean plasma concentrations of α-HTBZ) and β-HTBZ after oral administration of 25 mg and 50 mg of TBZ



(Sponsor's Figure 11.1 on page 66 of study-tbz-104-015)

Sponsor conducted non-compartmental analysis of the plasma concentrations of alpha and beta-tetrabenazine. The T_{max} of alpha- and beta-HTBZ is 1.5 hours indicating their rapid formation from TBZ. There is slightly more than dose proportional increase in the C_{max} of alpha and beta-HTBZ. The summary of the pharmacokinetic parameters are shown in Table 4.

Table 4: Summary of non-compartmental pharmacokinetic parameters for alpha-HTBZ after single dose of 25 or 50 mg in Study TBZ 104,015.

Dose	Parameter	Mean ± SD (Range)	Subject 0181	Subject 0198
TBZ 25 mg	C_{max} (ng/mL)	38.2 ± 17.9 (14.5 – 97.5)	40.1	60.9
	T_{max} (h)	1.50[1] (0.50 – 2.50)	1	1.5
	$AUC_{(0-t)}$ (h•ng/mL)	186 ± 104 (50.2 – 512)	398	414
	$AUC_{(0-\infty)}$ (h•ng/mL)	214 ± 131 (53.7 – 593)	521	515
	t½ (h)	6.26 ± 2.28 (2.58 – 11.6)	11.1	9.45
TBZ 50 mg	C_{max} (ng/mL)	88.4 ± 42.7 (16.9 – 263)	—[2]	143
	T_{max} (h)	1.00[1] (0.50 – 4.00)	—[2]	1.5
	$AUC_{(0-t)}$ (h•ng/mL)	426 ± 224 (141 – 1,144)	—[2]	1,036
	$AUC_{(0-\infty)}$ (h•ng/mL)	459 ± 264 (153 – 1,433)	—[2]	—[3]
	t½ (h)	6.49 ± 2.11 (3.67 – 11.2)	—[2]	—[3]

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

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

[3]Parameter could not be estimated.

TBZ=terbenazine

(Sponsor's Panel 11.3 on page 67 of study-tbz-104-015)

APPEARS THIS WAY
ON ORIGINAL

Table 5: Summary of non-compartmental pharmacokinetic parameters for beta-HTBZ after single dose of 25 or 50 mg in Study TBZ 104,015.

Dose	Parameter	Mean ± SD (Range)	Subject 0181	Subject 0198
TBZ 25 mg	C_{max} (ng/mL)	24.2 ± 17.3 (4.47 – 85.5)	85.5	60.9
	T_{max} (h)	1.50[1] (0.50 – 3.02)	3.02	2.00
	$AUC_{(0-t)}$ (h•ng/mL)	127 ± 210 (61.3 – 1,364)	1,364	629
	$AUC_{(0-\infty)}$ (h•ng/mL)	161 ± 314 (9.82 – 1,882)	1,882	1,091
	t½ (h)	4.23 ± 2.88 (1.21 – 19.8)	9.95	19.8
TBZ 50 mg	C_{max} (ng/mL)	61.4 ± 36.2 (5.65 – 173)	—[2]	151
	T_{max} (h)	1.00[1] (0.50 – 3.00)	—[2]	1.5
	$AUC_{(0-t)}$ (h•ng/mL)	274 ± 274 (38.1 – 1,429)	—[2]	1,429
	$AUC_{(0-\infty)}$ (h•ng/mL)	328 ± 404 (43.9 – 2,334)	—[2]	2,334
	t½ (h)	4.90 ± 2.60 (2.35 – 16.3)	—[2]	16.3

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

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

(Sponsor's Panel 11.4 on page 68 of study-tbz-104-015)

4.2.7.4.2 Exposure-Response Analysis

The PK/PD relationship for data collected over 24 hours post-dose was modeled using regression of individual change from baseline ECG parameters (HR, QT, QTcI, QTcF, and QTcB) versus corresponding plasma concentrations of α- HTBZ, β-HTBZ, and total metabolite (α-HTBZ + β-HTBZ). There was no statistically significant relationship between total metabolite concentration or α- HTBZ concentration and change from baseline QTcI ($p>0.05$), whereas a significant positive relationship between β-HTBZ concentrations and change from baseline QTcI was evident ($p=0.0017$). The findings for α- HTBZ and the sum were unexpected; however, given a Tmax of 1 to 1.5 hours and a half-life of 6.5 and 4 to 5 hours for α-HTBZ and β-HTBZ, respectively, analysis of the concentration response during a shorter post-dose interval may yield different results.

Reviewer's Comment: The sponsor's analysis did not account for the delay between total tetrabenazine concentrations or also referred to as total metabolite concentrations. Also the sponsor analyzed using baseline corrected QTcF and not placebo, baseline corrected QTcF. The reviewer's exposure-response analysis by considering the delay for baseline, placebo corrected QTcF is located in section 5.2.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

According to the sponsor's report, the upper bound of the 2-sided 90% CI for the mean difference between the 50-mg TBZ and placebo in the maximum time-matched (at 2.5 hours post-dose) QTcI interval changes from baseline was 10.4 ms (Table 1), which was above the 10 ms identified as the threshold of regulatory concern in the ICH E14 guideline. This is also true for females in the subgroup analyses performed by the sponsor. We surmise that TBZ at the highest therapeutic dose (i.e., 100-mg in divided doses) would further prolong QTc intervals because of expected higher systemic drug exposures. The magnitude of the effect, however, is unknown since there was no available QTcI data at 100-mg TBZ.

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

5.2.1 Exposure-Response Analysis

The reviewer analyzed the data from Study TBZ 104,015 and TBZ 107,018 using total (alpha+beta) HTBZ concentrations as measures of exposure and either change from baseline QTcF (ΔQTcF) or change from baseline and placebo QTcF (ΔΔQTcF) as response variable. For description of study design for TBZ 107,018 please refer to Appendix 6.2.

Figure 5 shows the relationship between ΔΔQTcF (Study TBZ 104,015) versus concentrations of total HTBZ.

Figure 6 shows the maximum mean change from baseline QTcF in Study 104,015 and Study 107,018. Although the study TBZ 107,018 is not a thorough QT study, it appears that at higher concentrations of total tetrabenazine the effects on QTcF do not increase significantly. However, these findings should be interpreted with caution as Study TBZ 107,018 is not a thorough QT study.

Figure 5: Relationship between ΔQTcF and ΔΔQTcF and Total HTBZ

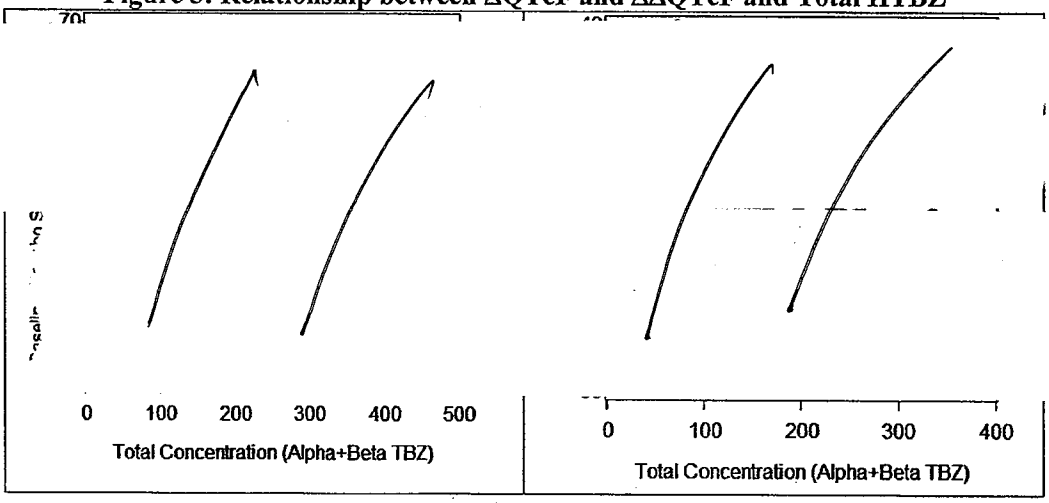


Figure 6: Relationship between C_{max} and ΔΔQTcF (study TBZ 104,015) and ΔQTcF (study TBZ 107,018)

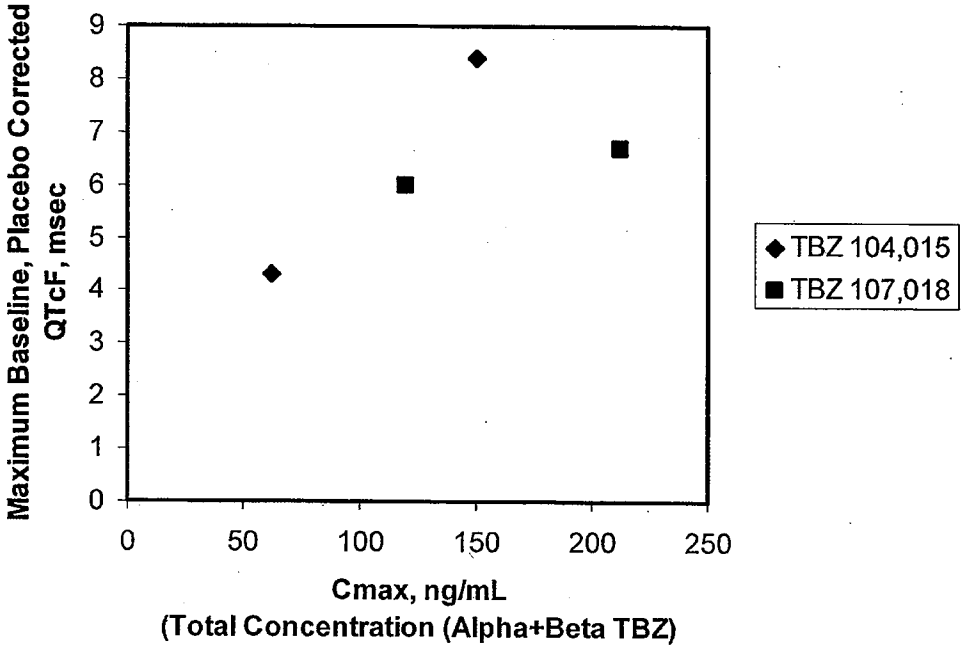
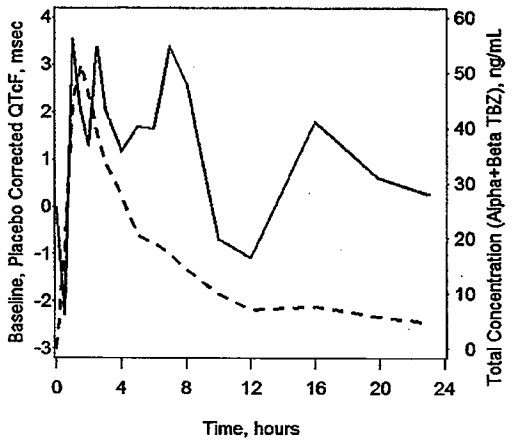


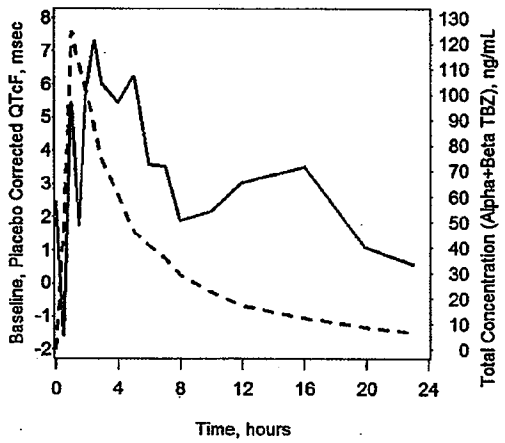
Figure 7 shows the observed mean time course of serum concentrations of total HTBZ and ΔΔQTcF. There appears to be a delay of 1-1.5 hours between the peak serum concentrations of total HTBZ and effects on ΔΔQTcF.

APPEARS THIS WAY
ON ORIGINAL

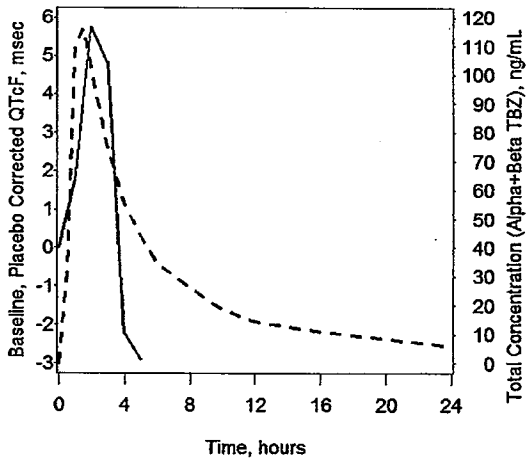
Figure 7: Mean time course of ΔΔQTcF and total HTBZ concentrations after single oral dose of 25 or 50 mg TBZ in Study TBZ 104,015. Shown also is the mean time course of change from baseline QTcF and total HTBZ concentrations after single oral dose of 50 mg TBZ with and without multiple doses of paroxetine (CYP2D6 inhibitor)



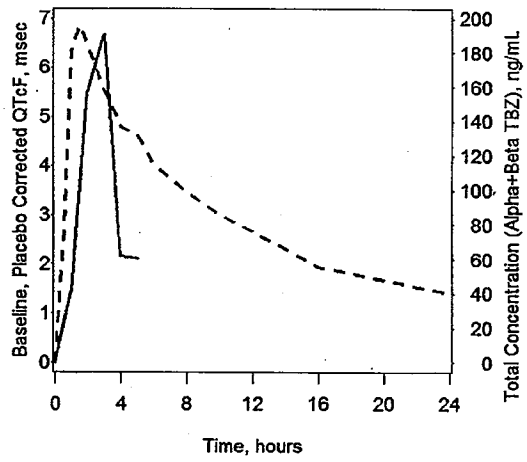
TBZ 104,015: 25 mg



TBZ 104,015: 50 mg



TBZ 107,018: 50 mg without paroxetine



TBZ 107,018: 50 mg with paroxetine

The reviewer conducted non-linear mixed effects analysis using pharmacokinetic and pharmacodynamic data from studies TBZ 104,015 and TBZ 107,018. One PK-PD model accounted for observed delay in the effects of TBZ on QT prolongation (delayed-effect model). The other model assumed no delay in the effects (direct effects).

Figure 8 shows the observed mean and typical model (PK-PD model with delay) predicted line for time course of total HTBZ concentrations and also for ΔΔQTcF for Study TBZ 104,015. Figure 9 shows the observed mean and typical model (PK-PD

model without delay) predicted line for time course of total HTBZ concentrations and ΔΔQTcF for Study TBZ 104,015. Figure 10 shows the observed and individual predicted data for total HTBZ concentrations and ΔΔ QTcF for Study TBZ 104,015. If the model fits are reasonable, the data points should be distributed around the unity line. Overall, the PK-PD model with delay fits the data reasonably well. The estimates of the parameters using PK-PD with delay for Study TBZ 104,015 are shown in Table 5 below.

Figure 8: Observed mean and typical model (PK-PD model <u>with</u> delay) predicted line for time course of total HTBZ concentrations and also for change from baseline, placebo QTcF for Study TBZ 104,015.

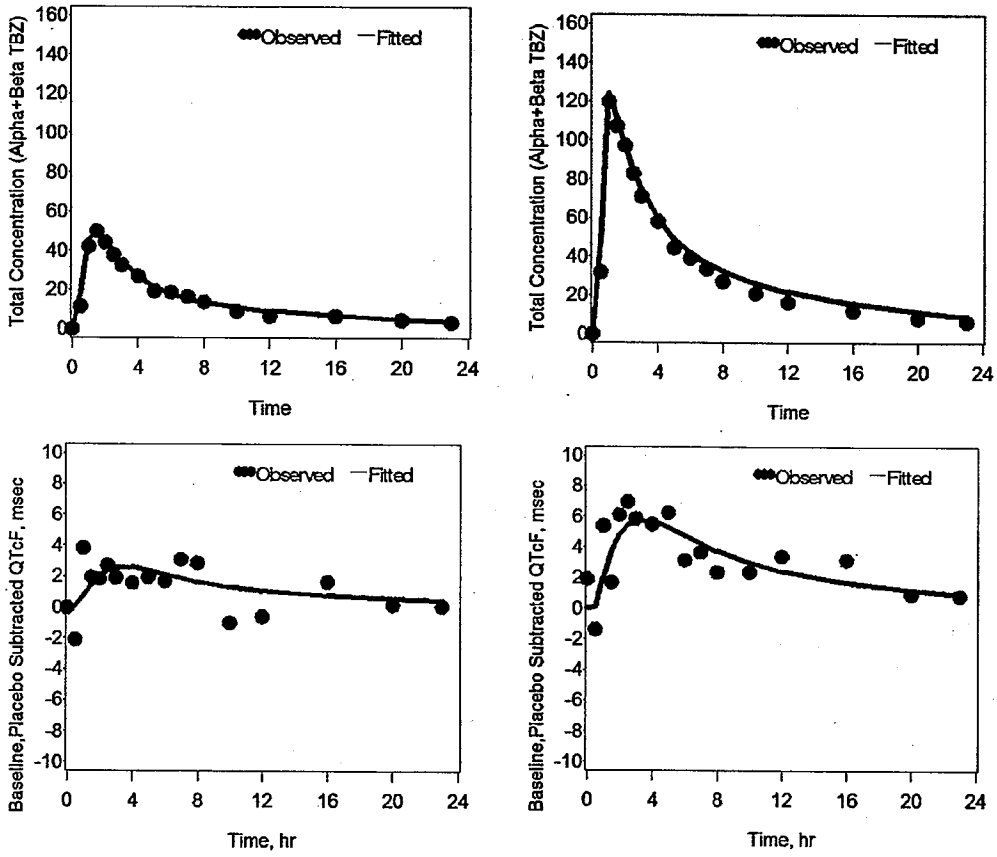


Figure 9: Observed mean and typical model (PK-PD model without delay) predicted line for time course of total HTBZ concentrations and also for change from baseline, placebo QTcF for Study TBZ 104,015.

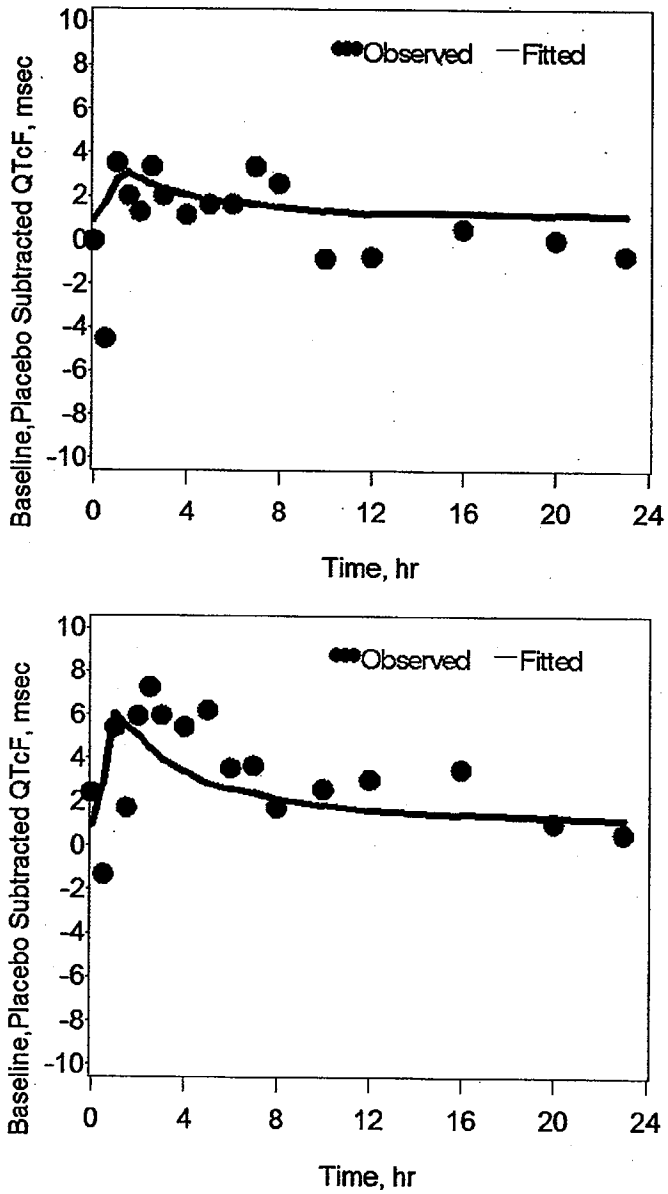
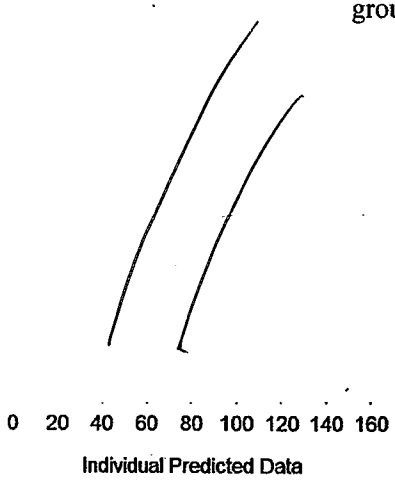
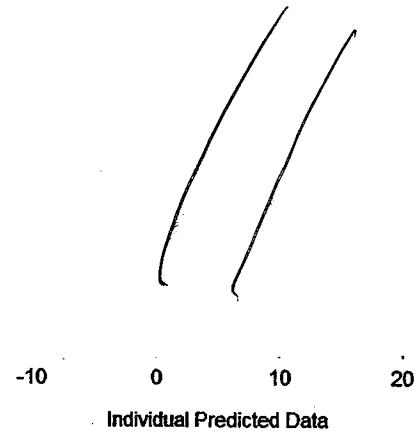


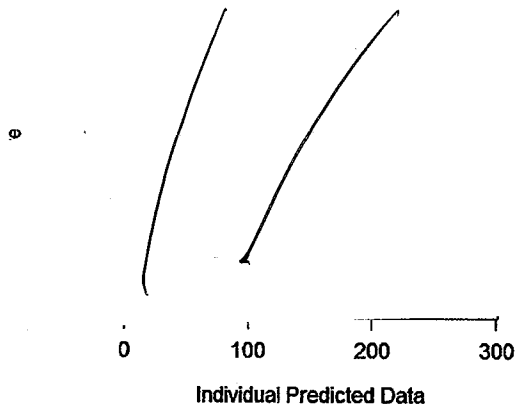
Figure 10: Observed vs. individual predicted (A) Total HTBZ concentrations (B) Change from baseline, placebo QTcF for Study TBZ 104,015 for 25 and 50 mg dose groups.



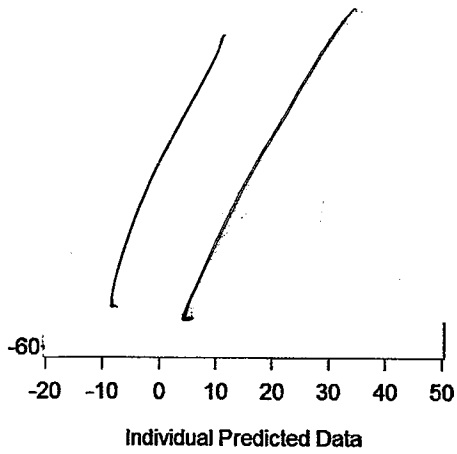
(A): 25 mg



(B): 25 mg



(A) 50 mg



(B) 50 mg

The estimates of the parameters derived from PK-PD model for Study TBZ 104,015 with delay are shown in Table 6. A proportional (22%) and additive (0.39 ng/mL) error model for PK and additive (13 ms) for QTcF was used to explain the residual variability.

Table 6: Estimates of the parameters using PK-PD with delay for Study TBZ 104,015. Shown are the estimates of mean and between subject variability

	Mean	% Between Subject Variability
PK Parameters		
Absorption rate constant, Ka, /hr 25 mg 50 mg	 2 5.6	131
Clearance from central compartment, CL, L/hr 25 mg 50 mg	 64.6 57.5	112
Central volume of distribution, L 25 mg 50 mg	 342 339	40
Intercompartment clearance, Q, L/hr 25 mg 50 mg	 71.9 54.5	99
Peripheral volume of distribution ,Vp, L 25 mg 50 mg	 355 253	76
Lag time 25 mg 50 mg	 0.35 0.43	26
PD Parameters		
Delay Constant, ke0, /hr	0.471	220
Slope, ms/ng/mL	0.0857	11
Intercept, ms	0.0414	331

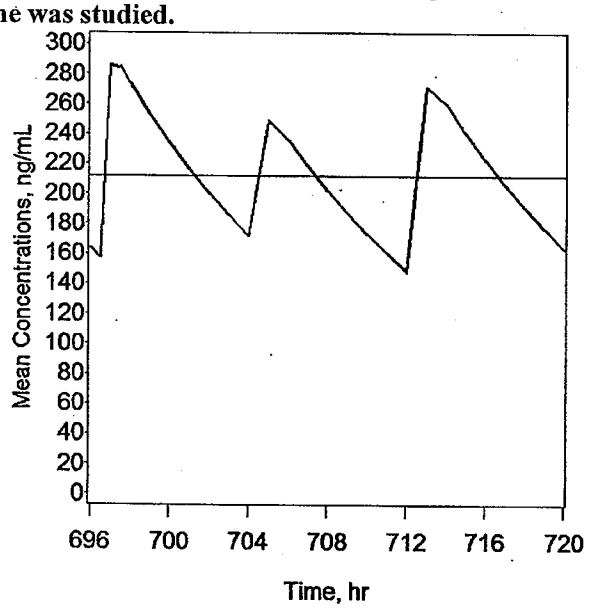
The reviewer conducted analysis for Study TBZ 017,018 using the PK-PD model with delay characteristics. The estimate of the slope for the relationship between total HTBZ concentration and change from baseline QTcF prolongation was 0.06 ms/ng/mL. However, the estimate should be interpreted with caution as it is not a thorough QT study.

5.2.2 Pharmacokinetic Simulations to Project Steady State TBZ

The main purpose of the QT study is to understand at the worst possible clinical scenario what would be the extent of QT prolongation. The sponsor did not explore the worst possible scenario which is patients taking multiple doses of 100 mg TBZ with background strong CYP2D6 inhibitors such as paroxetine.

The reviewer simulated the likely average steady state exposure using Pharsight Clinical Trial Simulator if patient are taking 100 mg total daily dose (given as 37.5 mg in morning, 25 mg in afternoon and 37.5 mg in evening) with paroxetine. By steady state it is implied that patients will be taking the combination of these two drugs for at least 30 days. The simulated average steady state exposures are shown in Figure 11. The predicted maximum concentration is 285 ng/mL which is ~70 ng/mL higher than the observed maximum concentrations (212 ng/mL) in Study TBZ 107,018. The effects of these higher concentrations of TBZ on QT prolongation are not known.

Figure 11: Steady state mean concentration of total HTBZ concentrations in patients taking 100 mg total daily dose of HTBZ and multiple doses of paroxetine. The horizontal reference line at 212 ng/mL is the maximum Cmax observed in Study TBZ 107,018 where interaction between single dose of TBZ and multiple doses of paroxetine was studied.



APPEARS THIS WAY
ON ORIGINAL

5.3 CLINICAL ASSESSMENTS

The only adverse event reported suggestive of proarrhythmic potential as specified in the ICH E14 Guideline (i.e., death, serious ventricular arrhythmia, seizure, or syncope) was a single episode of syncope. The sponsor's narrative of this event states that the heart rate was 58 and blood pressure was normal making it unlikely that the syncope was related to a serious ventricular arrhythmia.

APPEARS THIS WAY
ON ORIGINAL

6 APPENDIX

6.1 TABLE OF STUDY ASSESSMENTS

Study Period	Screening Day -21 to Day -2	[redacted]	End of Study[l]
Obtain Informed Consent[a]	X		
Demographics	X		
Prior/Concomitant Medication Assessment	X		X
Medical History	X		
Physical Exam	X		X[m]
Vital Signs – Routine	X		X
Standard paper 12-lead ECG	X		
Digital 12-lead Mortara ECG from H-12			
PK—Blood samples			
Clinical Lab tests[g]	X		X
Serum Pregnancy Test[h]	X		X
HIV, HepB, HepC Test	X		
Genotyping			
Urine Drug Screen and Ethanol Test	X		X
Adverse Event Assessment			X
Randomization			
Inclusion/Exclusion	X		
Dispense Study Medication			
Housing		X (Check-in)	
Meals		Lunch Dinner Snack	Breakfast Lunch Dinner Snack	Breakfast Lunch Dinner Snack	Breakfast	

NOTE: Procedures performed at Check-in (Day -1), Baseline (Day 0), Treatment (Day 1) and Discharge (Day 2) will be repeated for each of the 4 treatment periods (Periods I, II, III, IV) except as noted below in section m.

[a] A generic screening informed consent and a study-specific informed consent will be obtained at Screening.
[b] Abbreviated.
[c] Or at time of discontinuation.
[d] Standard paper 12-lead ECGs to be collected on Baseline (Day 0) at matching times to Treatment (Day 1) and Treatment (Day 1) at the following time points: predose, and 2 and 4 hours post-dose.
[e] On Day 0 and Day 1 digital Mortara H12 ECGs to be measured at the following time points: predose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 23 hours.
[f] On Day 1 PK samples to be obtained at the following time points: predose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 23 hours following dosing.
[g] Clinical lab tests (4-hour fasted) include hematology, serum chemistry, blood coagulation and urinalysis.
[h] Performed on all female subjects.
[i] Either placebo, active control (moxifloxacin) or TBZ 25 mg or TBZ 50 mg.
[j] Breakfast, lunch, dinner and snack will be given at 2 hr, 4 hr, 10 hr, and 13 hr post-dose on Treatment (Day 1) and at matching times on Baseline (Day 0).
[k] Provided following completion of discharge procedures as subject leaves clinic.
[l] Subject to complete end of study assessments within seven days from discharge of treatment period IV or early termination
[m] Treatment period 1 only.
[n] Vitals signs will be collected on Baseline (Day 0) at matching times to Treatment (Day 1) and Treatment (Day 1) at the following time points: pre-dose, and 2 and 4 hours postdose.
[o] Blood sample for genotyping as "extensive" or "poor metabolizers". A separate informed consent will be obtained for genotyping prior to collection of blood sample.

APPEARS THIS WAY
ON ORIGINAL

6.2 STUDY DESIGN FOR TBZ 107,018

Study TBZ 107,018 is a single-center open-label, sequential drug interaction study without randomization in CYP2D6 extensive metabolizers.

Thirty (30) subjects, 20 male and 10 female, received a single, oral 50 mg dose of TBZ on Treatment Day 1 and Day 10 and paroxetine 20 mg once daily on Treatment Days 3 to 11.

Pharmacokinetic (paroxetine) - Blood samples were drawn to determine plasma concentrations of paroxetine on Treatment Days 8-11 and Discharge Day 12 (24 hours after the dose on Treatment Day 11).

Pharmacokinetic (tetrabenazine, α-HTBZ, ß-HTBZ) - Blood samples were drawn to determine plasma concentrations of tetrabenazine and its two metabolites, α-HTBZ and ß-HTBZ, on Treatment Day 1 (pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours post-dose), Treatment Day 2 (24 and 36 hours pose-dose), Treatment Day 3 (48 hours post-dose), Treatment Day 10 (pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours post-dose), Treatment Day 11 (24, 30, and 36 hours pose-dose), and Discharge Day 12 (48 hours post-dose).

Pharmacodynamic – Twelve-lead electrocardiogram (ECG) data were digitally obtained using [redacted] ECG recorders. ECG data were read in a central ECG laboratory in a semi-automated manner and the reader was blinded to the subject's identifiers, treatment day/date, and the time of recording. On Treatment Days 1, 9 and 10, triplicate ECGs, separated by 1 minute, were obtained immediately prior to the scheduled times of the pharmacokinetic draws at each of the following time points: pre-dose, and at 1, 2, 3, 4, and 5 hours after dosing.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Christine Garnett
12/7/2007 01:30:30 PM
BIOPHARMACEUTICS

Atul Bhattaram
12/7/2007 02:02:25 PM
BIOPHARMACEUTICS

Joanne Zhang
12/7/2007 02:40:08 PM
BIOMETRICS

Moh-Jee Ng
12/7/2007 02:43:10 PM
BIOMETRICS

Stephen Grant
12/9/2007 06:04:01 PM
MEDICAL OFFICER

Norman Stockbridge
12/10/2007 12:55:43 PM
MEDICAL OFFICER

MEMORANDUM
March 23, 2006

TO: File
FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 21-894

I have read the pharmacology/toxicology review by Dr. Andrea Powell for Xenazine® (tetrabenazine) and the memorandum by the pharmacology/toxicology supervisor, Dr. Lois Freed, and concur with both that the nonclinical studies submitted to support the marketing application are inadequate. It is unusual to recommend a non-approval action based on nonclinical deficiencies, but in this case the decision is reasonable. The deficiencies (lack of carcinogenicity studies for a drug intended to be used chronically, inadequate analysis of data from repeat-dose toxicology studies, especially with respect to neuropathology, evidence of poor animal housing practices) may have been tolerated given the indication (chorea associated with Huntington's disease), but it is doubtful, based on available information, that the sponsor took adequate remedial actions.

As stated by the pharmacology/toxicology staff, although carcinogenicity bioassays may be conducted as a Phase IV commitment, the sponsor should demonstrate good faith by conducting preliminary studies prior to any favorable regulatory action. It is my opinion that the sponsor should be expected to commence these carcinogenicity studies prior to any action concerning the marketing application.

Kenneth L. Hastings, Dr.P.H., D.A.B.T.
Associate Director
Office of New Drugs

APPEARS THIS WAY
ON ORIGINAL

Memorandum

DATE: March 16, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-894

SUBJECT: Recommendation for action on NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease (HD)

NDA 21-894, for the use of Xenazine (tetrabenazine) in the treatment of the chorea of Huntington's Disease (HD), was submitted by Prestwick Pharmaceuticals on 4/22/05. The application was withdrawn by the sponsor in anticipation of a refusal to file action that was planned based on an inadequate Integrated Summary of Safety. The application was re-submitted on 9/26/05.

The application contains reports of two randomized controlled trials, Studies 004 and 005, as well as safety data. The safety database is quite small, and much of the data were obtained by the sponsor from Dr. Jankovic, an HD expert at Baylor College of Medicine in Texas, who has been treating patients with tetrabenazine for years under his own IND. The application has been reviewed by Drs. Carol Davis (efficacy) and Elizabeth McNeil (safety), medical officers, Dr. Tristan Massie, statistician, Dr. XXXXX, pharmacologist, Dr. XXXX, chemist, Dr. Sally Usuda, clinical pharmacologist, and Dr. John Feeney, Neurology drugs team leader. I will briefly review the relevant data, and offer the division's position for action on this application.

Study 004

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

The primary measure of efficacy was the difference between drug and placebo on the mean change from baseline in the Chorea Score for the average of Weeks 9 and 12. The Chorea Score is a subset of the Motor Assessment Scale

of the Unified Huntington's Disease Rating Scale (UHDRS). As described by Dr. Feeney, the UHDRS consists of 6 subscales:

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

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

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

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

The following results were seen for the secondary outcomes:

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

For each - say which favored

Functional Assessment		
Tetrabenzine	-0.81	
Placebo	0.37	0.0183*
Gait		
Tetrabenazine	0.0001	
Placebo	0.11	0.2410

*-favors placebo

Other endpoints were evaluated:

Behavioral Assessment (UHDRS Part 3)

Tetrabenazine	-0.96	
Placebo	-2.22	0.355*

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

Cognitive Assessment (UHDRS Part 2)

Tetrabenzine	-7	
Placebo	5	0.025*

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

Independence Scale (UHDRS Part 5)

Tetrabenazine	-1.98	
Placebo	0.55	0.135*

Functional Capacity (UHDRS Part 6)

Tetrabenazine	-0.43	
Placebo	-0.03	0.29*

Further examination of the effect on Chorea

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

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

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

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

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

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

Study 005

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

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

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

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

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

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

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

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

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

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

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

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

be combined because they both were to have been treated on Day 3 prior to the assessment).

The results of these two analyses are displayed below:

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

COMMENTS ON EFFECTIVENESS

The sponsor has submitted the results of two randomized controlled trials that purport to establish the effectiveness of tetrabenazine in the treatment of the chorea of HD. The results of Study 004 are quite robust in this regard, with the primary analysis yielding an extraordinarily low p-value, with extraordinary consistency of the finding across 14/15 centers, and with other ancillary analyses yielding very positive results.

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

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

I do not believe that the sponsor has submitted data that establish substantial evidence of effectiveness under the typical requirement of evidence from at least two independent adequate and well-controlled trials.

Is the evidence, though, consistent with the statutory standard of substantial evidence derived from a single adequate and well controlled trial plus confirmatory evidence?

The Agency's guidance related to the circumstances under which a single study might serve as substantial evidence of effectiveness suggests that such a standard should generally be applied when the drug has an effect on mortality or irreversible morbidity and when such a trial could not be practically or ethically repeated.

I do not believe that these criteria have been met in this case. The effect on chorea is symptomatic, and there would seem to be no ethical impediment to performing another trial.

However, the statute offers a standard that might be met by this data package.

Specifically, the sponsor has provided a single study that clearly could tribute to a finding of substantial evidence of effectiveness. Is there evidence that could fairly be considered confirmatory evidence?

I believe that there is.

First, many of the elements that the "evidence" document suggests could serve to support the use of single trial (putting aside, as noted above, that the effect is not one on mortality or irreversible morbidity) are present here, including a very small p-value, equivalent effects in sub-groups of different disease severity, and numerical superiority of drug compared to placebo in 14/15 study sites. Such findings could be considered to constitute confirmatory evidence (although this language is not used in the "evidence" document, these findings are included in that document to serve exactly the same ends as confirmatory evidence; that is, to support the use of a single adequate and well controlled trial as providing substantial evidence).

Further, the results of Study 005 are, in my view, confirmatory.

Specifically, as noted earlier, I believe the Group 1 vs Group 3 analysis is an appropriate analysis, given the error in the study conduct. The results of this analysis yielded an estimate of the treatment effect essentially identical to that seen in Study 004; further, although the between-treatment contrast did not significance, this is not unexpected, given the very small number of patients included. Ordinarily, I should note, a "failed" second study should not be

considered to "confirm" another, "positive" study. However, for the reasons stated above, I believe in this case that it is reasonable to consider the elements described above in Study 004, together with the results of Study 005, to constitute "confirmatory evidence". For these reasons, then, I consider that the sponsor has provided substantial evidence of effectiveness for tetrabenazine as a treatment for the chorea of HD.

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

Specifically, on many of the components of the UHDRS, patients receiving placebo performed better than those on tetrabenazine, with several of these differences achieving nominal statistical significance. Specifically, patients on placebo performed superiorly on the Functional Assessment, the Behavioral Assessment, the Independence Scale, the Functional capacity, and the Cognitive Assessment, the latter difference reaching nominal statistical significance.

These sorts, and frequency, of differences favoring placebo are unusual, in my experience. These findings do not undermine the effects on chorea, but they do raise significant questions about the approvability of the application. As noted by Dr. Feeney, Study 004 did not include a patient/caregiver assessment of the utility of the treatment; it is possible that the effects on the chorea did not compensate, in the patient's/caregiver's mind, for any of these potentially negative effects that the drug seems to be associated with (assuming any of these negative findings on these scales have detectable clinical consequences). Indeed, it may be difficult to assess in this population any (subtle) deleterious effects of the sorts suggested by these negative findings, although they may be present (and possibly progressive). This, in addition to the occurrence of several significant safety issues identified by the review team (including parkinsonism, EPS, somnolence, and dysphagia resulting in aspiration pneumonia [and potential significant underreporting of this event], as well as significant numbers of patients who discontinued treatment and who were lost to follow-up; I have not reviewed the safety data in depth) raises serious questions about the utility of this treatment.

MEMORANDUM

NDA 21-894 Xenazine (tetrabenazine)

FROM: John Feeney, M.D.
Neurology Team Leader

INDICATION: Treatment of Chorea in Patients with Huntington's Disease

DATE: March 21, 2006

Regulatory History

Xenazine has been proposed for the treatment of the chorea that accompanies Huntington's disease. In other countries, tetrabenazine (TBZ) has been approved for decades for the treatment of hyperkinetic movement disorders. In the United States.

but several hundred patients have been treated over the years under INDs sponsored by Dr.Joseph Jankovic (IND 16,161) and at Baylor University and respectively. As described below, much of the safety data in this NDA is derived from Dr.Jankovic's experience and Baylor was one of the sites in one efficacy study (Study 004) and the only site in the other efficacy study (Study 005). The current sponsor, Prestwick Pharmaceuticals, performed their studies under IND 63,909. In the past, Roche Some of the data collected by Roche is included in this NDA and is referred to as the Nitoman database.

The NDA for TBZ was submitted on April 22, 2005 by Prestwick Pharmaceuticals, Inc. In a June 13 letter, the sponsor withdrew the NDA after the division noted a deficient summary section for safety in the NDA. The resubmission with an updated safety section occurred on September 26, 2002. By prior agreement, the sponsor was granted Fast Track status; as such, TBZ received a priority review. There are no other drugs currently approved for the treatment of HD.

The clinical efficacy review was conducted by Dr.Carole Davis. The clinical safety review was conducted by Dr.Elizabeth McNeil. Dr.Sally Yasuda conducted the clinical pharmacology review. Dr.Andrea Powell reviewed the submitted pharmacology and toxicology data.

Huntington's Disease

Huntington's disease is an autosomal-dominant neurodegenerative disease characterized primarily by neuronal loss in the striatum of the brain. In 1993, the gene responsible for HD was identified on chromosome 4 through linkage analysis of a large