TETRABENAZINE

BRIEFING DOCUMENT FOR
PERIPHERAL AND CENTRAL NERVOUS SYSTEM
ADVISORY COMMITTEE

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Prestwick
PHARMACEUTICALS

EXECUTIVE SUMMARY

Huntington's disease (HD) is a fatal neurodegenerative disease marked by involuntary movements, cognitive decline and behavioral disruption. It afflicts approximately 30,000 patients in the United States (US) and accordingly, tetrabenazine has received Orphan Drug designation from the FDA for the treatment of chorea associated with HD. The adult onset form of HD, which typically manifests between 35 and 40 years of age, is characterized by progressive motor, cognitive, and behavioral symptoms that cause profound disability. The most common presenting symptoms of HD are involuntary movements, or chorea, which can affect all muscle groups. Chorea has significant potential to interfere with daily functioning: In its early stages, chorea can impair speaking, writing, and Activities of Daily Living (ADLs) such as feeding, dressing and bathing; in its later stages chorea causes gait instability and poor postural control, with an increased risk of injury from falling. There are no approved treatments for patients with chorea in the US; further, off-label use of neuroleptics is potentially associated with serious side effects, such as tardive dyskinesia.

Tetrabenazine was first approved in the United Kingdom (UK) for the treatment of chorea more than 30 years ago and is presently approved for treatment of various movement disorders, including Huntington's chorea in several European countries, Canada, Israel, Australia and New Zealand. By selectively inhibiting the central nervous system-specific enzyme vesicular monoamine transporter (VMAT)-2, tetrabenazine (TBZ) depletes pre-synaptic dopamine and decreases chorea in patients with HD. Prestwick Pharmaceuticals, Inc. (Prestwick) submitted a New Drug Application (NDA) in September, 2005 for TBZ in the treatment of chorea associated with HD. The product has been granted Fast Track Status by the US Food and Drug Administration (FDA) because chorea can cause serious disability in some patients and there are no approved treatments for chorea in the US; and TBZ has demonstrated that it can reduce the chorea associated with HD.

The NDA included the results of 7 clinical pharmacology studies, 2 adequate and well-controlled clinical studies (TBZ 103,004, hereafter Study 004; TBZ 103,005, hereafter Study 005) and other supporting information on the safety and efficacy of TBZ as a treatment for the chorea associated with HD. In one well-controlled

clinical trial conducted by the Huntington Study Group (HSG), (Study 004), TBZ consistently and robustly reduced chorea ($p<0.0001$). Efficacy was observed after one week of dosing and the difference from placebo reached statistiscal at 3 weeks and beyond. These findings were confirmed by a responder analysis using a clinically relevant, pre-specified criterion of a 3-point or greater reduction in chorea ($p<0.0001$) and a physician-assessed Clinical Global Impression (CGI) of change ($p=0.0063$). Some patients experienced a profound reduction in chorea associated with TBZ use as 50% of TBZ-treated patients, as compared to 6% of placebo-treated patients, had an improvement in chorea score by 6 more points. Nineteen percent of TBZ-patients had a reduction in chorea score by 10 points or more. The second well-controlled trial (Study 005) demonstrated a treatment effect comparable to that of Study 004. Both studies indicated no evidence of withdrawal of chorea following discontinuation from therapy. The safety of TBZ was demonstrated in more than 500 patients and the most common adverse effects of TBZ included somnolence and related events, insomnia, anxiety/anxiety aggravated, depressive symptoms and restlessness/akathisia. These adverse events are predictable based on the pharmacology of tetrabenazine, namely depletion of pre-synaptic dopamine and, to a lesser extent, serotonin and norepinephrine.

In Study 004, analyses of non-motor endpoints suggested the possibility of small differences in some functional and cognitive measures, favoring the placebo group. One of four functional measures evaluated, the Functional Assessment, revealed small differences that were nominally statistically significant in favor of placebo. However, some other functional measures, particularly those that assess Activities of Daily Living, favored TBZ. In addition, the long-term changes in non-motor endpoints among TBZ-treated patients were consistent with historical data from the placebo group from CARE-HD, one of the largest, prospective HD clinical trial completed to date (Huntington Study Group, 2001). In addition, there were small changes from baseline to Week 12 on cognitive parameters, none of which were clinically or statistically significant. Thus, the balance of evidence does not suggest that TBZ has an adverse effect on functional or cognitive measures.

The adverse events of TBZ, the most common of which include somnolence and related events, insomnia, anxiety/anxiety aggravated, depressive symptoms, and restlessness/akathisia, are consistent with the pharmacology of the drug, namely

depletion of pre-synaptic dopamine and, to a lesser extent, serotonin and norepinephrine. In the clinical trials, these AEs were detected by practitioners and, with dose reduction/discontinuation or other medical management, were reversible. In Studies 004 and 007, patients were titrated to their individualized "best dose": The dosage was to be increased on a weekly basis until: 1) the desired effect was obtained 2) intolerable adverse side effects occurred or 3) the maximum allowed dosage was reached. This dosing strategy allows each patient to receive a dose that balances efficacy and tolerability. AEs were more frequent during the titration period of dosing than during maintenance therapy.

In summary, there is a significant unmet medical need for treating chorea associated with HD. Tetrabenazine demonstrated robust efficacy in the development program and offered substantial benefit to many individual HD patients. The response to TBZ is rapid, often being observed within days, thus enabling the physician and patient to determine if the efficacy achieved outweighs potential adverse effects of treatment. Tetrabenazine has a safety profile that is well characterized and can be managed through careful titration and dose adjustment. Data from individual patients shows that dose adjustment or other medical management is successful in ameliorating the adverse events that emerge during treatment with TBZ. Accordingly, Prestwick strongly believes that the benefit-risk ratio for TBZ is favorable and warrants approval of TBZ for the treatment of chorea associated with HD.

TABLE OF CONTENTS

TABLE OF CONTENTS (CONTINUED)

TABLE OF IN-TEXT TABLES

TABLE OF IN-TEXT TABLES (CONTINUED)

TABLE OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine (serotonin)
ADE	Adverse Drug Event
ADL	Activities of Daily Living
ADR	adverse drug reaction
AE	adverse event
AKR	aldo-keto reductases
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate transaminase
β-HTBZ	β-dihydrotetrabenazine
BA	Behavior Assessment
BARNES	Barnes Akathisia Scale
b.i.d.	twice a day
BP	blood pressure
C	Colors sub-item of Stroop test
CAG	cytosine-adenine-guanine
CGI	Clinical Global Impression
C_{max}	Maximum plasma concentration
CNS	Central Nervous System
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CR	Complete Response
CRF	case report form
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CW	Color Words sub-item of Stroop test
CYP	Cytochrome P450
DA	dopamine
DAP	Data Analysis Plan
DAT	dopamine transporter
DDI	Drug-Drug Interaction
EC_{50}	effective concentration required to induce a 50% effect
ECG	electrocardiogram
ED_{50}	median effective dose
ESS	Epworth Sleepiness Scale
FA	Functional Assessment
FDA	Food and Drug Administration
FIS	Functional Impact Scale
GLP	Good Laboratory Practices
H	hour
HAM-D	Hamilton Depression rating scale
HD	Huntington's disease
hERG	human *ether-à-go-go* related gene
5-HIAA	5-hydroxyindoleacetic acid
HSG	Huntington Study Group
HTBZ	dihydrotetrabenazine
HVA	homovanillic acid
IC_{50}	inhibition concentration (concentration that reduces the effect by 50%)
ID	Identification
IND	Independence Scale
ISS	Integrated Summary of Safety
i.p.	intraperitoneal
ITT	Intent-To-Treat
i.v.	intravenous
Kg	kilogram
LOCF	Last Observation Carried Forward
m^2	meters squared
MAOI	monoamine oxidase inhibitor
MCA	Medicines Control Agency
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMS	Mini-Mental State
MRHD	Maximum Recommended Human Dose
msec	millisecond
MSN	medium spiny neuron
N	number
NDA	New Drug Application
NE	norepinephrine
ng	nanogram
NMS	Neuroleptic Malignant Syndrome
NNH	Number Needed to Harm
NOAEL	NO Adverse Effect Level
PD	pharmacodynamics
PDCMDC	Parkinson's Disease Center and Movement Disorders Clinic
PE	Physical Examination
PET	Positron Emission Tomography
P-gp	P-glycoprotein
PK	pharmacokinetics
p.o.	by mouth
Prestwick	Prestwick Pharmaceuticals, Inc.
q.d.	once daily
r	Pearson correlation coefficient
RiskMAP	Risk Minimization Action Plan
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SDR	short-chain dehydrogenases/reductases
SEM	standard error of the mean
$t_{½}$	half-life
TBZ	Tetrabenazine
TFC	Total Functional Capacity
THD	Tetra HD (subset-of CARE-HD similar to Tetra HD)
t.i.d.	3 times a day
t_{max}	time to reach Cmax
TMS	Total Motor Score
TQT	Thorough QT
UHDRS	Unified Huntington's Disease Rating Scale
UK	United Kingdom
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VMAT	vesicular monoamine transporter
W	Words sub-item of Stroop test
WHO	World Health Organization

1 BACKGROUND

1.1 Tetrabenazine

Tetrabenazine (TBZ), a hexahydro-dimethoxy-benzoquinolizine derivative, is a centrally acting oral agent that depletes presynaptic dopamine stores. It has a molecular formula of $C_{19}H_{27}NO_3$ and molecular weight of 317.4. It is formulated as a tablet for oral administration.

The structure of TBZ is shown below (Figure 1).

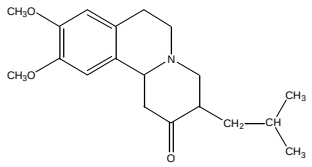


Figure 1. Structure of Tetrabenazine

1.2 Clinical Development History

1.2.1 Clinical Trials

Tetrabenazine was initially developed by Hoffmann-La Roche in the mid-1950s as an antipsychotic drug. Although the drug never gained widespread use for the treatment of schizophrenia it was found – in several small, randomized, controlled clinical trials conducted in the early 1970s and 1980s – to be effective for the treatment of chorea, especially the chorea associated with Huntington's disease (HD). In all, 35 papers reporting on 420 TBZ-treated chorea patients were published between 1960 and March 2007[1]. The double-blind studies and open-label studies reporting on 14 or more patients are summarized in Table 1. There was an improvement rate ranging from 55 to 100% across the published studies based on a variety of different assessments (e.g., blinded clinical observation from videotapes, modified Abnormal Movement Scale, global response scale, Clinical

[1] Bandrup, 1960; Moller-Christensen and Videbech, 1963; Sattes and Hase, 1964; Pakkenberg, 1968; Dalby, 1969; Fog and Pakkenberg, 1970; Soutar, 1970; Aminoff and Marshall, 1974; Astin and Gumpert, 1974; Gilligan et al., 1972; Swash et al., 1972; McLellan, 1972; McLellan et al., 1974; Fortemps and Laterre, 1976; Huang, 1976; McArthur et al., 1976; Hawkes and Nourse, 1977; Toglia et al, 1978; Kingston, 1979; Asher and Aminoff, 1981; Shoulson and Goldblatt, 1981; Lang and Marsden, 1982; Lubbe and Walker, 1983; Moss and Stewart, 1986; Gimenez-Roldan and Mateo, 1989; Schott et al., 1989; Noel, 1992; Linazasoro et al., 1993; Jankovic and Beach, 1997; Shanahan et al., 2001; Ondo et al., 2002; Chatterjee and Frucht, 2003; Paleacu et al., 2004; Sitburana and Ondo, 2006; Kenney et al., 2007.

Global Impression of Change, clinical observations by investigator, patient subjective rating).

Table 1. Published Tetrabenazine Studies* in Patients with Chorea

Author/Investigator	Year	No. of Patients	TBZ Improvement Rate
Double-Blind Placebo-Controlled Crossover Studies			
Gilligan et al	1972	6	– †
McLellan et al	1974	10	8/10 (80%)
Asher and Aminoff	1981	8	6/8 (75%)
Jankovic	1982	19 §	16/19 (84%)
Double-Blind Comparator Crossover Study			
Swash et al	1972	7	6/7 (86%)
Open-Label Studies			
Sattes and Hase	1964	14	14/14 (100%)
McLellan	1972	23	13/23 (57%)
Astin and Gumpert	1974	26	24/26 (92%)
Kingston	1979	31	30/31 (97%)
Jankovic and Beach	1997	29 §	28/29 (97%)
Ondo et al	2002	19	15/19 (79%)
Paleacu et al	2004	28	19/28 (68%)
Kenney et al	2007	98	80/98 (81%) ‡

* Double-blind studies or open-label studies with ≥ 14 patients.
† Benefit in 11/18 patients with hyperkinetic disorders; results for 6 of these patients with chorea of HD were not reported.
‡ Marked or moderate reduction in abnormal movements, excellent or very good improvement in function.
§ Nineteen patients reported in Jankovic (1982) are also reported in Jankovic and Beach (1997)

In the United States (US), HD patients have been receiving TBZ for several years under 3 physician-initiated Investigational New Drug Applications. One of these Investigational New Drug Applications is with the Parkinson's Disease Center and Movement Disorder Clinic (PDCMDC) at Baylor College of Medicine (Baylor). The other 2 are with the Neurological Institute at Columbia-Presbyterian Medical Center and the Neurology Clinical Research Organization at Duke University Medical Center.

The first study conducted at Baylor was a double-blind, placebo-controlled, crossover study in 19 patients with hyperkinetic movement disorders, including HD chorea (Jankovic, 1982). The study showed that TBZ (mean ± SD dose 171±50) was significantly superior to placebo in reducing abnormal movements and that the drug was well tolerated. After the double-blind study was completed, the investigators continued to enroll and to treat patients at Baylor in an open-label fashion. In 1997, results of the first 400 patients with various hyperkinetic

movement disorders treated with TBZ between 1980 and 1995 were published; the investigators reported favorable clinical response, particularly in chorea, as well as good tolerability and safety (Jankovic and Beach, 1997). The same group recently reported on the long-term efficacy and tolerability of TBZ for an additional 448 patients treated between 1997 and 2004 (Kenney et al., 2007).

In 2004, data collected in all chorea patients (N=145) treated at Baylor from January 1, 1979 to February 29, 2004 were analyzed by Prestwick Pharmaceuticals, Inc. (Prestwick). This analysis included patients with chorea associated with HD (N=98) and patients with chorea associated with other diseases (N=47). In 2005, data collected for all patients with hyperkinetic movement disorders excluding chorea (most common diagnoses were tardive dyskinesia [n=87], Tourette's syndrome [n=66], cranial dystonia [n=26], and cervical dystonia (torticollis) [n=20]) treated between January 1, 1997 and March 31, 2002 were analyzed (N=280). Safety data from these Baylor chorea and non-chorea patients treated with TBZ are presented in this Briefing Document.

1.2.2 Regulatory History

Tetrabenazine was first approved in the United Kingdom (UK) for the treatment of organic movement disorders in 1971. In 2007, TBZ was approved for HD chorea or hyperkinetic movement disorders in the Netherlands, Italy, and Germany. A complete list of current approvals can be found (Table 2).

Table 2. Regulatory Approvals of Tetrabenazine

Country	Indication(s)	Year of Approval
Netherlands	Huntington's chorea	2007
Germany	Huntington's chorea and tardive dyskinesia	2007
Italy	Organic movement disorders and tardive dyskinesia	2007
France	Huntington's chorea and hemiballismus	2005
Israel	Organic movement disorders and tardive dyskinesia	2005
Portugal	Organic movement disorders and tardive dyskinesia	2003
Canada	Organic movement disorders and tardive dyskinesia	1995
Denmark	Hyperkinesias	1980
Australia	Organic movement disorders and tardive dyskinesia	1979
New Zealand	Organic movement disorders and tardive dyskinesia	1973
Ireland	Organic movement disorders (tardive refused)	1971
UK	Organic movement disorders and tardive dyskinesia	1971

Approvals in Norway (1982) and Hong Kong (1983) have lapsed. A marketing application has been submitted recently in Spain.

Tetrabenazine was granted Orphan Drug designation by FDA in 2004 for the indication "treatment of HD." In 2005, the FDA granted fast track designation with priority review for TBZ for "chorea associated with HD" because: 1) Chorea contributes to the serious disability observed in HD and alone can be considered to be seriously disabling in some patients, 2) Treatment of HD chorea represents an unmet medical need, as there are no approved drugs for the treatment of chorea in HD, and 3) Preliminary studies suggest a potential benefit of TBZ in treating chorea associated with HD.

The objective of Prestwick's clinical development program in the US was to confirm and extend the existing efficacy and safety clinical experience with TBZ. The US clinical program consisted of:

- Twelve (12) Phase 1 studies;
- Two (2) double-blind, prospective, placebo-controlled studies in HD patients (Study TBZ 103,004 [hereafter Study 004] and Study TBZ 103, 005 [hereafter Study 005]);
- Two (2) open-label, long-term extension studies to the double-blind studies (Study TBZ 103,007 [hereafter Study 007] and Study TBZ 103,006 [hereafter Study 006]); and
- Investigator-initiated studies conducted at Baylor, as described above (including chorea and non-chorea patients).

A New Drug Application (NDA) for tetrabenazine was filed by Prestwick in September 2005 for the proposed indication of treating chorea associated with Huntington's disease. In its March 2006 Approvable Letter, the FDA acknowledged that Prestwick has "provided substantial evidence of effectiveness for tetrabenazine as a treatment for chorea in patients with Huntington's disease." In addition, they commented that the efficacy of TBZ "seems to be present regardless of the baseline degree of severity of chorea." The FDA went on to express concern about a consistent tendency of non-motor outcomes to favor placebo in Study 004, specifically behavioral, functional, and cognitive measures. The FDA noted that although the differences were numerically small, some reached nominal statistical significance. The FDA acknowledged that the impact of these small effects on patient function is unknown. The FDA also expressed concern about TBZ's capacity to cause parkinsonism, depression, akathisia, and

dysphagia and whether practitioners could readily identify these events and consider the possibility that they may be drug related.

1.3 Huntington's Disease

Huntington's disease is a fatal neurodegenerative familial disorder marked by involuntary movements, cognitive decline, and behavioral disruption. The relentless functional decline that patients experience may be due to difficulties in any of these domains, either in isolation or combination. The hallmark physical sign of HD is chorea, and the clinical diagnosis is based on the presence of the characteristic movement disorder in a patient with a family history of the disease. Although cognitive and behavioral symptoms may antedate the motor features of HD (Kirkwood, et al., 2001), the sequence of the emergence of cognitive and behavioral changes in HD is not well characterized. Early in the disease process, the cognitive deficits tend to be focal, with preservation of language and insight but deficits in executive functioning, short-term memory and visuospatial processing. Later in the disease the cognitive deficits become more widespread (Lawrence, et al., 1996). The behavioral changes have no clear progression, but can be debilitating at any stage of the disease (Folstein, et al., 1983). Affective disorders are the most prevalent of the behavioral disturbances, with rates of major depression and mania/hypomania of up to 50% and 12%, respectively (Purdon et al., 1994). There are no known interventions to slow the progression of HD, and there are currently no FDA-approved drugs for any symptomatic features of the illness.

1.3.1 Epidemiology and Pathology of Huntington's Disease

HD is an autosomal dominant disorder characterized by progressive loss of medium spiny neurons in the striatum and to a lesser extent of pyramidal neurons in the cortex. The disease is due to a trinucleotide $(CAG)_n$ repeat in the *huntingtin* gene located on Chromosome 4.

The average age of HD onset is between 35 and 40 years, but there is a wide variability of symptom onset spanning pediatric to geriatric populations. In the US, the prevalence rate of HD has been reported to be in the ranges of 4-5 to 8-10 per 100,000 (Marshall and Shoulson, 1997; Minager et al., 2000), with approximately 30,000 affected individuals.

Progression of the disease is slow and inexorable, with death ensuing approximately 10 to 20 years after onset of the first symptoms. Pneumonia is the leading cause of death (1/3 of events) in HD patients, followed by cardiovascular disease and suicide (Schoenfeld et al. 1984, Farrer 1986). Pneumonia typically results from aspiration associated with the swallowing dysfunction from the underlying dysphagia. This dysfunction, which may include lingual chorea, incoordination of swallowing, and the inability to regulate respiration, is independent of the clinical severity of the disease and is a major source of morbidity, especially in late-stage disease.

Suicide rates for symptomatic HD patients have been reported to be 7- to 10-fold higher than for the general US population (Bird 1999; Paulsen 2005). The caudate dysfunction of HD is associated with impaired impulse control, which is thought to contribute to the increased rate of suicide in HD patients. The progressive nature of the disease and the lack of available treatments may also be contributing factors.

1.3.2 Chorea Associated With Huntington's Disease

Chorea is an involuntary jerky movement that is purposeless and abrupt. Somatic muscles are affected in a random manner, and chorea flows from one part of the body to another (Cudkowicz, et al., 1999; Fahn, 2000). Each abnormal choreic movement is a single isolated muscle contraction, a short, rapid, uncoordinated jerk. These jerks can be proximal or distal and are of enough magnitude to move the involved limb. The simultaneous or successive occurrence of 2 or more such isolated movements can result in complex movement patterns (Klawans and Kramer, 1980). The superimposition of chorea causes disruption of voluntary movements; in patients with severe chorea, most voluntary movements become impossible. The severity of chorea in patients with HD varies, but abnormal movements usually become gradually more severe and many patients finish their years with very severe chorea that compromises motor function. In patients with particularly late onset (older than age of 55), chorea is often the most prominent component of HD (Harding, 1993).

Huntington's disease was originally termed Huntington's *chorea*, owing to the motor manifestations that characterize the illness. Despite the fact that chorea can be extremely disabling in some patients, few publications actually link chorea with impaired function. Although some prior studies have failed to demonstrate a

correlation between chorea and functional measures (Mahant et al., 2003), previous analyses have focused on scale totals rather than on specific aspects of function.

Other studies have demonstrated that chorea has a substantial impact on day-to-day functioning and that chorea contributes greatly to the HD patient's disability (Kirkwood, et al., 2001). Chorea of the trunk and legs, in combination with poor postural control, worsens gait instability and increases the risk of serious injury and falling, which may result in fractures and head trauma (Harding, 1993; Koroshetz, 1996; Haddad and Cummings, 1997; Duus, 1998; Cudkowicz et al., 1999). The resulting injuries from these abnormal movements have been reported to be serious (Klawans and Kramer, 1980).

Large amplitude chorea in the upper extremities can interfere with voluntary movements. Chorea impairs the ability of HD patients to communicate by talking, keyboarding and handwriting. Chorea contributes to the patient's disability not only as a direct result of disruption of voluntary motor function, but because it can be a source of extreme embarrassment (Cudkowicz et al., 1999). Such embarrassment may result in social isolation and consequent loss of quality of life. Many HD patients experience difficulty finding or maintaining employment due to their abnormal appearance long before the loss of motor function becomes functionally limiting. As chorea increasingly interferes with eating, dressing, bathing and other Activities of Daily Living (ADLs), HD patients become dependent on others.

To understand the impact of chorea on function, baseline data from a large, well-controlled study were analyzed (Frank, et al., 2004). Logistic regression was used to examine correlations between chorea score and individual items of the Functional Assessment (FA). Patients with more severe chorea were less likely to be employed in either accustomed work ($p<0.003$) or any work ($p<0.0007$), supervise children independently ($p<0.003$) or operate an automobile ($p<0.003$). In the subgroup of patients least affected by non-chorea domains of HD, decreased function was correlated with total maximal chorea ($r = -0.24$, $p=0.03$). The analysis showed that total maximal chorea is a predictor of disability as measured by specific items on the FA. Overall, the more complex individual items such as employment, driving, and caring for children significantly worsen with increasing severity of chorea. The authors suggested that when assessing

correlates of disability, specific tasks should be analyzed as well as overall functional status.

A study of 97 institutionalized HD patients demonstrated that they were more impaired in motor, psychiatric and behavior domains than were their counterparts who were living at home (Wheelock, et al., 2003). Analysis revealed that motor correlates alone, and not psychiatric or behavioral correlates, were predictive of institutional care. The study therefore concluded that treatment strategies that delay the progress of motor dysfunction may postpone the need for institutionalization.

The ability to perform a complex motor task in HD has recently been shown to have a strong inverse correlation with the degree of chorea burden (Aldrich, 2007), both at baseline and after 3 years of follow-up. The decline in ability to perform a complex motor task was more tightly correlated with worsening chorea than with any other measured component of the Unified Huntington Disease Rating Scale (UHDRS), including measures of bradykinesia, dystonia, oculomotor, or functional scales.

1.3.2.1 Current Treatment Options for Chorea

Given the disabling nature of HD chorea and its impact on affected patients' day-to-day functioning, an agent that reduces the chorea or improves voluntary motor control would provide a major health benefit for HD patients. Currently there is no FDA-approved treatment for chorea associated with HD. Drugs that block dopamine (DA) transmission (neuroleptics or reserpine) are currently used, but central and peripheral adverse effects limit their use. Unlike TBZ, reserpine binds irreversibly to the vesicular monoamine transporter (VMAT)-2 (see Section 2.2.2) and acts both centrally and peripherally, resulting in persistent adverse events including hypotension. In an evidence-based review of publications from 1969-2005, Bonelli and Wenning pointed out that there is currently no agent that is demonstrated to be "efficacious" or "likely efficacious" for chorea, primarily due to a lack of level 1a trials (i.e., randomized, controlled, and study quality >75%). Not surprisingly, agents used in clinical practice today were recently classified as having insufficient evidence with regard to their efficacy (Bonelli and Wenning, 2006).

1.3.3 Rating Scales in Tetrabenazine Trials

Outcome measures employed in the TBZ clinical trials included the UHDRS, the Clinical Global Impression (CGI), and the Functional Impact Scale (FIS), all of which are discussed below. Well-established scales to assess neurological side effects were also employed, including the Hamilton Depression rating scale (HAM-D), the Barnes akathisia rating scale (BARNES), the Epworth Sleepiness Scale (ESS) and the dysphagia and dysarthria components of the Unified Parkinson's Disease Rating Scale (UPDRS).

1.3.3.1 The Unified Huntington's Disease Rating Scale (UHDRS)

The UHDRS was developed by the Huntington Study Group (HSG) to assess performance in 4 clinical domains of HD: motor assessment, cognitive assessment, behavioral assessment and function (assessment, capacity and independence). Table 3 summarizes the UHDRS (parts 1 through 6) and provides the range of scores and domains assessed.

Table 3. UHDRS Domains and Functional Impact Scale Discussed in Briefing Document

Domain Scale	No. Items	Range of Score	Best Score [1]	Areas Assessed
Motor				
Total Motor Score	15*	0 – 124	0	Ocular pursuit, saccade initiation/velocity, dysarthria, tongue protrusion, parkinsonism, luria, dystonia, chorea (7 regions, as below)
Chorea Score	1	0 – 28	0	Face, bucco-oral-lingual (BOL), trunk, arms,legs
Cognition				
Symbol Digit	1	0 – 120	120	Psychomotor speed, attention
Verbal Fluency	1	–	–[2]	Memory, attention
Stroop Interference Score	3	–	–[2]	Selective Attention, executive functions
Behavioral Assessment (BA)	11*	0 – 88	0	Depressed mood, low self esteem, anxiety, suicidal thought, aggression, irritability, obsession, compulsion, delusions, hallucination, apathy.
Functional Assessment (FA)	25 *	0 – 25	25	Gainful employment in accustomed work; any gainful employment; any volunteer/non-gainful work. Without help, can: manage finances, shop for groceries, handle money, supervise children, safely operate an automobile, perform own housework, do own laundry, prepare own meals, use telephone, take medications, feed self, dress self, bathe self, use public transportation, walk to destination in neighborhood, walk, walk without falling, comb hair, transfer between chairs, get in/out of bed, use toilet/commode. Ability to receive care at home
Independence Scale (IND)	1	10 – 100	100	Level of independence
Total Functional Capacity (TFC)	5 *	0 – 13	13	Occupation, finances, domestic chores, ADL, and care level
Functional Impact Scale (FIS)	5 *	0 – 15	0	Bathing, dressing, feeding, social isolation, and toileting

* Appendix 1 provides an item-by-item listing of these parts of the UHDRS and of the FIS.
[1] Best score indicates no impairment.
[2] No Best Score. Higher score reflects better performance.

Part 1 of the UHDRS includes 17 items that assess motor status (e.g., ocular pursuit, saccade initiation and velocity, dysarthria, tongue protrusion, gait, tandem walking, maximal dystonia). Item 12 of part 1 provides a Maximal Chorea Score (ranging from 0= absent to 28 = marked/prolonged) based on assessments of the face, bucco-oral-lingual, trunk, and extremities. Part 2 of the UHDRS evaluates cognition using verbal fluency, symbol digit modalities, and Stroop (color naming, word reading, and interference) tests. In the Behavioral Assessment (part 3), a 5-point rating scale is used to quantify the frequency and severity of depressed mood, low self-esteem/guilt, anxiety, suicidal thoughts, disruptive or

aggressive behavior, irritable behavior, perseverative/obsessional thinking, compulsive behavior, delusions, hallucinations, and apathy.

The UHDRS includes three assessments of function (assessment, capacity and independence). The FA (part 4) consists of 25 items that are scored as 0 (No) or 1 (Yes), with the composite score computed from summing the item scores. The TFC consists of scores for occupation, finances, domestic chores, ADLs and care level. Occupation, finances and ADLs are scored as 0, 1, 2 or 3, with "3" reflecting "normal"; domestic chores and care level are scored as 0, 1 or 2, with "2" reflecting "normal" and "home," respectively. The Independence Scale (IND) is an investigator-assigned score ranging between 10 and 100, with 100 reflecting "no special care needed" and 10 reflecting "tube fed, total bed care." Of note, a higher score indicates improved function on the FA, IND, and TFC.

The UHDRS was intended as a tool to monitor progression of illness in HD longitudinally (Huntington Study Group, 1996). As the authors sought to develop a tool for evaluating interventions that modify disease progression, they suggested the UHDRS may be suitable for tracking longitudinal changes. The instrument was not intended to assess the impact of short-term treatment effects, although it has been used for such purposes. There is no measure within the UHDRS that specifically measures disability due to chorea. The FA, TFC, and the IND are inadequate to measure potential functional benefit from chorea reduction alone. For this reason, the FIS, which is a more direct measure of ADLs, was piloted in Study 004.

In a UHDRS development-study, longitudinal changes in the domains of HD clinical performance were evaluated with the aim of determining the usefulness of the UHDRS in tracking these changes (Siesling et al., 1998). The changes from baseline in UHDRS were assessed in 78 patients at 1 year and 13 patients at 2 years. A significant decline in motor function, as assessed by the Total Motor Score, was seen at 1 year. The Total Dystonia Score, but not the Total Chorea Score, showed a statistically significant increase at 1 year. The IND, FA, TFC, and Symbol Digit were also statistically significantly decreased at 1 year. There was a decline in the IND and TFC and an increase in the Total Motor Score at 2 years. The authors concluded that the UHDRS is a useful tool for monitoring disease progression and recommended a total motor evaluation yearly and a total UHDRS rating every 2 years.

The utility of the FA as a measure of change in function has several important limitations. First, the FA was intended to be used as a checklist to gather information regarding a HD patient's abilities to perform specific tasks. As such, the FA is comprised of 25 items of widely varying significance. For example, on one end of the spectrum the FA includes several questions about employment and finances, and on the other end, questions about ability to comb hair or perform other less significant daily care tasks. The score for each of the 25 items is weighted equally in the calculation of the overall FA score, despite the fact that a patient with a score change on gainful employment would seemingly be affected differently than a patient having the same score change for ability to use the telephone without help. Many of the FA items (e.g., drive a car, gainful employment, supervise children) would not generally be expected to improve within a 12-week study period.

Secondly, there is no clear way to distinguish acute, transient effects from long-term, more permanent disruption of tasks captured by the FA. At any visit that the FA is assessed, acute self-limiting illness or adverse event (AE) (e.g., somnolence, anxiety) from medication could interfere with task performance, thereby adversely affecting FA score. The only way to differentiate acute from persistent study drug effects is to examine each patient's longitudinal data, but even this approach may not provide clarity since HD is a progressive illness (i.e., decline in FA is expected) with a variable course.

FA, as well as all other functional measures used in HD, does not capture the basis for impairment: The scales do not ascertain whether chorea, cognition or behavior accounts for the functional impairment. Most of the FA items, including those closely linked with motor function can be negatively impacted by not only motor impairment, but importantly, also by the cognitive and behavior effects of HD. The IND and TFC are also similarly affected by the motor, cognitive and behavioral effects of HD. Hence, none of these functional scales appear suitable to specifically measure functional change that could occur from a reduction in chorea alone.

Given the various limitations of the functional scales in the UHDRS and their non-specificity for chorea, the Study 004 Steering Committee agreed to pilot the FIS in Study 004. The FIS uses 4-point scoring (0, 1, 2 or 3) for 5 ADLs – bathing, dressing, feeding, social isolation and toileting – with "0" reflecting

"independent" or "no difficultly going outside of home (excluding physical limitations)." The FIS is much closer to standard ADL scales used in clinical research, certainly a more specific itemization of ADLs than in Question 73 of the TFC.

1.3.3.2 Other Scales Utilized in the Briefing Document

Additional scales employed in the TBZ clinical trials and presented in this Briefing Document are summarized in Table 4. CGI-Improvement assesses global improvement from baseline (Appendix 1); scores of 1, 4, and 7 represent very much improved, no change, and very much worse, respectively. Investigators were instructed that CGI-Improvement should be used as a measure of patients' global improvement, not as a proxy measure of improved chorea.

The ESS, HAM-D, and BARNES were performed periodically during the clinical trials to monitor the safety of TBZ.

Table 4. Other Scales Discussed in Briefing Document

Domain Scale	No. Items	Range of Scores	Best Score*	Areas Assessed
BARNES Akathisia Rating Scale	4	0-14	0	Objective and subjective assessments of restlessness; global clinical rating of akathisia
Clinical Global Impression - Improvement	1	0-7	0	Improvement vs. baseline
Epworth Sleepiness Scale	8	0- 24	0	Chance of dozing when: sitting and reading; watching TV; sitting, inactive in a public place; as a passenger in a car; lying down to rest in the afternoon; sitting and talking to someone; sitting after lunch; in a cap stopped for a few minutes in traffic
Hamilton Depression Rating Scale	17	0 –52	0	Depressed mood, feeling of guilt, suicide, insomnia (early, middle, late), work and activities, retardation, agitation, anxiety (psychic, somatic). Somatic symptoms (gastrointestinal, general), genital symptoms, hypochondriasis, weight loss, insight

* Best score indicates no impairment.

1.3.4 Natural History of Huntington's Disease

As discussed in Section 1.3, HD is a chronic, disabling disorder characterized by involuntary movements, cognitive decline, and behavioral disorders, resulting in progressive decline in function. Each of these areas contributes to the functional disability seen in HD.

In order to characterize the natural history of HD, data from CARE-HD, the largest, prospective, well-controlled clinical trial of patients with mild HD completed to date, were examined (Huntington Study Group, 2001). The CARE-HD study stands as an independent source for estimating the natural history of functional decline that would be expected to occur in HD patients. The CARE-HD study randomized 347 patients with mild HD into 4 treatment groups using a factorial design as follows: (1) remacemide, (2) coenzyme Q10, (3) remacemide + coenzyme Q10, or (4) double placebo. Patients were evaluated every 4 to 5 months for up to 30 months. As no treatment effect was observed in this study, these data provide meaningful data on the natural history of HD.

The majority of patients in the CARE-HD population were Caucasian (95%), just over half (51%) were male, and the mean (± SD) age was 47.9 (± 10.5) years. The mean (± SD) time since onset of symptoms was 4.9 (± 3.0) years. Consistent with the known natural history of HD, declines in function and cognition and increases in chorea and Total Motor Score were observed at 16 weeks and thereafter over the course of the study (Figures 2-5).

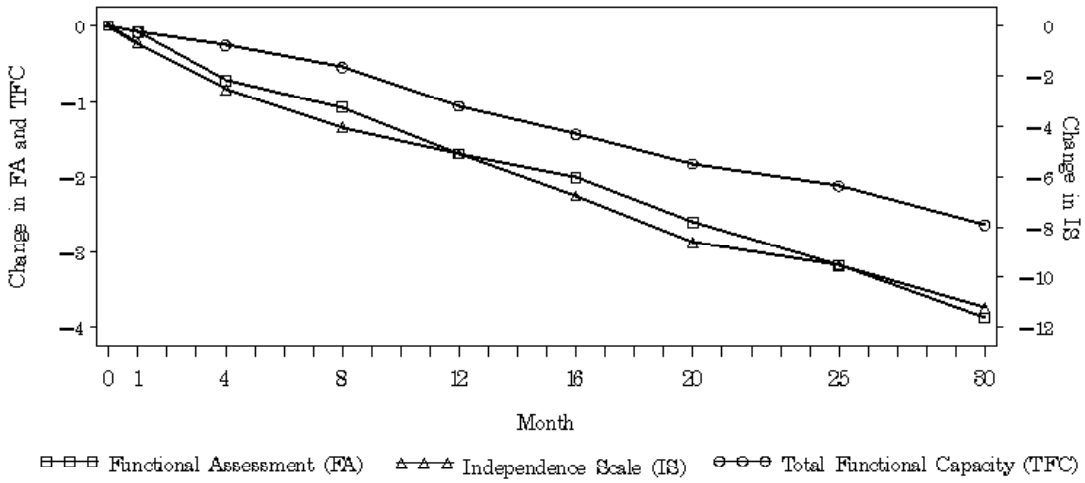


Figure 2. Mean Change in Functional Measures in CARE-HD: All Subjects

Note: Higher scores on FA are associated with better function.

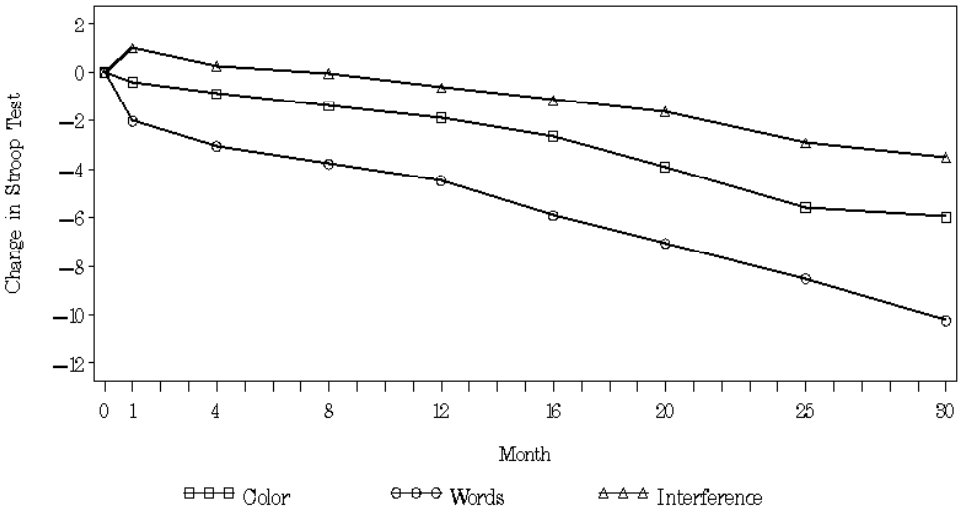


Figure 3. Mean Change in Cognitive Parameters (Stroop Test) in CARE-HD: All Subjects

NOTE: Higher scores on cognitive tests are associated with improvement.

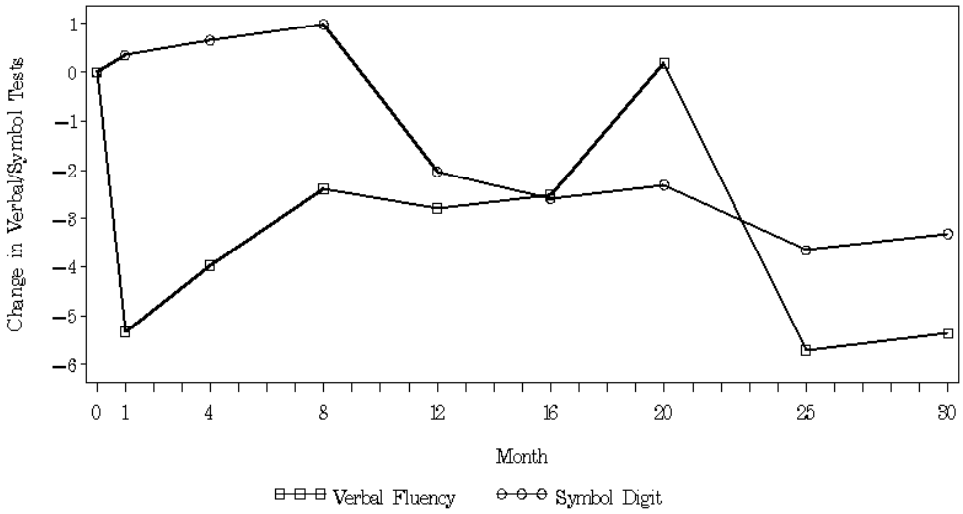


Figure 4. Mean Change in Cognitive Parameters (Verbal Fluency, Symbol Digit) in CARE-HD: All Subjects

Note: Higher scores on cognitive tests are associated with improvement.

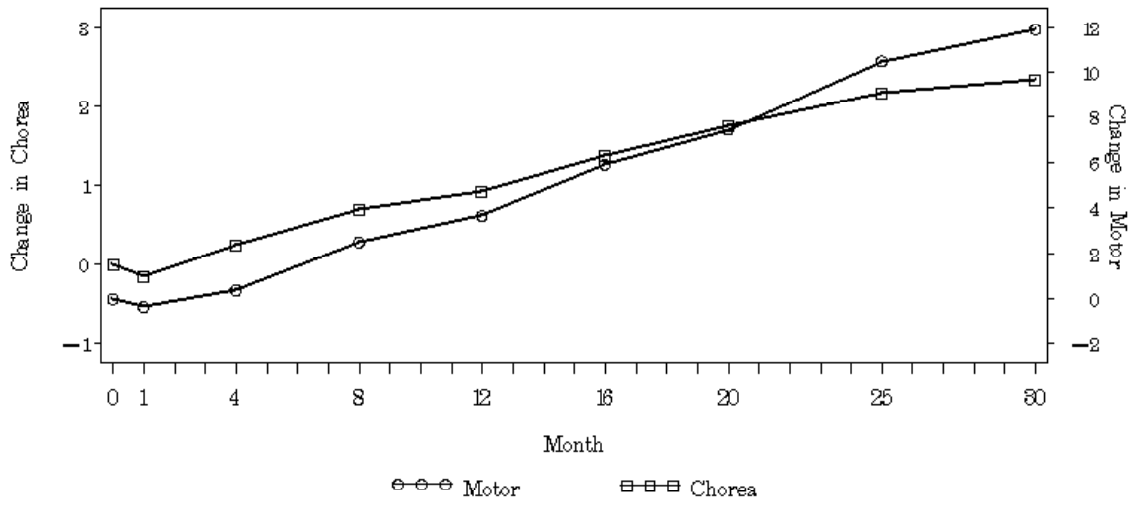


Figure 5. Mean Change in Chorea and Motor Score in CARE-HD: All Subjects

Note: Lower chorea scores are associated with better function.

2 NON-CLINICAL PHARMACOLOGY

2.1 Rationale for Reducing Dopaminergic Neurotransmission in Huntington's Disease

The connection between DA and HD was first established when over a third of asymptomatic relatives of HD patients developed dyskinesias in response to levodopa treatment (Klawans et al., 1980). The same response can be elicited in HD patients when brain levels of DA are increased after receiving levodopa. In the transgenic mouse model, DA contributes to the deleterious effects of mutated huntingtin on striatal function, and this is accompanied by enhanced formation of huntingtin aggregates (Cyr et al., 2006). Moreover, persistent elevation of striatal DA levels exacerbates the behavioral motor deficits and degeneration of striatal medium spiny neurons in the transgenic mouse model of HD (Tang et al., 2007). HD appears to show oversensitivity to DA stimulation, resulting in the appearance of involuntary movements and possibly contributing to striatal neurodegeneration. The mutation in the polyglutamine extension of the huntingtin protein, which is characteristic of HD, might be responsible for a preferential vulnerability of medium spiny neurons (MSNs) to DA, leading to protein aggregation and neurotoxicity by oxidative stress (Charvin et al., 2005). The foregoing data implicate excess DA in the pathogenesis of involuntary movements when there is a genetic predisposition to HD and suggest that a drug such as tetrabenazine, which depletes presynaptic DA, has potential in treating such abnormal movements.

2.2 Mechanism of Action

2.2.1 Tetrabenazine-Induced Monoamine Depletion

Tetrabenazine has been known since the late 1950s to be a potent and selective depletor of monoamines from nerve terminals (Quinn et al., 1959; Pletscher et al., 1962; Butcher and Anden, 1969; Bagchi, 1983). The effects of TBZ are largely restricted to neurons within the central nervous system (CNS) (Pettibone et al., 1984). The CNS selectivity of TBZ clearly differentiates it from reserpine, a drug that produces both central and peripheral depletion. In a study by Pettibone et al., TBZ dose-dependently reduced brain norepinephrine (NE), dopamine (DA), and serotonin (5-HT) concentrations in rats (Figure 6) (Pettibone, et al., 1984). For all 3 neurotransmitters, the effect of TBZ was maximal at 15 minutes and lasted throughout the 2-hour duration of the experiment.

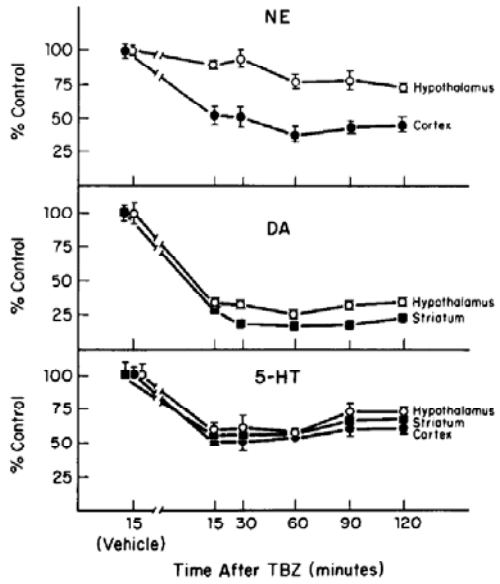


Figure 6. Monoamine Depletion Induced by Tetrabenazine in Various Brain Regions

Source: Pettibone et al., 1984

Dose response to TBZ in various brain regions. Animals received TBZ or vehicle s.c. and were sacrificed 45 minutes later. Values are percent control. Each point represents a group mean. DA=dopamine, 5-HT=serotonin, NE=norepinephrine, TBZ=tetrabenazine.

Other studies showed that monoamine depletion induced by a single dose of TBZ is reversible and lasts only a few hours (Pletscher, et al., 1962). This feature also clearly differentiates TBZ from reserpine, a drug that causes irreversible, long-lasting monoamine depletion.

As shown in Figure 6 and in Table 5, TBZ affects DA more than it affects NE or 5-HT. For example, at a dose of 2 mg/kg s.c., TBZ depleted striatal DA by approximately 80%, but did not induce more than a 50% reduction in cortical NE and 5-HT. Furthermore, at a dose of 0.5 mg/kg, TBZ depleted striatal DA by approximately 60%, but induced only a modest 15 to 20% reduction in striatal 5-HT and cortical NE. As shown in Table 5, 45 minutes after s.c. drug administration, the ED_{50} for DA depletion was approximately 0.4 mg/kg for DA, but was approximately 5-fold higher for both NE and 5-HT.

Table 5. ED_{50} Values (mg/kg s.c.) for Tetrabenazine-Induced Monoamine Depletion 45 Minutes After Drug Administration

Monoamine	ED_{50} (mg/kg s.c.)
DA (striatum)	~ 0.4
NE (cortex)	~ 2.0
5-HT	~ 2.0

Source: Pettibone et al., 1984.
DA=dopamine, 5-HT=serotonin, NE=norepinephrine.
ED_{50} = median effective dose

Similar results were obtained in post-mortem brains from HD patients with or without a history of TBZ treatment (Pearson and Reynolds, 1988). The TBZ-treated group showed a general reduction in brain monoamines, the greatest reduction being in DA in the caudate. DA depletion in the striatum probably explains the antichorea efficacy of TBZ in HD patients, whereas 5-HT depletion in the cortex may underpin the risk of depression. Since the doses of TBZ required to deplete 5-HT are higher than the doses required to deplete DA, it seems possible to achieve antichorea efficacy while minimizing the risk of depression.

Positron Emission Tomography (PET) scan studies conducted in humans also suggest a preferential effect of TBZ on DA. PET scan studies show that TBZ selectively labels the striatum (abundant in DA and the likely site of antichorea efficacy), but not the cerebral cortex (rich in 5-HT and NE) (Figure 7). In published PET scan studies, tracer retention was highest in the striatum, and approximately 70% lower in the thalamus, frontal cortex and cerebellum (Koeppe et al., 1997; Koeppe et al., 1999).

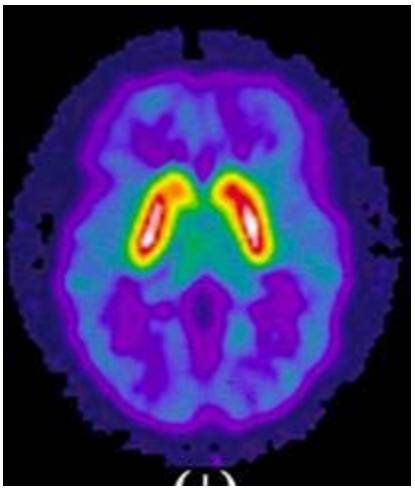


Figure 7. Transaxial PET Images Depicting the Preferential Distribution of the α-[^{11}C]HTBZ at Basal Ganglia in a Normal Human Subject

In both animals and in humans, TBZ is rapidly and almost completely transformed by first-pass metabolism to dihydrotetrabenazine (HTBZ) (a mixture of diasteriomers α-HTBZ and β-HTBZ). The ratio of α-HTBZ to β-HTBZ varies among species, including humans, and within individuals in a species. Mehvar and Jamali studied the *in vivo* effects of HTBZ (3 mg/kg i.p.) on rat brain monoamine content, and compared these effects to those of a same dose of TBZ (3 mg/kg i.p.) (Mehvar et al., 1987). Brain monoamine content was determined pre-dose and at 0.5, 2, 5, and 24 hours post-dose. In addition, brain and serum concentrations of TBZ and its main metabolite, HTBZ, were measured at the same timepoints. HTBZ readily crosses the blood brain barrier. Monoamine depletion at any timepoint following the administration of HTBZ was at least as great, if not greater than, following the administration of TBZ. As previously reported by Pettibone *et al*., DA was the most affected and 5-HT was the least affected by TBZ (Pettibone, et al., 1984). The same was observed with HTBZ. Brain levels of monoamines returned to control values 12 hours post-administration of either TBZ or HTBZ.

The CNS monoamine-depleting effects of TBZ were maintained unchanged during chronic treatment (12-month; 6.0-6.7 mg/kg/day; rats) (Hong et al., 1987). These results indicate that tolerance does not develop to the effects of TBZ.

2.2.2 Vesicular Monoamine Transporter (VMAT)

Tetrabenazine depletes presynaptic monoamines, such as DA by inhibiting vesicular monoamine transporter (type 2). Two distinct classes of monoamine transport systems participate in synaptic transmission. One, the plasma membrane dopamine transporter (DAT), is found at the synapse and serves to terminate the action of a transmitter by removing it from the synapse (Stahl and Meltzer, 1978; Rostene et al., 1992). The other is found inside the neurons and more specifically within and spanning the membranes of synaptic vesicles. This transporter, referred to as the principal brain synaptic VMAT, translocates monoamines from the cytoplasm into the synaptic vesicle for storage.

Further research revealed the existence of 2 VMAT isoforms, VMAT1 and VMAT2, encoded by 2 distinct but highly related genes (Peter et al., 1993; Surratt et al., 1993). In humans, VMAT2 is expressed nearly exclusively in the brain, whereas VMAT1 is expressed in peripheral tissues (Gonzalez et al., 1994).

Packaging of neurotransmitters in synaptic vesicles is essential for 2 reasons: to protect monoamines from degradation in the cytoplasm and to regulate the release of monoamines into the synaptic cleft. Inhibition of VMAT causes monoamines to remain in the cytoplasm, where they are rapidly degraded by monoamine oxidases, depleting their storage (Scherman et al., 1986).

By using *in vitro* brain homogenates, TBZ and its active metabolites α- and β-HTBZ, have been shown to be selective, high affinity inhibitors of monoamine uptake into the synaptic vesicles of monoaminergic neurons. As compared to β-HTBZ, α-HTBZ exhibits a 3- to 4-fold greater *in vitro* binding affinity to VMAT2.

The relative potencies of TBZ and its primary metabolites to inhibit VMAT-2 are displayed in Table 6.

Table 6. Inhibitory Concentrations of VMAT-2 by Tetrabenazine and Primary Metabolites *

Compounds	EC_{50} (nM)
TBZ	3.0
α-HTBZ	6.0
β-HTBZ	20.0

Source: Scherman, et al., 1988.
* Data from bovine chromaffin granules.
HTBZ=dihydrotetrabenazine, TBZ=tetrabenazine, VMAT=vesicular monoamine transporter.

2.3 Interactions with Other Receptors and Channels

Tetrabenazine and its primary metabolites do not show interaction with any of the classic neurotransmitter-related receptors such as DA, gamma-aminobutyric acid (GABA), glutamate, glycine, histamine, NE, or ion channels.

3 CLINICAL PHARMACOLOGY

3.1 Human Pharmacokinetics

3.1.1 Absorption and Distribution

Following oral administration of TBZ, the extent of absorption is at least 85%. After single oral doses of tetrabenazine tablets ranging from 12.5 to 50 mg, plasma concentrations of TBZ are generally below the limit of detection. Tetrabenazine undergoes rapid and extensive hepatic metabolism via carbonyl reductase to form α-HTBZ and β-HTBZ as the primary active metabolites. Peak plasma concentrations (C_{max}) of α-HTBZ and β-HTBZ are reached within 1 to 1.5 hours post-dosing (Table 7).

Table 7. Summary of Tetrabenazine's Clinical Pharmacology Profile

	α-HTBZ	β-HTBZ
T_{max} (hours)	1-1.5	1-1.5
C_{max} (ng/mL) *	51.1 ± 31.9	21.0 ± 20.3
AUC (ng·hr/mL) *	205 ± 119	68.4 ± 55.3
$t_{1/2}$ (hours)	2-6	2-4

* Day 4, 25 mg bid
AUC = area under the concentration vs. time curve; C_{max}=maximum concentration in plasma; $t_{1/2}$=elimination half life; HTBZ=dihydrotetrabenazine; TBZ=tetrabenazine; T_{max}=time at C_{max}.
NOTE: Plasma concentrations of TBZ are sparse and when quantifiable, are only slightly greater than the limit of quantitation. Consequently, pharmacokinetic parameters cannot be estimated for TBZ.

The effects of food on the bioavailability of TBZ were studied in subjects administered a single dose with and without a high fat/high calorie meal. Food has no effect on either mean plasma concentrations, C_{max}, or area under the plasma concentration time curve (AUC) of α-HTBZ or β-HTBZ.

Steady-state plasma concentrations with α-HTBZ and β-HTBZ are achieved after approximately 1 to 2 days of dosing. Following administration of single oral TBZ doses of 12.5 mg, 25 mg, and 50 mg, mean plasma concentrations, C_{max}, and AUC of α-HTBZ increased slightly greater than proportionally to dose. At steady state, there is an approximate 30%-60% increase (accumulation) in plasma concentrations of α-HTBZ and an approximate 40%-70% increase in plasma concentrations of β-HTBZ.

Results of PET-scan studies in humans show that radioactivity is rapidly distributed to the brain following i.v. injection of ^{11}C-labeled TBZ or α-HTBZ. Binding was highest in the striatum and lowest in the cortex.

The *in vitro* protein binding of TBZ, 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%.

3.1.2 Metabolism

After oral administration, TBZ is extensively metabolized to its primary metabolites α-HTBZ and β-HTBZ. The ratio of α-HTBZ to β-HTBZ is approximately 3 to 1, while it can potentially vary more than 20-fold between individuals; this variation is largely explained by differences in clearance of β-HTBZ. The clinical significance of the ratio of α-HTBZ to β-HTBZ has not been determined. The mean terminal elimination half-life of α-HTBZ is between 2 and 6 hours whereas that of β-HTBZ is between 2 and 4 hours.

In vitro studies with human-derived systems identified carbonyl reductase as the major enzyme responsible for converting TBZ to α-HTBZ and β-HTBZ. The carbonyl reductase present in red blood cells converted TBZ to α-HTBZ only, but did so at a very low rate, indicating that the reduction of TBZ to α-HTBZ and β-HTBZ occurs largely in the liver. Experiments with cytochrome P (CYP) enzymes identified CYP1A2 as largely responsible for the oxidative metabolism of TBZ by human liver microsomes, but, compared with carbonyl reductase, this pathway has a minor role in the overall metabolism of TBZ.

In vitro studies indicate that α-HTBZ and β-HTBZ are *O*-dealkylated and hydroxylated by human liver microsomes, but their metabolism is primarily catalyzed by different CYP enzymes: CYP2D6 and CYP3A4 in the case of α-HTBZ and CYP2D6 in the case of β-HTBZ. A mass balance study in healthy volunteers (N=6) confirmed that formation of the major circulating and urinary metabolites of TBZ involves reduction of TBZ to primary metabolites α-HTBZ and β-HTBZ, their subsequent conversion to secondary metabolites, *O*-dealkylated HTBZ, followed by formation of sulfate and/or glucuronide conjugates.

3.1.3 Excretion

After oral administration, TBZ is extensively metabolized, and the metabolites are primarily eliminated by the kidney. In a mass balance study in healthy volunteers (N=6), approximately 75% of the dose was excreted in the urine; fecal recovery accounted for approximately 7% to 16% of a dose. Unchanged TBZ has not been found in human urine. Urinary excretion of α-HTBZ or β-HTBZ accounted for less than 10% of the administered dose. Circulating metabolites, including sulfate and/or glucuronide conjugates of HTBZ metabolites, as well as products of oxidative metabolism, account for the majority of metabolites in the urine.

3.2 Drug-Drug Interactions

3.2.1 *In Vitro* Summary of Metabolism

As mentioned in the previous section, *in vitro* metabolism studies identified carbonyl reductase as the major enzyme responsible for converting TBZ to α-HTBZ (a pharmacologically active metabolite) and to β-HTBZ (a less active metabolite). Furthermore, TBZ, α-HTBZ, and β-HTBZ are all *O*-demethylated and hydroxylated by human liver microsomes, but their metabolism is primarily catalyzed by different cytochrome enzymes. The routes of TBZ metabolism were elucidated in 4 *in vitro* studies of TBZ, α-HTBZ, and β-HTBZ and in human- and animal-derived test systems.

The results of reaction phenotyping studies indicate that CYP3A4 and CYP2D6 are both responsible for metabolizing α-HTBZ. Similar *in vitro* work demonstrated that CYP2D6 is the major enzyme responsible for metabolizing β-HTBZ, with CYP3A4 playing a partial role in the formation of one of the minor metabolites of β-HTBZ. The *in vitro* finding that CYP2D6 is primarily responsible for metabolizing β-HTBZ and only partially responsible for metabolizing α-HTBZ is entirely consistent with clinical observations.

In vitro studies indicate that neither TBZ, α-HTBZ, nor β-HTBZ inhibit cytochrome P450 isoenzymes at clinically relevant concentrations. Also, studies with human hepatocytes indicate that neither TBZ, α-HTBZ, nor β-HTBZ induce microsomal CYP enzymes.

Tetrabenazine and it metabolites were evaluated as potential substrates and inhibitors of P-glycoprotein (P-gp). The potential of TBZ, α-HTBZ, and β-HTBZ

as P-gp substrates was assessed in: 1) Mardin-Darby canine kidney cells transfected with the human P-glycoprotein gene (MDR1-MDCK) and 2) MDCK cells by performing the bidirectional permeability assay in the absence and in the presence of the P-gp inhibitors, cyclosporin A and ketoconazole. The potential to inhibit P-gp was assessed by testing the bidirectional permeability of digoxin in the absence and in the presence of TBZ, α-HTBZ, and β-HTBZ in human colon adenocarcinoma cells (Caco-2) cell monolayers. The results of these studies showed that TBZ and it metabolites are not substrates for P-glycoprotein-mediated transport nor do they inhibit digoxin efflux at clinically relevant doses ($C_{max}/IC_{50} < 0.002$).

3.2.2 Human Drug-Drug Interaction Studies

Two drug-drug interaction studies were conducted to assess the possible interaction between TBZ and protein transporter P-gp and between TBZ and CYP2D6.

The first was a digoxin interaction study (Study TBZ 203,009), a single center, open-label study designed to assess the effect of repeated doses of oral TBZ (25 mg in the morning and 25 mg in the evening for 4 days) on the protein transporter P-gp. In the gut, P-gp transports digoxin through the intestinal epithelium. The bioavailability of digoxin when co-administered with TBZ therefore served as a marker of a potential *in vivo* interaction between P-gp and TBZ. Subjects were enrolled in the study and were treated with digoxin alone from Day 1 to Day 6. From Day 7 to Day 10, subjects continued to receive digoxin and in addition received TBZ. A total of 16 subjects were enrolled in the study (6 males and 10 females); 12 (6 males and 6 females) completed the study. PK results showed that the concomitant use of TBZ and digoxin did not alter the PK characteristics of either drug.

The paroxetine (potent CYP-2D6 inhibitor) interaction study (Study TBZ 107,018) was a single-center open-label, sequential drug interaction study that was conducted to assess the possible interaction between TBZ and the potent CYP2D6 inhibitor 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. The exposure to α-HTBZ and β-HTBZ, as measured by C_{max} and $AUC_{0-\infty}$, was increased when TBZ was administered after treatment with the strong CYP2D6

inhibitor paroxetine. For both α-HTBZ and β-HTBZ, the effect of CYP2D6 inhibition on AUC was substantially larger than the effect on C_{max}. With robust CYP2D6 inhibition, the α-HTBZ C_{max} increased by approximately 45% and the β-HTBZ C_{max} increased by approximately 2.7-fold. The $AUC_{0-\infty}$ for α- and β-HTBZ increased by 3.4- and 9.6-fold, respectively. Thus, the increases in exposure to β-HTBZ, for which CYP2D6 is responsible for the vast majority of the metabolism, were greater than those for α-HTBZ, which is metabolized to a similar extent by both CYP2D6 and CYP3A4.

3.2.3 Special Populations

Gender: There is no apparent effect of gender on the pharmacokinetics of α-HTBZ or β-HTBZ based on population pharmacokinetics.

Renal Disease: The effect of renal insufficiency on the pharmacokinetics of TBZ and its primary metabolites has not been studied.

Hepatic Impairment: The disposition of TBZ was compared in 6 patients with mild to moderate chronic hepatic impairment (Child-Pugh scores of 5-9) and 6 age- and gender-matched subjects with normal hepatic function who received a single 25-mg dose of TBZ. Tetrabenazine C_{max} (56 ng/mL) was approximately 30-fold higher in hepatic impairment than the maximum observed concentration (1.8 ng/mL) in healthy subjects. Exposure (AUC) and elimination half-life increased as the Child-Pugh score increased. The times to peak concentration (T_{max}) for α-HTBZ and β-HTBZ were later than in age-matched controls (1.75 hrs versus 1.0 hrs), and the elimination half-lives of α-HTBZ and β-HTBZ were prolonged by approximately 34% and 62%, respectively. The exposure to α-HTBZ and β-HTBZ was approximately 15% and 20% greater, respectively, in patients with hepatic impairment compared to age-matched controls. For both α-HTBZ and β-HTBZ, AUC and elimination half-life increased as the Child-Pugh score increased. However, the range of α-HTBZ to β-HTBZ AUC ratios observed was not dependent upon hepatic function. Since the relationship between the increased exposure to TBZ and exposure to other circulating metabolites is unknown, and the contribution of TBZ or those metabolites to safety and efficacy is not known, it is not possible to adjust the dosage of TBZ for hepatic impairment.

3.3 Human Pharmacodynamics

The precise mechanism by which TBZ exerts its anti-chorea effects is unknown, but is thought to be related to its effect as a reversible and short-acting depletory of monoamines (such as DA, 5-HT, NE, and histamine) from nerve terminals. Tetrabenazine and its primary metabolites, α-HTBZ and β-HTBZ, reversibly inhibit the human VMAT-2, resulting in decreased uptake of monoamines, predominantly DA, into synaptic vesicles, thereby reducing dopaminergic neurotransmission. As compared to β-HTBZ, α-HTBZ exhibits a 3- to 4-fold greater *in vitro* binding affinity to bovine VMAT-2. Tetrabenazine exhibits weak *in vitro* binding affinity at the dopamine D2 receptor (Ki = 2100 nM).

3.3.1 Cardiac Repolarization

Peak concentrations of TBZ, α-HTBZ, and β-HTBZ following single dose administration of a 50 mg dose, when corrected for protein binding, were more than 100-fold lower than the IC_{50} of the hERG (human *ether-à-go-go* related gene) channel current.

In a Thorough QT (TQT) study, 42 healthy volunteers received 4 treatments including placebo, TBZ 25 or 50 mg, and moxifloxacin 400 mg. The maximum time-matched, placebo-corrected change from baseline in QTcI was 3.6 (90% CI, 1.0, 6.2) and 7.7 (5.0, 10.4) msec for TBZ 25 mg and 50 mg, respectively. Similarly, outlier analyses did not demonstrate a signal of concern. The comparative result for moxifloxacin was 12.5 (9.7, 15.3) msec (Table 8).

Under conditions expected to cause nearly complete inhibition of CYP2D6, the C_{max} for α-HTBZ and β-HTBZ increased by approximately 45% and 2.7-fold, respectively. The small effect of TBZ and its metabolites on the QTc in conjunction with the modest increases in metabolite C_{max} levels following strong CYP2D6 inhibition indicate that the clinical use of TBZ at recommended doses is unlikely to lead to clinically significant increases in QTc. This conclusion is further supported by pharmacodynamic data from the CYP2D6 interaction study, where the maximum change from pre-dose in QTcF was essentially the same when TBZ 50 mg was administered alone (6.0 msec [3.5, 8.6]) and after robust CYP2D6 inhibition (6.7 msec [3.9, 9.4]) (Table 8).

Table 8. Summary of Maximal Plasma Concentrations of α- and β-Dihydrotetrabenazine (HTBZ) and Key QTc* Parameters from the Thorough QT (TQT) and CYP2D6 Interaction Studies

	TQT Study			CYP2D6 Interaction	
Parameter	**TBZ 25 mg**	**TBZ 50 mg**	**Moxi 400 mg**	**TBZ 50 mg**	**TBZ 50 mg + Paroxetine**
C_{max} of α-HTBZ (ng/mL)	38.2 ± 17.9	88.4 ± 42.7	–	77.3 ± 26.1	107 ± 26.8
C_{max} of β-HTBZ (ng/mL)	24.2 ± 17.3	61.4 ± 36.2	–	42.9 ± 24.2	105 ± 32.9
Maximum Change in QTc † (90% CI)	3.6 (1.0, 6.2)	7.7 (5.0, 10.4)	12.5 (9.7, 15.3)	6.0 (3.5, 8.6)	6.7 (3.9, 9.4)
Absolute QTc new >500 ms	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
Absolute QTc new >450 ms	4 (8.0)	4 (9.1)	4 (9.8)	0 (0.0)	0 (0.0)
Change in QTc ≥60 ms	0 (0.0)	0 (0.0)	0 (0)	0 (0.0)	0 (0.0)
Change in QTc ≥30 and <60 ms	3 (6.0)	5 (11.4)	4 (9.8)	2 (6.7)	1 (3.7)

* QTcI for TQT and QTcF for CYP2D6.

† Time-matched, placebo-corrected change from baseline for TQT; Change from pre-dose for CYP2D6.

C_{max}=maximum concentration, CYP=cytochrome, HTBZ =dihydrotetrabenazine, Moxi=moxifloxacin, ms=milli seconds, ng/mL=nanogram/milliliter, TBZ = tetrabenazine.

4 CLINICAL EFFICACY

4.1 Efficacy Overview

The clinical development history of TBZ is described in Section 1.2.

The US development program for TBZ consisted of 2 controlled clinical trials in HD patients (Study 004 and Study 005), 2 open–label, follow-up studies (Study 007 and Study 006, respectively), and 2 analyses of data obtained from an open-label study at the Baylor College of Medicine in HD and non-HD chorea patients and non-chorea patients. An overview of the patient population in the clinical database is provided in Figure 8 and protocols' design, in Table 9. All clinical trials summarized in this table were conducted with TBZ, with the exception of the CARE-HD study, as described in Section 1.3.2, which is a clinical trial of other interventions for HD (study conducted by the HSG) and provides a context for understanding the natural history of HD progression.

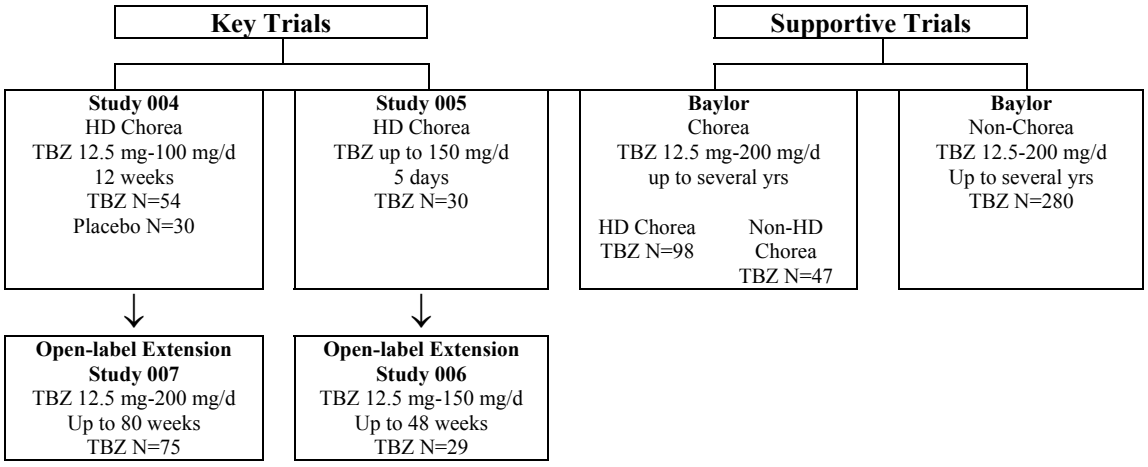


Figure 8. Patient Populations in the Tetrabenazine Clinical Trials
TBZ=tetrabenazine

Table 9. Summary of Studies Cited in the Briefing Document

Protocol Number	Protocol Design (Study Duration)	Type of Patients Enrolled	No. of Patients Exposed to TBZ	Dose of TBZ (range, mg/day)	No of Study Sites
Prestwick-Sponsored Studies of Tetrabenazine					
TBZ 103, 004 (Study 004)	Randomized, double-blind, placebo-controlled (12 weeks)	HD Chorea	54 †	Titrated to best dose 12.5-100	16
TBZ 103,007 (Study 007)	Open-label, extension of Study 004 (up to 80 weeks)	HD Chorea	75 †	Titrated to best dose 12.5-200	16
TBZ 103,005 (Study 005)	Randomized, double-blind, placebo-controlled, staggered withdrawal (5 days)	HD Chorea	30 ‡	Withdraw from up to 150 mg/day	1
TBZ 103,006 (Study 006)	Open-label extension of Study 005 (up to 48 weeks)	HD Chorea	29 ‡	Not titrated 12.5-150	1
Investigator-Initiated Studies of Tetrabenazine					
Baylor Chorea *	Prospective, open-label, dose- titration study (up to several years)	HD Chorea	98	Titrated to best dose 12.5-200	1
		Non-HD Chorea	47		
Baylor Non-Chorea *	Open-label, compassionate use	Hyperkinetic Movement Disorders	280	Titrated to best dose 12.5-200	1
Other Clinical Studies of HD (not Tetrabenazine)					
CARE-HD	Randomized, double-blind, placebo-controlled (30 months)	Early HD	0 (347 enrolled and randomized to other interventions)	NA	23

* Patients were treated with TBZ at Baylor College of Medicine since 1979, including 145 chorea patients (98 associated with HD, 47 associated with other diseases) reported in CSR TBZ 103,011, and 280 with hyperkinetic movement disorders other than chorea, reported in "Baylor Non-Chorea Report".
† Subjects treated in Study 007 were also treated in Study 004.
‡ Subjects treated in Study 006 were also treated in Study 005.
HD=Huntington's disease, TBZ = tetrabenazine

4.2 Study 004 (Placebo-Controlled)

A Randomized, Double-Blind, Placebo-Controlled, Study of Tetrabenazine for the Treatment of Huntington's Chorea

This was a 13-week, randomized, placebo-controlled trial conducted at HSG centers in the US. Patients with manifest HD were treated with either TBZ (N = 54) or placebo (N = 30) for 12 weeks. During the first 7 weeks of the study, the dose of study drug was titrated upward weekly by 12.5 mg increments to best tolerated dose, which was continued until the end of week 12. A 1-week double-blind washout period followed the 12-week treatment phase. The primary outcome measure was the change in Total Maximal Chorea Score (item 12 of the

UHDRS, Appendix 1; score ranges from 0-28) from baseline to maintenance therapy. Secondary and exploratory outcomes are shown in Table 10.

In addition to evaluation of AEs, vital signs, physical examination, 12-lead electrocardiogram (ECG), and laboratory parameters, safety was assessed based on: the 17-item HAM-D; the UHDRS parkinsonism score; the BARNES; the UPDRS dysphagia and dysarthria scores; and the Epworth Sleepiness Scale (Appendix 1).

Table 10. Study 004: Summary of Study Design

Design	Double-blind, randomized (2:1), placebo-controlled
Population	Manifest HD, total chorea score ≥ 10, independently ambulatory
Treatment	12 weeks treatment (titrated to best dose) with: • TBZ, 12.5 mg-100 mg/day or • Placebo Followed by 1-week double-blind washout period
Primary Endpoint(s)	Change in Total Maximal Chorea Score from baseline to maintenance therapy (the average of the values at week 9 and week 12). All study participants enrolled in the study were included in the primary and secondary analyses.
Secondary Endpoints	Tested in hierarchical manner: • Clinical Global Impression – Improvement • Total Motor Score of the UHDRS • FA of the UHDRS • Gait score of the UHDRS
Centers	16 Huntington Study Group sites

CGI-Clinical Global Impression, FA=Functional Assessment, HD=Huntington's Disease, TBZ=tetrabenazine, UHDRS=United Huntington's Disease Rating Scale.

4.2.1 Demography and Baseline Characteristics

The mean age of the study patients was 49 years, over 60% were female, and the majority (94%) were white (Table 11). As shown in Table 12, TBZ patients were more severely affected in functional, cognitive, and behavioral domains at baseline than were placebo patients. These differences achieved statistical significance for the FIS and the Symbol Digit Modalities test.

Table 11. Baseline Demographic Characteristics of Patients in Study 004

Variable	TBZ (N=54)	Placebo (N=30)	p-value *
Age, mean ± SD	49.4 ± 12.3	48.8 ± 10.5	0.83
Gender, n (%)			1.0
Male	21 (39%)	11 (37%)	
Female	33 (61%)	19 (63%)	
Race			0.65
White	50 (93%)	29 (97%)	
Other	4 (7%)	1 (3%)	
Disease duration, yr	8.7 ± 4.7	7.5 ± 4.5	0.25

* Fisher's Exact test for gender and race, t-test for all age and disease duration.
TBZ = tetrabenazine.

Table 12. Baseline Demographic and Clinical Characteristics of Patients in Study 004

Variable	Items Best Score	TBZ (N=54)	Placebo (N=30)	p-value *
CGI-Severity	0	3.98	3.83	0.36
Total Maximal Chorea Score	0	14. 69	15.20	0.57
Total Functional Capacity	13	8.28	8.60	0.56
Functional Assessment	25	18.80	19.63	0.38
Independence Scale	100	76.94	80.17	0.20
Functional Impact Scale	0	1.28	0.40	< 0.01
Stroop Word Reading	100	53.83	56.27	0.61
Symbol Digit Modalities Test	120	18.07	24.37	0.02
Behavioral Assessment	0	7.39	6.60	0.62

* t-test for all other variables.
TBZ = tetrabenazine.

4.2.2 Primary Endpoint: Assessment of Chorea

There was a highly statistically significant treatment effect of 3.5 units ($p < 0.0001$, ANCOVA stratified by clinical site with baseline score as a covariate) based on the primary analysis of change in chorea score from baseline to the maintenance phase (Figure 9). The results were consistent across sites (15 of 16 sites TBZ). According to a sub-group analyses and ANCOVA, response was not affected by gender.

As noted in the FDA Approvable Letter, the TBZ development program as presented in the NDA provides substantial evidence of effectiveness for TBZ as a treatment for chorea in patients with HD.

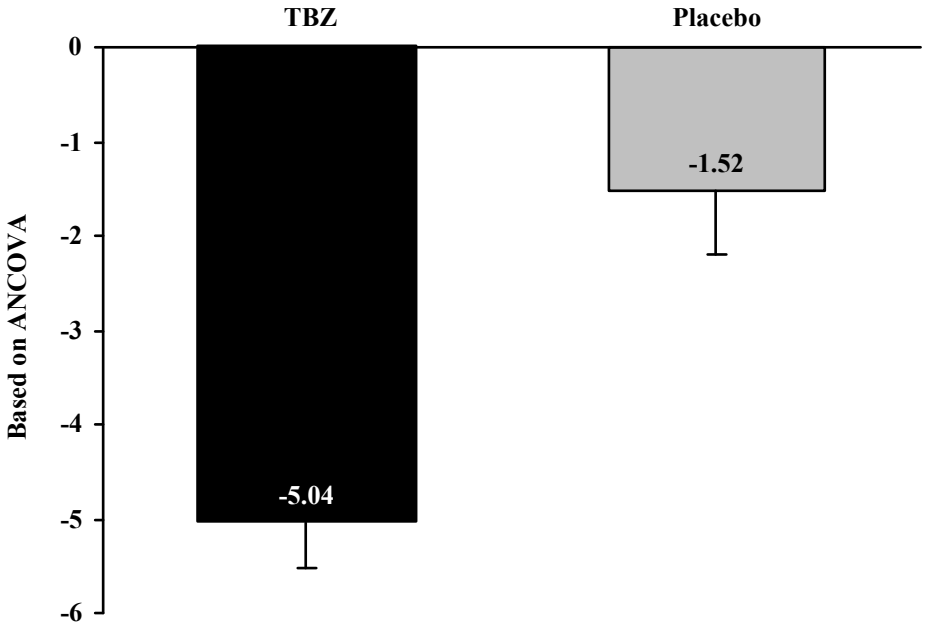
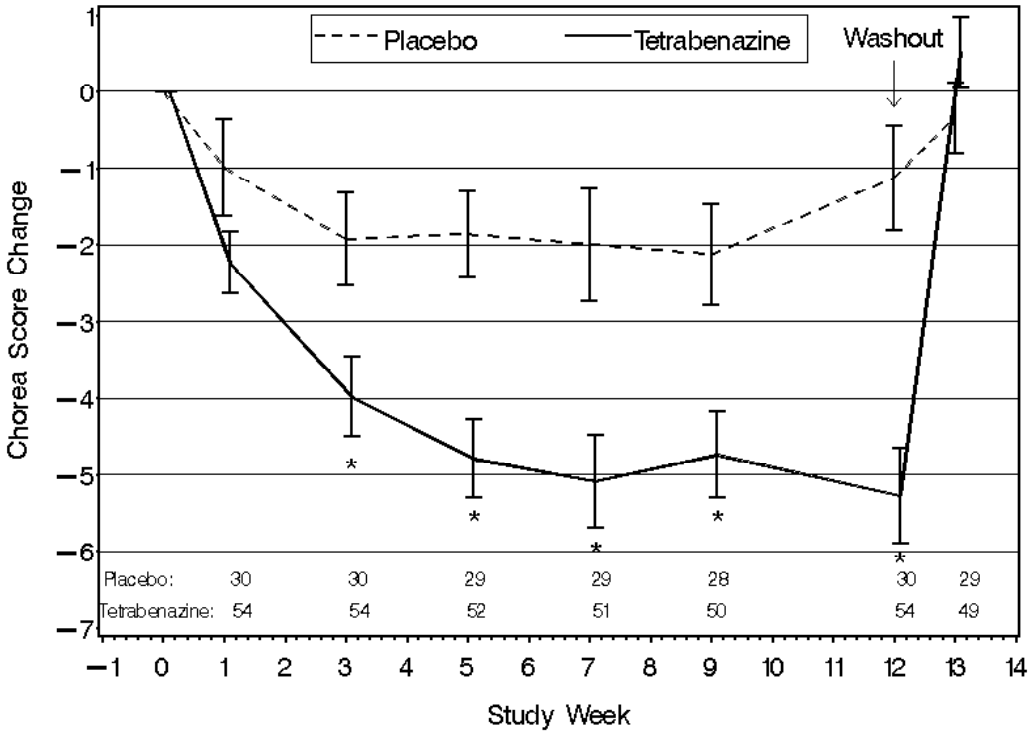


Figure 9. Adjusted Mean Change (± SEM) from Baseline to Maintenance Therapy in Total Chorea Score in 84 HD Participants Treated with Tetrabenazine (N=54) or Placebo (N=30) in Study 004

The reduction in chorea was observed as early as 1 week after the initiation of TBZ, with statistically significant treatment group differences emerging at Week 3 and at all timepoints thereafter (Figure 10).



(error bars are ± SEM)

Figure 10. Mean (± SEM) Change in Total Chorea Score Over Time in 84 HD Patients Randomized to Tetrabenazine (N=54) or Placebo (N=30)

At the end of treatment, 56% (30/54) of TBZ-treated patients and 13% (4/30) of placebo-treated patients no longer met the inclusion criterion of chorea score ≥ 10 (p = 0.0002, Chi-square analysis).

A "responder" criterion was pre-specified prior to study conduct by the Study 004 Steering Committee (Drs. Stanley Fahn, Stuart Factor, Joseph Jankovic, Fred Marshall, David Oakes, Ira Shoulson and Francis Walker) defining a reduction of 3 or more points in total maximal chorea score as clinically significant. Based on this criterion, 69% (37/54) of TBZ-treated patients as compared to 23% (7/30) of placebo patients had clinically significant reductions in total maximal chorea (Figure 11). Moreover, 50% (27/54) of TBZ-treated patients compared to 6% (2/30) of placebo-treated patients had an improvement in chorea score of 6 points or above. This finding is consistent improvement as determined in the categorical analysis of the Clinical Global Impression (CGI) - Improvement (refer to Figure 12).

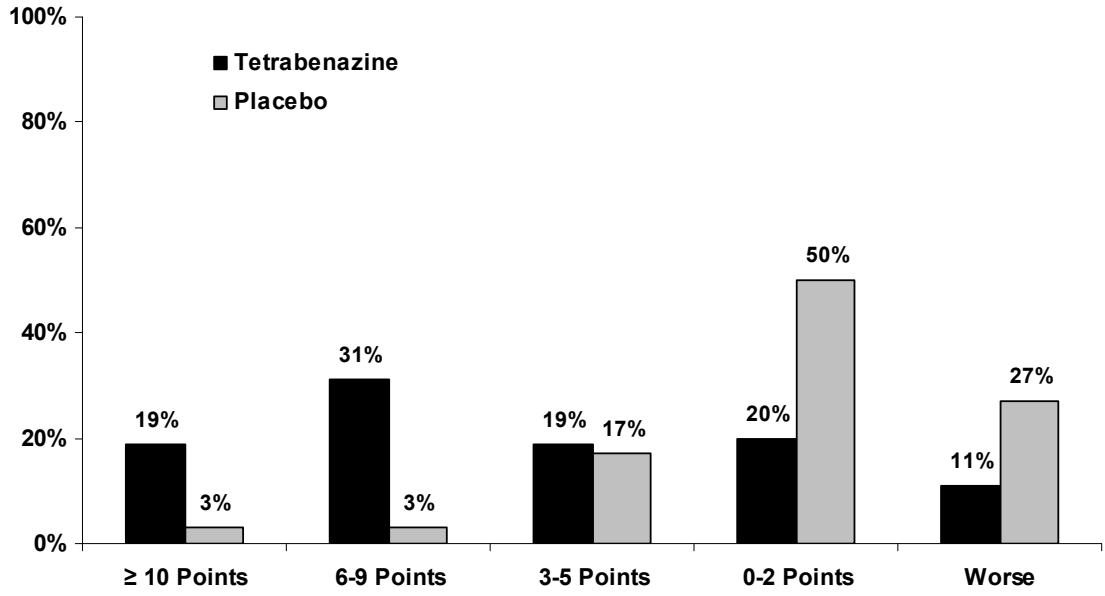


Figure 11. Categorical Analysis of Decrease in Chorea Score (% of Patients)

Missing scores were replaced by last available assessment.

Of note, in an analysis of response in those who had upward dose titration discontinued due to an AE (n=28), response was maintained after TBZ dose reduction in the majority of patients who were responders prior to dose reduction (79%, 19/24).

At the Week 13 (follow-up) visit, which was conducted 1 week after the discontinuation of study drug, there was no evidence of a rebound effect on chorea, defined as a worsening as compared to baseline (Table 13).

Table 13. Raw Mean (± SD) Total Chorea Scores at Baseline, End of Treatment and Follow-up Visit in HD Participants Randomized to Tetrabenazine (N=54) or Placebo (N=30)

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

TBZ=tetrabenazine.

The Study 004 protocol was amended to include the addition of videotaping while study subjects were on study drug (Week 12) and off study drug (Week 13) based on feedback from the FDA. Videotaping of participants was performed to enable rating of chorea in a blinded fashion. Neither sites nor patients were pre-selected for videotaping. Rather, the sites still participating at the time the amendment was approved were eligible to participate.

A blinded reviewer with expertise in HD reviewed videotapes of 23 patients (14 TBZ and 9 placebo) who completed the study. The reviewer, who was blinded to treatment, site, and date/order of videotaping of the motor examination at the Week 12 (on study drug) and Week 13 (off study drug) visits, assigned a chorea score on the basis of the videotaped assessment. There was good correlation between the site evaluation and the blinded reviewer at both Week 12 ($r = 0.76$, $p < 0.0001$) and Week 13 ($r = 0.68$, $p = 0.0004$). Furthermore, the treatment effect for videotaped subjects from Week 12 to 13 (4.08 points on the total chorea score) was comparable to the treatment effect observed over the same period for the study population.

4.2.3 Secondary Endpoints

The Data Analysis Plan (DAP) for Study 004 specified that the 4 secondary study endpoints were to be tested in the order:

1. CGI-Improvement
2. Total Motor Score (TMS)
3. FA
4. Gait score

Statistical testing was to terminate as soon as any p-value exceeded 0.05. Accordingly, CGI-Improvement analysis was conducted first. As shown in Table

14, the result of this analysis was consistent with the results of the chorea reduction analysis, both showing a statistically significant treatment group difference favoring TBZ.

Table 14. Adjusted Mean (± SEM) Change from Baseline for Secondary Outcome Measures in 84 HD Participants Treated with Tetrabenazine (N=54) or Placebo (N=30)

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

* CGI-Improvement was analyzed using only Week 12 data (3 participants on tetrabenazine and 1 participants on placebo were missing Week 12 values). For the other secondary outcome measures, the change from baseline to the average of Week 9 and Week 12 scores was analyzed.
† CGI analysis and corresponding p-value based on an ANOVA instead of an ANCOVA.
ANCOVA = analysis of covariance; UHDRS = Unified Huntington's Disease Rating Scale

In a categorical analysis of CGI-Improvement (Figure 12), 69% of TBZ-treated patients as compared to 24% of placebo patients were assessed as improved by the investigator at the end of treatment (p=0.0063).

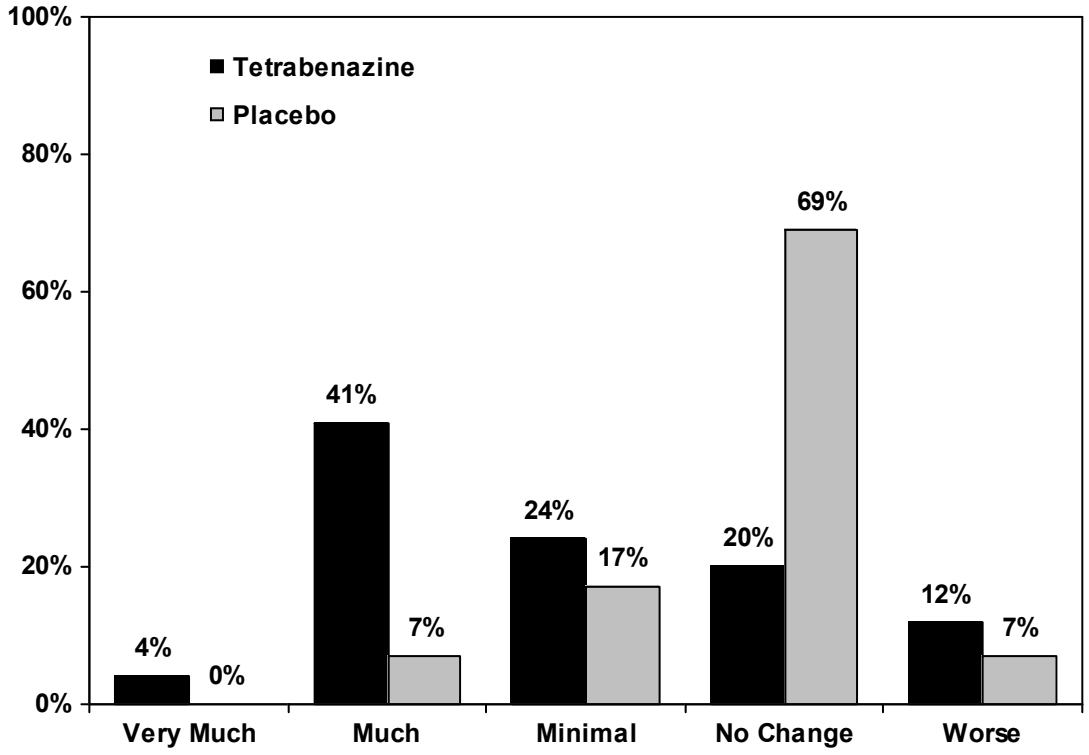


Figure 12. Categorical Analysis of Response at the Week 12 Visit on the CGI-Improvement in 80 HD Participants Treated with Tetrabenazine (N=51) or Placebo (N=29)

The next secondary endpoint to be analyzed in the pre-specified sequence was change from baseline to maintenance therapy for Total Motor Score. As indicated in Table 14, TBZ-treated patients had a reduction (improvement) in Total Motor Score of 6.84 points. Although this exceeded the reduction observed in placebo-treated subjects, the difference did not reach statistical significance (p=0.0752). In accordance with the DAP, testing of the remaining secondary endpoints was not performed.

4.3 Study 005 (Placebo-Controlled)

A Randomized, Double-Blind, Placebo-Controlled, Staggered Withdrawal Study in Patients with Huntington's Disease Treated with Tetrabenazine

Study 005 was the second pivotal trial. The rationale for conducting this study was based on the premise that since chorea in HD is chronic, and since treatment

with TBZ is only palliative, withdrawal of TBZ should lead to re-emergence of chorea, providing that TBZ is effective and is the reason chorea had abated.

To be eligible for study enrollment, patients must have had manifest HD for which they had received a stable dose of TBZ for at least 2 months prior to randomization. During that time, the dose of TBZ must have provided moderate to marked improvement in the patient's condition while either causing no side effects or side effects that did not significantly interfere with the patient's functioning. Eligible patients were randomized to withdrawal of TBZ after their morning dose on Day 1 (Group 1, n=12), or Day 3 (Group 2, n=12) or to continuation of study drug (Group 3, n=6).

The primary efficacy variable was the Change in Total Maximal Chorea Score from baseline to Day 3, and the primary analysis was the comparison of patients withdrawn on Day 1 (Group 1 – Off TBZ), to patients continuing TBZ on Day 3 (Groups 2 and 3 – On TBZ). Secondary and additional outcomes are shown in Table 15.

In addition to evaluation of AEs, vital signs, neurological and physical examination, 12-lead ECG, and laboratory parameters, safety was assessed based on: the UHDRS parkinsonism score and the TFC subscale of the UHDRS.

Table 15. Study 005: Summary of Study Design

Design	Double-blind, randomized, placebo-controlled
Population	Manifest HD, treatment with "best dose" of TBZ for at least the 2 months prior to randomization
Treatment	• Group 1 – Placebo x 5 days • Group 2 – TBZ x 2 days and placebo x 3 days • Group 3 – TBZ x 5 days
Primary Endpoint	Change in Total Chorea Score from baseline to Day 3 of Group 1 compared to Groups 2 and 3, combined. All participants who were randomized were included in the efficacy analyses.
Secondary Endpoint	TFC of the UHDRS
Centers	1

TBZ=tetrabenazine; TFC=Total Functional Capacity, UHDRS=United Huntington's Disease Rating Scale.

4.3.1 Demography and Baseline Characteristics

The treatment groups were comparable for baseline demographic characteristics of gender, age, and race and clinical characteristics of disease duration, CGI-Severity score distribution, and TFC (Table 16). Group 3, the treatment group randomized to remain on TBZ throughout the entire 5-day study, was more impaired (i.e. had higher baseline scores) at baseline based on Total Motor Score ($p = 0.0016$) across groups.

Table 16. Demographic and Clinical Characteristics of 30 HD Patients Enrolled in Study 005

Variable	Group 1 (N= 12)	Group 2 (N=12)	Group 3 (N=6)	p-value
Gender, n (%)				
Male	5 (42%)	4 (33)	3 (50%)	0.8912 *
Female	7 (58%)	8 (67)	3 (50%)	
Age (years)				
Mean ± SD	56.08 (±9.69)	55.92 (±8.48)	59.83 (±14.22)	0.7171 †
Race, n (%)				
White	12 (100%)	10 (83%)	6 (100%)	0.3379 *
Other	0	2 (17%)	0	
Disease Duration (yrs)				
Mean ± SD	10.22 (±4.51)	9.18 (±6.10)	11.41 (±4.77)	0.6925 ‡
CGI-Severity, n (%)				
Not Ill	0	0	0	0.2411 *
Borderline Ill	0	0	0	
Mildly Ill	0	2 (17%)	0	
Moderately Ill	7 (58%)	7 (58%)	2 (33%)	
Markedly Ill	4 (33%)	1 (8%)	1 (17%)	
Severely Ill	1 (8%)	2 (17%)	3 (50%)	
Among the most extremely ill patient	0	0	0	
Total Maximal Chorea Score				
Mean ± SD	9.42 (±1.42)	9.08 (±1.79)	11.17 (±1.82)	0.7337 ‡
TFC				
Mean ± SD	6.25 (±0.75)	7.58 (±1.01)	5.00 (±1.15)	0.2340 ‡
Total Motor Score				
Mean ± SD	34.75(±2.81)	28.00 (±3.79)	50.00 (±3.57)	0.0016 ‡

* Fisher's Exact test; † ANCOVA; ‡ ANOVA.
CGI-Clinical Global Impression, HD=Huntington's Disease, TFC=Total Functional Capacity.

4.3.2 Primary Endpoint: Assessment of Chorea

The mean (±SD) chorea score for patients in Group 1 increased by 5.33 (±3.47) units following withdrawal of TBZ. The corresponding mean (±SD) change from baseline to Day 3 for Groups 2 and 3 combined was 2.94 (±3.52). Although the treatment effect was in the hypothesized direction with an estimated treatment effect of 2.39 units, patients in Group 2 were prematurely withdrawn from TBZ by approximately 12 hours. As Group 2 subjects were supposed to be on TBZ at the time of their Day 3 evaluation, the planned analysis did not make sense in that they were withdrawn prematurely. Instead, a post hoc analysis comparable to the planned analysis was conducted. This analysis examined the change from baseline to Day 3 for Groups 1 and 3, the results of which are summarized in Figure 13.

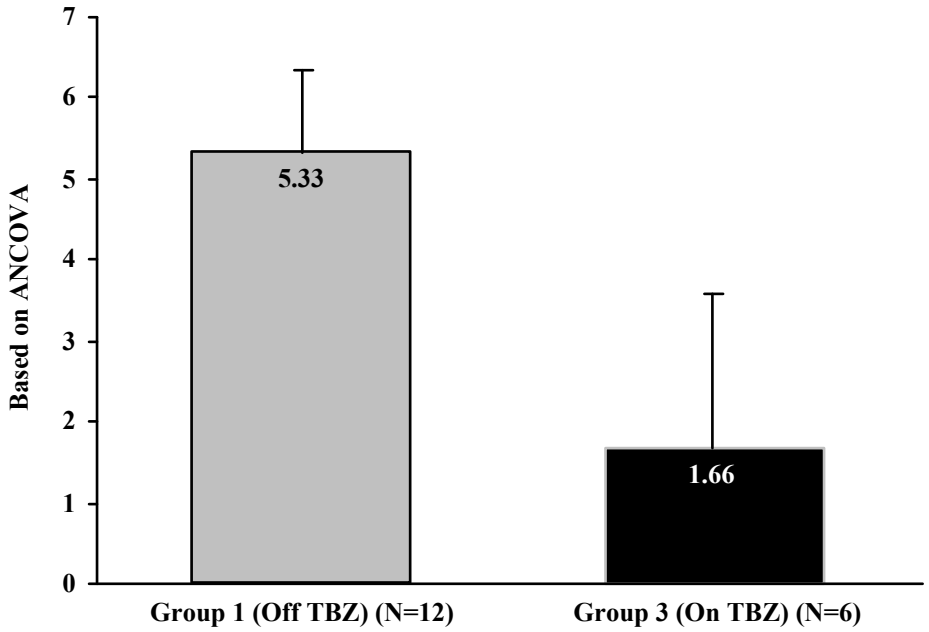


Figure 13. Mean (SEM) Change from Baseline to Day 3 in Total Maximal Chorea Score

Group 1 patients had a 5.33-point increase in chorea following TBZ withdrawal as compared to a 1.66 point increase in placebo-treated subjects. Although the between-group difference was not statistically significant (p=0.11), the analysis was only based on 18 patients. Furthermore, the treatment effect observed in Study 005 (3.67) was comparable to that observed in Study 004 (3.52). In addition, a post hoc trend analysis considering Group 2 as an "intermediate" group between Groups 1 and 3 was statistically significant, with a p-value of 0.0486 (Figure 14).

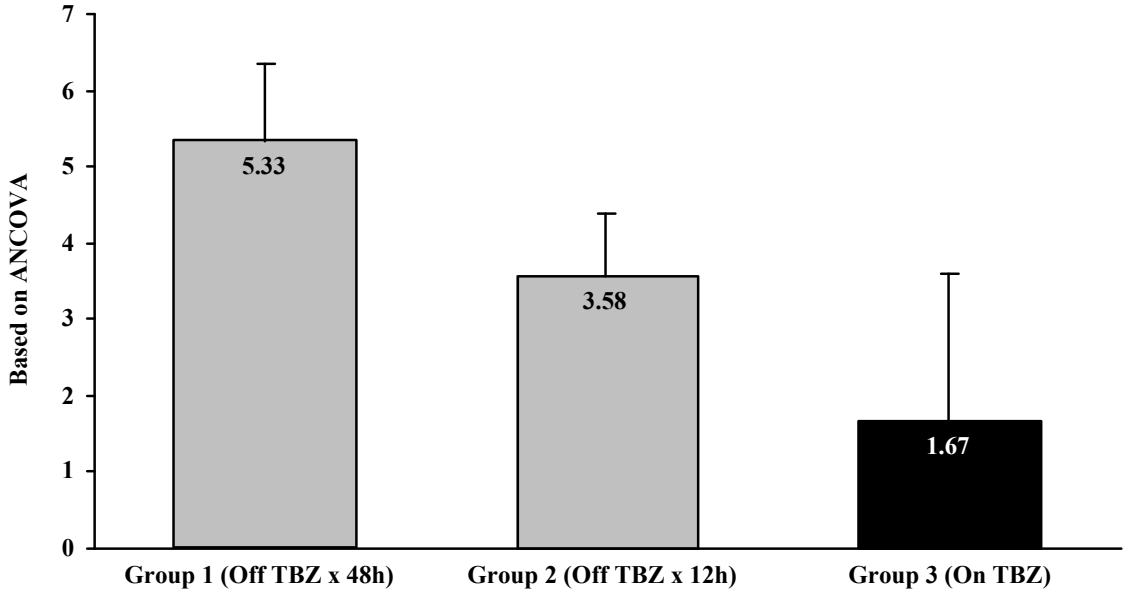


Figure 14. Mean (SEM) Change from Baseline to Day 3 in Total Maximal Chorea Score (Study 005)

TBZ=tetrabenazine.

Taken together, the magnitude of the treatment effect, when Groups 1 and 3 were compared in combination with statistically significant trend analysis demonstrate the efficacy of TBZ in Study 005. These results also confirm the rapid reversibility of the anti-chorea effects of TBZ.

4.3.3 Secondary Endpoints

The secondary efficacy endpoint for Study 005 was the TFC. Of the 30 study participants, 26 (87%) had no change in their TFC from the baseline to Day 3 and 18 (60%) had no change in the TFC between baseline and Day 5. From baseline to Day 3, the mean TFC score for Group 1 was unchanged while participants in Groups 2 and 3 declined by an estimated 0.389 units (adjusted mean) ($p = 0.2180$). The comparative analysis of the 3 groups from baseline to Day 3 ($p = 0.1476$) and from Day 3 to Day 5 ($p = 0.3217$) demonstrated treatment effects that were not statistically significant.

4.4 Study 007 (Open-Label)

Open-Label, Up to 80-Week Extension Study of Tetrabenazine for the Treatment of Huntington's Chorea Follow-On to TBZ 103,004 (Tetra HD)

The objective of Study 007 was to primarily document the long-term tolerability and safety of TBZ and, secondarily to confirm that the anti-chorea effect of TBZ was maintained during long-term treatment. The study was conducted on an open-label basis at multiple HSG sites in the US. Only patients who completed Study 004 (described in Section 4.2) were enrolled in this study (N=75). During the first 11 weeks of the study, the dose of study drug was titrated upward weekly by 12.5 mg increments to best dose, which was continued until study end unless an intolerable, treatment-related AE occurred.

The primary efficacy variable was the change in Total Maximal Chorea Score from baseline to the mean of values at weeks 24, 48, and 80. Secondary and additional variables are shown in Table 17. In addition to evaluation of AEs, vital signs, physical examination, 12-lead ECG, and laboratory parameters, safety was assessed based on: the 17-item HAM-D; the UHDRS parkinsonism score; the BARNES; the UPDRS dysphagia and dysarthria scores; and TFC subscale of the UHDRS.

Table 17. Study 007: Summary of Study Design

Design	Open label
Population	HD patients who completed their participation in Study 004
Treatment	TBZ at "best dose" (25-200 mg daily) up to 80 weeks
Primary Endpoint	Change in Total Chorea Score from baseline to the mean of values at Weeks 24, 48, and 80.
Secondary Endpoints	CGI-Improvement Total Motor Score FA of UHDRS Gait Score
Centers	16

CGI-Clinical Global Impression, FA=Functional Assessment, HD=Huntington's Disease, TBZ=tetrabenazine, UHDRS=United Huntington's Disease Rating Scale.

4.4.1 Demography and Baseline Characteristics

The patients who entered Study 007 were very similar at baseline to those enrolled in Study 004 based on demographic and clinical characteristics, as would be expected for a follow-on study (Table 18).

Table 18. Baseline Demographic and Clinical Characteristics of 75 HD Patients Enrolled in Study 007

Variable	Patients Enrolled in Study 004		Patients Enrolled in Study 007
	Randomized to Placebo N=30	Randomized to TBZ N=54	N=75
Gender, n (%)			
Male	11 (37%)	21 (39%)	26 (35%)
Female	19 (63%)	33 (61%)	49 (65%)
Age (years)			
Mean ± SD	48.8	49.4	50.94
Race, n (%)			
White	29 (97%)	50 (93%)	71 (95%)
Other	1 (3%)	4 (7%)	4 (5%)
Disease Duration (years)			
Mean ± SD	7.5 ± 4.5	8.7 ± 4.7	8.5 ± 4.5
CGI-Severity, n (%)			
Not Ill	0	0	0
Borderline Ill	0	0	0
Mildly Ill	12 (22%)	10 (33%)	17 (23%)
Moderately Ill	32 (59%)	16 (53%)	49 (65%)
Markedly Ill	9 (17%)	3 (10%)	8 (11%)
Severely Ill	1 (2%)	1 (3%)	1 (1%)
Among the most extremely ill patient	0	0	0
Total Maximal Chorea Score			
Mean ± SD	14.69 ± 3.84	15.20 ± 4.41	14.95 ± 3.67
Total Motor Score			
Mean ± SD	47.00 ± 16.67	44.77 ± 15.45	47.57 ± 15.81

Baseline for patients enrolled in Study 007 was defined as Week 13 (Visit 7) of Study 004. However, 44 of 75 patients (56%) did not enroll at Week 13 (Visit 7) of Study 004 because they had to wait for IRB approval to be enrolled in the study. For these patients, baseline occurred as a separate visit within 3 weeks of initiating treatment in the long-term extension study.
CGI=Clinical Global Impression, TBZ=tetrabenazine.

4.4.2 Primary Endpoint: Assessment of Chorea

Table 19 presents the results of the primary efficacy analysis.

Table 19. Mean (± SD) Change from Baseline to Week 24, Week 48, and Week 80 in Total Maximal Chorea Score

Mean Change in Total Maximal Chorea Score			
Evaluation Point	**N**	**Mean Change**	**Paired t-test p-value**
Week 24	72	-5.75 ± 4.98	<0.0001
Week 48	57	-5.49 ± 5.44	<0.0001
Week 80	45	-4.60 ± 5.55	<0.0001

Baseline for patients enrolled in Study 007 was defined as Week 13 (Visit 7) of Study 004. However, 44 of 75 patients (56%) did not enroll at Week 13 (Visit 7) of Study 004 because they had to wait for IRB approval to be enrolled in the study. For these patients, baseline occurred as a separate visit within 3 weeks of initiating treatment in the long-term extension study.

As presented in Table 19 above and Figure 15, below, chorea scores improved (decreased) during the study (≤ 0.002 at all timepoints), supporting maintained efficacy of TBZ over time in treating chorea associated with HD. The overall longitudinal p-value was <0.0001.

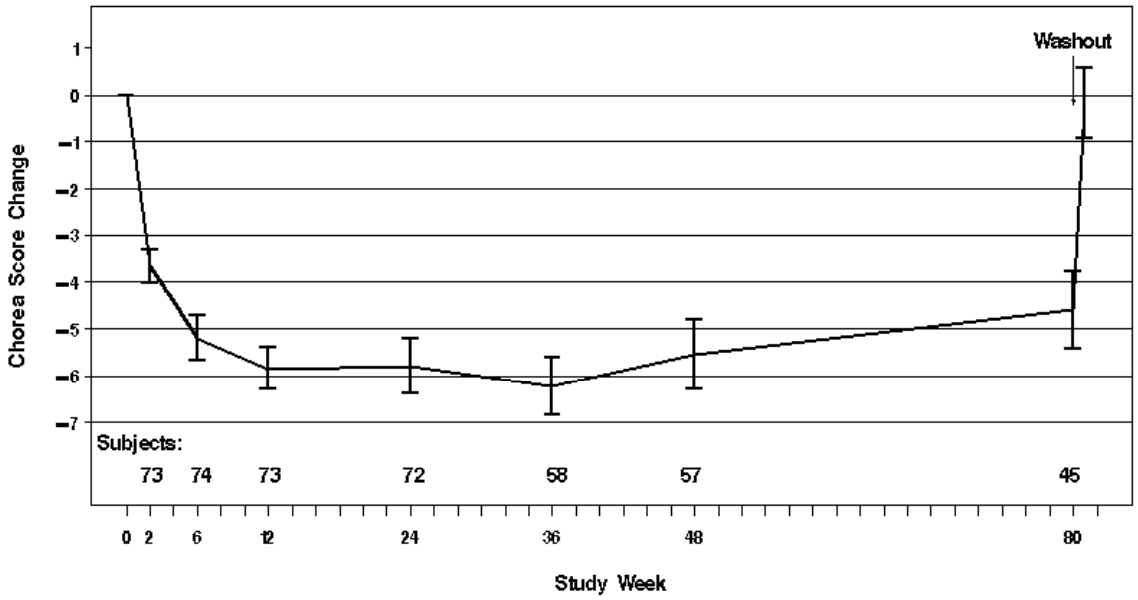


Figure 15. Mean (± SD) Change in Total Maximal Chorea Score from Baseline for Week 2 through Week 81

Baseline for patients enrolled in Study TBZ 103,007 is defined as Week 13 (Visit 7) of Study TBZ 103,004. However, 44 of 75 patients (56%) did not enroll at Week 13 (Visit 7) of Study TBZ 103,004 because they had to wait for IRB approval to be enrolled in the study. For these patients, baseline occurred as a separate visit within 3 weeks of initiating treatment in the long-term extension study.

The increase (reflecting clinical worsening) of mean chorea score at Week 81 reflects the fact that all of the patients had discontinued treatment at that time. The observed clinical worsening upon withdrawal of TBZ is comparable to that observed in Study 005 and in Study 004 (Week 13), providing additional support for the efficacy of TBZ in the treatment of chorea.

A total of 76%, 68%, and 69% of patients were classified as having a clinically meaningful decrease in chorea score ("responders"; defined a priori by the Steering Committee as ≥ 3 point decrease in chorea score) at the Week 24, Week 48, and Week 80 evaluations, respectively.

4.4.3 Secondary Endpoints

Mean change from baseline to Weeks 24, 48, and 80 for the secondary endpoints of Study 007 are presented in Table 20.

Table 20. Mean (± SD) Change from Baseline to Week 24, Week 48, and Week 80 for Secondary Outcome Measures of Study 007

Secondary Outcome Measure	Week 24	Paired t-test p-value	Week 48	Paired t-test p-value	Week 80	Paired t-test p-value
CGI-Improvement	2.73 ±1.11 N=71	<0.0001	2.82 ± 1.34 N=57	<0.0001	3.38 ± 1.53 N=45	<0.0001
Total Motor Score (UHDRS 1-15)	-7.49 ± 9.72 N=72	<0.0001	-5.37 ± 12.14 N=57	0.0015	-0.18 ± 11.00 N=45	0.9142
Functional Assessment (UHDRS 43-67)	-0.36 ± 2.51 N=73	0.2299	-1.09 ± 2.32 N=57	0.0008	-2.56 ± 3.26 N=45	<0.0001
Gait score (UHDRS 13)	-0.07 ± 0.61 N=72	0.3394	0.04 ± 0.71 N=57	0.7090	0.18 ± 0.75 N=45	0.1177

Baseline for patients enrolled in Study TBZ 103,007 was defined as Week 13 (Visit 7) of Study TBZ 103,004. However, 44 of 75 patients (56%) did not enroll at Week 13 (Visit 7) of Study TBZ 103,004 because they had to wait for IRB approval to be enrolled in the study. For these patients, baseline occurred as a separate visit within 3 weeks of initiating treatment in the long-term extension study.

On categorical analysis of the CGI-Improvement, 81%, 77%, and 53% of patients had at least minimal improvement at the Week 24, Week 48, and Week 80 evaluations, respectively.

4.5 Study 006 (Open-Label)

An Open-Label, 48-Week Treatment Study of Tetrabenazine in Patients with Huntington's Chorea: Follow-on Protocol to Protocol TBZ 103,005

The objective of Study 006 was to primarily document the long-term tolerability and safety of TBZ and, secondarily to examine whether it is possible to rapidly resume a patient on his/her previous "best dose" of TBZ, without titration. The best dose was defined as the dose that provided moderate to marked improvement in the patients' condition while causing either no side effects or side effects that did not significantly interfere with the patients' functioning.

The study was conducted on an open-label basis at the Movement Disorder Clinic at the Baylor College of Medicine in Houston. Only patients who completed Study 005 (described in Section 4.3) were enrolled in this study (N=29). Patients initiated treatment with TBZ at "best dose," without titration. The dose of study drug could be adjusted (increased or decreased) at each study visit. The study began as an open-label, 24-week trial and was subsequently extended (by protocol amendment) to 48 weeks.

The primary efficacy variable was the change in Total Maximal Chorea Score from baseline to the mean of values at weeks 24 and 48. Secondary and additional variables are shown in Table 21. In addition to evaluation of AEs, vital signs, physical examination, 12-lead ECG, and laboratory parameters, safety was assessed based on: the 17-item HAM-D; the UHDRS parkinsonism score; the BARNES; the UPDRS dysphagia and dysarthria scores; and TFC subscale of the UHDRS.

Table 21. Study 006: Summary of Study Design

Design	Open label
Population	HD patients who completed their participation in Study 005
Treatment	TBZ at "best dose" (25-150 mg daily) up to 48 weeks
Primary Endpoint	Change in Total Chorea Score from baseline to the mean of values at Weeks 24 and 48
Secondary Endpoints	CGI-Improvement Total Motor Score FA of UHDRS Gait Score
Centers	16

CGI-Clinical Global Impression, FA=Functional Assessment, HD=Huntington's Disease, TBZ=tetrabenazine, UHDRS=United Huntington's Disease Rating Scale.

4.5.1 Demography and Baseline Characteristics

The mean (± SD) age of study patients was 57.4 (±10.1) years, 59% were female, and 93% were white. Maximal chorea score at baseline was 14.38 (± 6.13).

4.5.2 Primary Endpoint: Assessment of Chorea

Efficacy as judged by mean change from baseline in chorea was maintained throughout the study. Mean reduction of the chorea score was 4.30, 6.59, and 7.77 at Weeks 12, 24, and 48 ($p=0.0005$, $p<0.0001$, $p<0.0001$, respectively) (Table 22). The overall longitudinal p-value is <0.0001.

Table 22. Mean (± SD) Change from Baseline to Weeks 12, 24, and 48 in Total Maximal Chorea Score

Evaluation Point	N	Mean Change	Paired t-test p-value
Week 12	27	-4.30 ± 5.57	0.0005
Week 24	27	-6.59 ± 5.16	<0.0001
Week 48	26	-7.77 ± 5.24	<0.0001

NOTE: Baseline (Day 0) was defined as enrollment into study TBZ 103,006 on Day 5 of study TBZ 103,005 or within 2 weeks of completion of study TBZ 103,005.

The magnitude of the decrease in chorea score is similar to that observed in Study 004 and Study 007. The continuing improvement in mean chorea score over time in study is likely explained by an increase in TBZ dosage that occurred at Week

12 (6 patients) and Week 24 (8 patients), rather than by any increase of drug efficacy over time.

In a responder analysis, the cumulative percentage of patients with a decrease of chorea score ≥3 was 69% and 66% at the Week 24 and Week 48 evaluations, respectively.

4.5.3 Secondary Endpoints

Mean change from baseline to Weeks 24 and 48 for the secondary endpoints of Study 006 are presented in Table 23.

Table 23. Mean (± SD) Change from Baseline to Week 24 and Week 48 for Secondary Outcome Measures of Study 006

Secondary Outcome Measure	Week 24 (N=27)	Paired t-test p-value	Week 48 (N=26)	Paired t-test p-value
CGI-Improvement	2.63 ± 1.08	<0.0001	2.88 ± 1.45	<0.0001
Total Motor Score (UHDRS 1-15)	-11.67 ± 13.33	0.0001	-10.46 ± 11.86	0.0001
Functional Assessment (UHDRS 43-67)	-0.56 ± 1.48	0.0614	-1.54 ± 2.60	0.0057
Gait score (UHDRS 13)	-0.04 ± 0.65	0.7693	0.12 ± 0.59	0.3269

Baseline enrollment (Day 5 of study TBZ 103,005 or within 2 weeks of completion of study TBZ 103,005).

In a categorical analysis of CGI-Improvement, 85% and 73% of patients had at least minimal improvement and 56% and 50% of patients were judged to be "much" or "very much improved at the Week 24 and 48 evaluations, respectively.

4.6 Non-Motor Endpoints

All parts of the UHDRS that were not specified as primary or secondary efficacy endpoints (see Sections 4.2.2 and 4.2.3) were also analyzed (Table 24). These outcomes included the non-motor domains of behavior, function and cognition. Due to the limitations of the functional measures contained within the UHDRS, the HSG piloted a new functional scale (Functional Impact Scale or FIS) in Study 004 that focuses on Activities of Daily Living. Although the Functional Assessment (FA) was indicated as a secondary endpoint in Study 004, testing of secondary endpoints was performed in a hierarchical manner such that formal

testing was to stop once a non-significant p-value was obtained. As non-significance occurred at the secondary endpoint before FA, this parameter was not formally analyzed, but rather is reported in the present section. Table 24 summarizes the non-motor outcomes assessed in Study 004 as well as long-term studies 006 and 007.

Table 24. Non-Motor Outcomes Assessed in Studies 004, 007, and 006

Study	Outcome Measures	Timepoints Assessed
004	FA of the UHDRS *	Baseline and Weeks 1, 3, 5, 7, 9, and 12
	TFC of UHDRS	Baseline and Weeks 7 and 12
	IND of UHDRS	Baseline and Weeks 1, 3, 5, 7, 9, and 12
	FIS	Baseline and Weeks 7 and 12
	BA of UHDRS	Baseline and Weeks 1, 3, 5, 7, 9, and 12
	Cognitive assessment (Verbal fluency, Symbol digit, Stroop test)	Baseline and Weeks 7 and 12
006	BA of UHDRS	Baseline and Weeks 24 and 48
	IND of UHDRS	Baseline and Weeks 24 and 48
	TFC of UHDRS	Weeks 24 and 48
	Cognitive assessment (Verbal fluency, Symbol digit, Stroop test)	Baseline and Weeks 24 and 48
007	BA of UHDRS	Baseline† and Weeks 24, 48, and 80
	IND of UHDRS	Baseline† and Weeks 24, 48, and 80
	TFC of UHDRS	Baseline† and Weeks 2, 6, 12, 24, 36, 48, 64, and 80
	Cognitive assessment (Verbal fluency, Symbol digit, Stroop test)	Baseline† and Weeks 24, 48, and 80

* Secondary outcome not formally tested (see text).
† For patients enrolled directly from Study 004, these procedures were not repeated.
BA=Behavioral Assessment, FA=Functional Assessment, FIS=Functional Impact Scale, IND= Independence scale, TFC=Total Functional Capacity, UHDRS = Unified Huntington's Disease Rating Scale.

Table 25 summarizes the change from baseline to Week 12 for non-motor endpoints in Study 004.

Table 25. Adjusted Mean Change from Baseline (N) to Maintenance Therapy (using LOCF) for Non-Motor Endpoints in Study 004

Parameter	No. of Items	Best Score	Change to Average of Week 9 and 12 *				
			TBZ	% of Scale §	PBO	% of Scale §	p-value †
Behavioral Assessment	11	0	-1.01	-1.1%	-2.24	-2.5%	0.3581
Functional Measures							
Functional Assessment (FA)	25	25	-0.79	-3.2%	0.36	1.4%	0.0232
Independence Scale (IND)	1	100	-1.80	-1.8%	0.59	0.6%	0.1536
Total Functional Capacity (TFC) *	5	13	-0.33	-2.5%	-0.02	-0.2%	0.3635
Functional Impact Scale (FIS) *	5	0	0.02	0.1%	0.08	0.5%	0.8193
Cognitive Measures *							
Symbol Digit	1	120	2.30	1.9%	2.97	2.5%	0.6104
Verbal Fluency	1	– ‡	-2.57	–	-1.24	–	0.3126
Stroop Interference Score ¶	1	– ‡	-0.51	–	0.39	–	0.5385

* Average of Weeks 9 and 12 for BA, FA, and IND; Week 12 for TFC, FIS, and Cognitive tests.
† By ANCOVA.
‡ No Best Score. Higher score is better.
§ Percent of scale is change/scale range.
¶ Interference Score calculated as Raw Color Word (CW) score – predicted CW score
BA=Behavioral Assessment, FA=Functional Assessment, FIS=Functional Impact Scale, IND=Independence scale, LOCF=Last Observation Carried Forward, PBO=placebo, TFC=Total Functional Capacity.

As shown in Table 25, there were small declines in some functional and cognitive measures among TBZ-treated patients relative to placebo, some of which were statistically significant (FA, p=0.0232). Although these changes were small, the FDA expressed concern that multiple endpoints favored placebo. The FDA acknowledged that the impact of these small effects on patient functioning was unknown, however, they felt that if they were to lead to progressive deterioration, physicians might not be able to distinguish drug-induced effects from progression of HD.

To address these concerns, Prestwick re-analyzed all endpoints in Study 004 to determine if baseline between-group differences in behavior and function affected the treatment-group differences that emerged during the study[2]. Changes in functional endpoints were then examined by the extent of change in measures that have the potential to reflect TBZ adverse effects (e.g., anxiety as reflected by changes in HAM-D)[3] in order to determine if the functional changes were associated with established AEs of tetrabenazine. As this re-analysis focused on safety rather than efficacy, it employed an Observed Cases methodology rather than a last-observation-carried-forward (LOCF) imputation typically used to

[2] For key parameters (chorea, FA, BA, and CGI-severity), effects of baseline and change from baseline during the study on mean and mean change in function and behavior were examined descriptively.
[3] In addition to HAM-D, the BA and ESS were used for analyzing change in function.

analyze efficacy data. The Observed Cases method evaluates available data at specific timepoints, whereas the LOCF method "carries forward" data in the event data are missing (e.g., if patient prematurely discontinues). Categories for each instrument used to analyze change in function were defined by choosing cutpoints that numerically apportioned the patients for the combined study population as evenly as possible into the categories.

Finally, data from TBZ-treated patients were compared with historical data from the CARE-HD study, one of the largest prospective HD clinical trials completed to date (Huntington Study Group, 2001) in order to determine if the functional and other changes among TBZ-treated patients were consistent with the expected natural decline in HD patients.

4.6.1 Behavior in Study 004

As summarized in Table 25, the Behavioral Assessment for both TBZ- and placebo-treated patients improved minimally over 12 weeks, as reflected by small decreases in the BA score. The mean change was -1.01 and -2.24, respectively, favoring placebo. An Observed Cases analysis revealed that, in contrast to the original analysis that marginally favored placebo, the change from baseline to Week 12 marginally favors TBZ (See Table 26). Thus, based on an Observed Cases analysis, there is no evidence for a decline in the BA score, as the overall treatment effect was -0.36, consistent with slight improvement favoring TBZ. This re-analysis demonstrates that small apparent differences between treatments are very sensitive to the analytical methodology employed.

Table 26. Mean and Mean Change in Behavioral Assessment* (BA) by Week (Observed Case)

	Mean (N)		Mean Change (N)			
Timepoint	TBZ	Placebo	TBZ	Placebo	p-value t-test	Unadjusted Effect Size
Baseline	7.39 (54)	6.60 (30)				
Week 7	6.04 (50)	5.48 (29)	-1.48 (50)	-1.34 (29)	0.9227 †	-0.14
Week 12	5.60 (47)	4.83 (29)	-2.36 (47)	-2.00 (29)	0.8194	-0.36

* Lower score is better.
† Unequal variance t-test.

Due to the overlap of some domains assessed in the BA and the HAM-D, the latter was analyzed similarly. As with the BA, both TBZ- and placebo-treated patients improved minimally on the HAM-D over 12 weeks, as reflected by a

mean change of -1.00 and -2.66, respectively, favoring placebo. Analysis of individual items of the HAM-D revealed that differences in insomnia (early), insomnia (late), and anxiety (psychic) accounted for most of the between-group difference (+1.66). A by-item analysis of the BA also revealed an increase in anxiety frequency and severity. The detection of anxiety on the BA and the HAM-D, as well as insomnia on the HAM-D, is consistent with the known AE profile of tetrabenazine. (See Section 5).

4.6.2 Function in Study 004

The between-group difference in the FA at Week 12 that favored placebo was approximately 1 unit on a 25-point scale, reflecting a small treatment effect on a 25-point scale (Table 25). An individual item analysis of the FA, which assesses diverse activities and includes some complex tasks (e.g., managing finances, supervising children, using public transportation), indicated no large between group differences for any single item. Furthermore, there was no evidence of a significant between-group difference for the 3 other functional scales: TFC, IND, and the FIS. In fact, the Activities of Daily Living (ADL) component of the TFC and the Functional Impact Scale (FIS), which is also assesses function through ADLs (e.g., bathing, dressing) showed that patients treated with TBZ performed better than placebo using an Observed Cases Analysis.

In addition to the planned analysis outlined above, Prestwick conducted post hoc analyses of function to determine if known AEs of TBZ in some patients could be contributing to the apparent mean decline in some of the functional measures. As outlined in Section 4.6.1, an analysis of the HAM-D indicated that insomnia and anxiety largely contributed to between-group differences in the HAM-D score. The analysis in Figure 16 presents the change in FA and other functional scales by the change in HAM-D score at Week 12 for TBZ-treated patients. While the overall change in FA from baseline to Week 12 was small at -0.40 points, patients with improvement in HAM-D had an increase of 0.62 points on the FA, consistent with improvement, whereas those with minimal change in HAM-D had a small change of -0.31 on the FA, and those with worsening of HAM-D had a change in FA of -1.22. Similar analyses of IND, TFC, and FIS showed that patients with improvement in HAM-D had little or no decrease from baseline whereas those with worsening in HAM-D had decline in these functional measures. Similar findings were observed for an analysis of the change in functional measures by the degree of change in the BA and ESS, although results for the FA were the

most consistent. These post hoc analyses suggest that some patients with adverse effects of TBZ may have a temporally associated decline in functional measures. As outlined in Section 5.8, however, the AEs of TBZ are readily recognized by treating physicians and are reversible with medical management, including dose reduction.

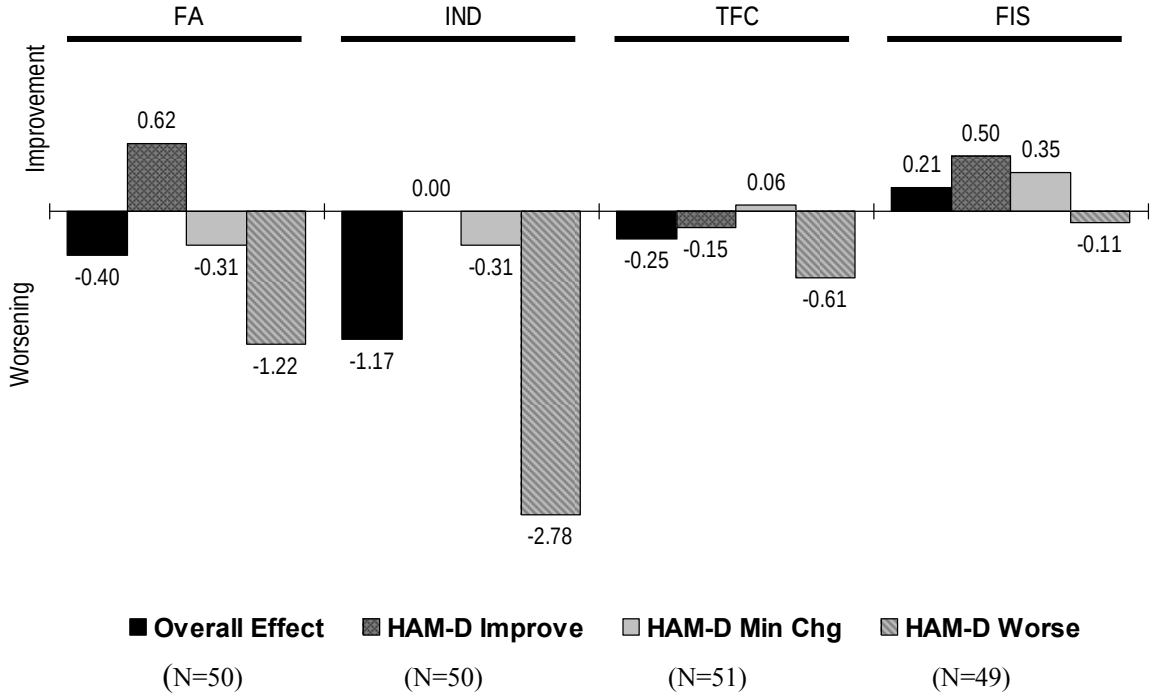


Figure 16. Change in Functional Scales at Week 12 for TBZ-Treated Patients by Change in HAM-D in Study 004 (observed cases)

4.6.3 Function: Tetrabenazine versus Historical Data

Due to the relatively small size and short duration of Study 004 and to further address questions raised by the FDA, Prestwick sought to compare the changes in functional measures among TBZ-treated patients with long-term clinical to determine if the Study 004 findings were consistent with the natural history of HD. To accomplish this task, the sponsor requested descriptive analyses of the CARE-HD study population by the Huntington Study Group, which conducted the trial. The CARE-HD is a large, well-controlled interventional trial of 347 patients with mild HD who were followed for up to 30 months.

Among 347 patients enrolled in CARE-HD, 87 were randomized to placebo and these patients are used for comparison to TBZ-treated patients in Study 006 (up to 48 weeks) and Study 007 (up to 80 weeks). As indicated in Table 27, TBZ-treated patients had a longer disease duration, had more severe chorea, and were more functionally impaired at baseline compared to CARE-HD placebo patients. Nonetheless, as depicted in Figure 17, the changes from baseline in FA, TFC, and IND out to 20 months were comparable between TBZ and CARE-HD placebo patients. When TBZ-treated patients are compared to All CARE-HD Patients as well as a subset of All Patients with comparable baseline disease severity, similar observations are found. These data indicate that when compared to a historical control, there is no evidence that TBZ treatment leads to progressive functional decline.

Table 27. Mean (SD) Baseline Demographic and Disease Characteristics for Studies 006 and 007 vs. CARE-HD Placebo Subjects

	Tetrabenazine		CARE-HD
	Study 006 (N=29)	**Study 007 (N=75)**	**Placebo (N=87)**
Age	57.4 ± 10.1	50.1 ± 11.5	48.6 ± 10.4
Gender, N (%) Female	17 (59%)	49 (65%)	48 (55%)
Race, N (%) Caucasian	27 (93%)	71 (95%)	80 (92%)
Time Since Sx Onset *	9.8 ± 4.8	8.5 ± 4.5	4.7 ± 3.7
Chorea Score †	14.4 ± 6.1	15.0 ± 3.7	9.1 ± 4.4
Functional Assessment	14.6 ± 7.0	18.2 ± 4.7	22.5 ± 1.8
Total Functional Capacity	5.83 ± 3.20	7.6 ± 2.4	10.3 ± 1.7
Independence	68.6 ± 14.6	75.7 ± 11.4	87.4 ± 8.8

* N = 31 for the CARE-HD Placebo group.
† N = 86 for the CARE-HD Placebo group.
Sx=symptoms.

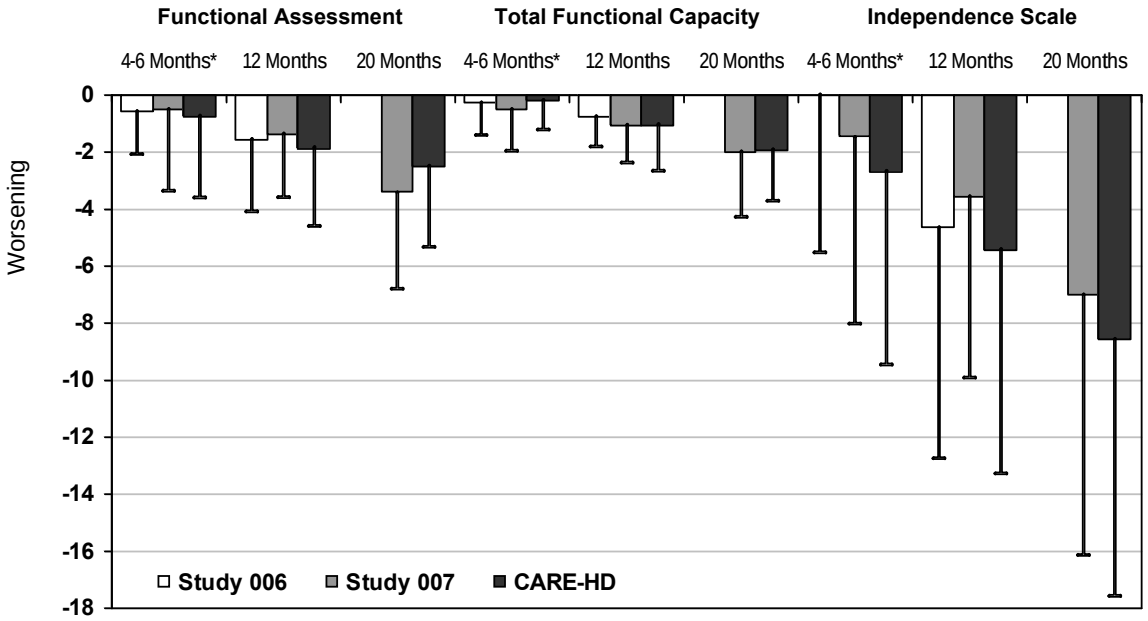


Figure 17. Mean (SD) Change from Baseline in Functional Measures: Long-term Data from Studies 006 and 007 vs. CARE-HD[1] Placebo Subjects (Observed Cases)

[1] HSG 2001.
* 4 months in CARE-HD and 6 months in Studies 006 and 007.

In summary, a small decline in some functional measures was noted in TBZ-treated patients as compared to placebo in Study 004. In contrast, Activities of Daily Living, as assessed by the TFC and FIS, trended in favor of TBZ suggesting that significant daily tasks may be improved with TBZ use. An analysis of the change in functional measures by the degree of change in instruments such as the HAM-D, which may capture TBZ AEs, suggests that some patients with AEs may have an associated decline in functional measures. A comparison of long-term data from TBZ-treated patients with historical data from CARE-HD shows similar declines in functional measures that are consistent with the natural progressive decline observed in HD. Thus, the balance of evidence does not suggest that TBZ has an adverse effect on function.

4.6.4 Cognition in Study 004

The 3 cognitive tests employed in Study 004 evaluate attention and concentration, as these are among the first cognitive domains to deteriorate in HD. The Stroop test is a measure of selective attention and cognitive flexibility. The Verbal Fluency and Symbol Digit tests measure memory and psychomotor speed,

respectively, but also require a significant component of attention and concentration.

The Stroop test (Golden and Freshwater, 2002) is comprised of 3 sub-items, each consisting of a card: Words (W), Colors (C), and Color Words (CW). In these cards are represented: black words depicting colors (W), colors (C), and words depicting colors written in a colored ink (incongruent with the color depicted by the word) (CW). The purpose of the test is to assess the ability to suppress a habitual response (reading words) in favor of a less familiar one (naming colors). The Stroop Interference score is calculated as Raw CW – Predicted CW. Thus, a higher score is better. The Verbal Fluency test evaluates the spontaneous production of words under restricted search conditions (i.e., name words that begin with the letter F). In the Symbol Digit Modality Test, a coding key is presented consisting of 9 abstract symbols each paired with a number; the respondent is required to scan the key and write down the number corresponding to each symbol, as rapidly as possible. These tests are a measure of attention since both require a selection process in completing the task. The Symbol-Digit Modality Test also requires complex visual scanning, motor speed, and memory.

At baseline, the TBZ group was more cognitively impaired than placebo, with the between-group difference reaching the level of statistical significance for Symbol Digit (p=0.0176) (Table 28).

Table 28. Mean Baseline and Change from Baseline to Week 12 in Cognitive Measures in Study 004 (Observed Cases)

	Baseline			Change from Baseline to Week 12		
Cognitive Measure	TBZ N=54	Placebo N=30	p-value	TBZ	Placebo	p-value
Symbol Digit	18.1 (11.5)	24.4 (11.3)	0.0176	+ 2.88	+ 2.52	0.7920
Verbal Fluency	18.9 (9.1)	18.7 (10.8)	0.9322	- 2.69	- 1.07	0. 3007
Interference Score*	- 0.71 (6.6)	- 0.43 (7.1)	0.6133	- 0.60	+ 0.32	0.551

* Interference Score was calculated as Raw CW – predicted CW, where predicted CW = (RawW*RawC)/ (RawW+RawC).
TBZ=tetrabenazine.

As indicated in Table 28, Symbol Digit scores improved in both TBZ-treated and placebo patients, whereas Verbal Fluency scores declined in both groups. The between-group differences were not statistically significant. There was a small decline in Stroop Interference in TBZ-treated patients and a small increase in the placebo group, but this difference was not clinically or statistically significant.

4.6.5 Conclusions on Non-Motor Outcomes

Analyses of the BA are sensitive to differences in methodology and do not suggest an overall decline in behavioral measures with TBZ as compared to placebo. Furthermore, an individual item analysis of this scale, as well as the HAM-D, indicates that anxiety and insomnia increased during treatment with TBZ, consistent with the known AE profile of the drug.

A small decline in some functional measures was noted in TBZ-treated patients as compared to placebo in Study 004. In contrast, Activities of Daily Living, as assessed by the TFC and FIS, trended in favor of TBZ suggesting that significant daily tasks may be improved with TBZ use. An analysis of the change in functional measures by the degree of change in instruments such as the HAM-D, which may capture TBZ AEs, suggests that some patients with AEs may have an associated decline in functional measures. A comparison of long-term data from TBZ-treated patients with historical data from CARE-HD shows similar declines in functional measures that are consistent with the natural progressive decline observed in HD. Thus, the balance of evidence does not suggest that TBZ has an adverse effect on function.

Regarding cognition, TBZ-treated patients were more cognitively impaired at baseline than placebo-treated patients, and this difference achieved statistical significance for the Symbol Digit test. Overall, there were small changes from baseline to Week 12 on cognitive parameters, none of which were clinically or statistically significant.

4.7 Efficacy Conclusions

The clinical development program provides substantial evidence of effectiveness for TBZ as a treatment for chorea in patients with HD. In Study 004, a 12-week, placebo-controlled study, TBZ consistently and robustly reduced chorea ($p < 0.0001$), findings that were confirmed by a responder analysis using a clinically relevant, prespecified criterion of a 3-point or greater reduction in chorea ($p < 0.0001$) and a physician-assessed CGI of change ($p = 0.0074$). Furthermore, 50% of TBZ-treated patients, as compared to 6% of placebo-treated patients, had an improvement in chorea score by 6 more points. Nineteen (19%) of TBZ-patients had a reduction in chorea score by 10 points or more. These results were confirmed in Study 005, which showed a comparable treatment effect

to that observed in Study 004. Study 005 also demonstrated rapid reversibility of the anti-chorea effects of TBZ upon discontinuation of study drug and no evidence for withdrawal symptoms.

Study 007 showed that the anti-chorea effects of TBZ are sustainable over a prolonged duration of treatment. The magnitude of the effect observed over the 80-week observation period in TBZ-treated patients in Study 007 was identical to that at the final evaluation in Study 004. In keeping with Study 007, the results of the open-label, long-term extension Study 006 also demonstrated the continued efficacy of TBZ over time for the treatment of chorea associated with HD. The clinical response observed was rapid in onset and was maintained over the 48-week observation period in this study.

5 CLINICAL SAFETY

5.1 Overview of Safety

The safety information on TBZ is derived from controlled and open-label clinical trials sponsored by Prestwick and open-label trials conducted under Investigator IND 16,161 at Baylor College of Medicine and an approximate ~40 years of post-marketing experience in Europe, Canada, Australia, and New Zealand. Included are 5 clinical trials of TBZ in patients with HD (1 also included patients with non-HD chorea), 1 clinical trial of hyperkinetic disorders other than chorea, as well as 12 clinical pharmacology trials in normal volunteers. The overall clinical safety experience from the 18 trials comprises a total of 773 unique patients who received TBZ and 146 patients who received placebo.

In Prestwick-sponsored Studies 004 and 007, TBZ was titrated according to the following scheme. During the first 7 weeks of Study 004 and the first 11 weeks of Study 007, the dosage of study drug was to be increased at the end of each week by 12.5 mg (1 tablet) increments until: 1) the desired effect was obtained, 2) intolerable adverse side effects occurred, or 3) the maximum allowed dosage was reached (100 mg/day in Study 004; 200 mg/day in all other studies). In Study 006, the TBZ dose was not titrated upward; in this study patients resumed treatment with the dose they were receiving in Study 005. The study patients treated at Baylor were titrated using a dose-optimization schedule, as follows: The initial dose of TBZ was 12.5 mg/day, which was then increased in increments of 12.5 to 25 mg/day approximately every 3-7 days until improvement in chorea or the occurrence of dose limiting AEs occurred. For most patients, the initial target dose was 150 mg/day (recommended before 1990) or 75 mg/day (recommended after 1990). Dose increases continued to 300 mg/day in divided doses in rare cases.

The published literature suggests the need for upward titration of TBZ based on a wide inter-individual difference in the dose of TBZ that causes dose-limiting AEs (25 mg/day to 200 mg/day). These dose-limiting AEs usually consist of sedation, akathisia, parkinsonism, and depressive symptoms, and are considered to be an extension of the monoamine-depleting properties (VMAT2 inhibition) of TBZ. It is not yet possible to predict which patient will experience dose-limiting AEs with low (25 mg/day) versus high (200 mg/day) doses of TBZ. Thus, upward titration is justified to safely achieve efficacy while limiting adverse effects.

The mean ± SD TBZ dose and exposure in studies of TBZ trials are summarized in Table 29.

The most frequently reported AEs by body system were related to psychiatric disorders, consistent with the pharmacology of TBZ (i.e., depletion of monoamines). For example, in Study 004, the most commonly reported AEs among the patients randomized to TBZ that were not observed at similar rates in the placebo group were sedation (31%), fatigue (22%), insomnia (22%), and depression (15%). The majority of AEs with TBZ were of mild to moderate intensity and occurred mainly during the upward dose titration phase of the study. The profile of AEs observed in Study 004 is similar to that observed in the other Prestwick-sponsored studies as well as the investigator-initiated studies.

Table 29. Summary of Exposure to Tetrabenazine and Mean Dose in Patient Studies Submitted in the NDA

Study/Project	Study Design (Study Duration)	Type of Patients Enrolled	Total (n)	>12 Weeks (n)	> 24 Weeks (n)	> 48 Weeks (n)	> 104 Weeks (n)	> 5 Years (n)	> 10 Years (n)	Mean Dose ± SD Range (mg/day)
Prestwick-Sponsored Studies of TBZ										
Clinical Pharmacology Studies (12 total)	Varied design (single- and multi-dose PK or PK/PD, < 5 days)	Volunteers	259	NA	NA	NA	NA	NA	NA	NA
TBZ 103,004 (Study 004)	Randomized, double-blind, placebo-controlled, (12 weeks)	HD Chorea	54	NA	NA	NA	NA	NA	NA	72.4 ± 29.54‡ 12.5 - 100
TBZ 103,007 (Study 007)	Open-label extension of Study 004 (up to 80 weeks)	HD Chorea	75	73	65	58	NA	NA	NA	73.64 ± 41.03 12.5 - 200
TBZ 103,005 (Study 005)	Randomized, double-blind, placebo-controlled, staggered withdrawal (5 days)	HD Chorea	30	NA	NA	NA	NA	NA	NA	52.92 ± 27.40 12.5 - 150
TBZ 103,006 (Study 006)	Open-label extension of Study 005 (up to 48 weeks)	HD Chorea	29	28	27	21	NA	NA	NA	68.21 ± 35.53 12.5 - 150
Investigator-Initiated Studies of TBZ										
Chorea*§	Prospective, open-label, dose-titration study (up to several years)	HD and non-HD Chorea	145¶	126	117	98	71	23	2	65.3 ± 35.4 †† 12.5 - 300
Non-chorea*	Open-label, compassionate use	Hyperkinetic Movement Disorders	280**	203	150	117	92	47	18	57.7 ± 34.6 6.25 - 225
Total Unique Number of Subjects/Patients†			**773**	**402**	**332**	**273**	**163**	**70**	**20**	

* Patients were treated with TBZ at Baylor College of Medicine since 1979.

† Patients enrolled in Studies 005 and 006 are also included in the Baylor chorea patients and are therefore not double-counted; 49 of the 75 patients enrolled in Study 007 were treated with TBZ in Study 004 and are therefore not double-counted.

‡ Based on Weeks 9 and 12 only (maintenance phase of study).

§ A total of 22 patients with chorea associated with HD treated under Baylor Non-Chorea withdrew from the study to enroll in Study TBZ 103,005.

¶ One HD patient in Baylor Chorea has an unknown duration of treatment; this patient is therefore listed conservatively in the Total column.

** A total of 33 patients are missing data on treatment duration in the Baylor Non-Chorea Report; these patients are therefore listed conservatively in the Total column.

†† Two patients have unknown doses in Baylor chorea.

HD = Huntington's disease, n=number of patients, NA=not applicable, TBZ = tetrabenazine.

5.2 Demographic and Exposure Data

5.2.1 Demography and Illness Characteristics at Baseline

The demographic and illness characteristics of patients with chorea are compared across all the studies that included chorea patients and that were submitted in the NDA. The summary characteristics of these patients are also compared to those of patients with other hyperkinetic movement disorders. Table 30 below presents the demographic characteristics of patients enrolled in the Prestwick-sponsored Studies 004, 005, and 007 as well as chorea patients and patients with non-chorea, hyperkinetic movement disorders enrolled at Baylor.

Table 30. Baseline Demographic Characteristics in Patient Studies

	Study 004			Study 007	Study 005/006*	Baylor Chorea		Baylor
	TBZ (N=54)	Placebo (N=30)	Total (N=84)	Total (N=75)	Total (N=30)	HD (N=98)	Non-HD† (N=47)	Non-Chorea‡ (N=280)
Gender								
Male	21 (39%)	11 (37%)	32 (38%)	26 (35%)	12 (40%)	40 (41%)	18 (38%)	121 (43%)
Female	33 (61%)	19 (63%)	52 (62%)	49 (65%)	18 (60%)	58 (59%)	29 (62%)	159 (57%)
Age (years)								
Mean ± SD	49.4 ± 12.3	48.8 ± 10.5	49.2 ± 11.7	50.9 ± 11.5	56.8 ± 10.0	54.8 ±11.8	44.0 ± 28.3	49.1 ± 23.2
Median	49.5	49	49.5	52.0	59.5	55	54	-
Range	25-77	28-67	25-77	29-77	39-75	31-79	3-80	4.3-87.6
Race								
White	50 (93%)	29 (97%)	79 (94%)	71 (95%)	28 (93%)	78 (80%)	34 (72%)	-
Other	4 (7%)	1 (3%)	5 (6%)	4 (5%)	2 (7%)	19 (19%) §	13 (28%)	-
Years of Education								
Mean	13.7 ± 2.34	13.7 ± 2.25	-	13.8 ± 2.32	-	-	-	-
Median	13.5	13.5	-	14.0	-	-	-	-
Range	6-18	9-18	6-18	6-18	-	-	-	-

* 29 of 30 patients in Study 005 were rolled over into Study 006.
† Most common causes of chorea were: Syndenham's chorea (n=7), tardive chorea (n=7), and hemi-chorea (n=6).
‡ Most common diagnoses were: tardive dyskinesia (n=87), Tourette's syndrome (n=66), cranial dystonia (n=26), and cervical dystonia (torticollis) (n=20).
§ One subject missing information
HD = Huntington's disease, - = not recorded, TBZ = tetrabenazine.

As shown in Table 30, across all studies submitted in the NDA and across all diagnoses, there was a slight female preponderance. Subjects enrolled in the Clinical Pharmacology studies ranged in age from 18 to 66 years; patients enrolled in the Prestwick-sponsored studies ranged in age from 25 to 77 years. Children were not enrolled in the Prestwick-sponsored studies in HD patients (HD rarely starts during childhood and when it does, it is not associated with chorea), whereas children with chorea and non-chorea, hyperkinetic movement disorders were enrolled at Baylor (age of 3-80 years). In the studies that enrolled HD patients, 80% to 93% of patients were white, consistent with the reported low incidence of HD in Blacks and in Asians (Marshall and Shoulson, 1997; Fahn, 2000).

The demographic characteristics of the patients enrolled in the 2 Prestwick-sponsored double-blind, placebo-controlled studies (Studies 004 and 005) were similar. Across both studies, there was a slight preponderance of females, and the majority of patients (94%) were white. There was, however, a slight difference in mean age, but not age range. The difference in mean age may reflect the differences in disease severity. The demographic characteristics of Baylor chorea and non-chorea patients were comparable to those of the patients enrolled in the Prestwick-sponsored double-blind trials, with the exception that children were enrolled at Baylor.

Based on CGI-Severity, 57%, 14%, and 2% of patients enrolled in Study 004 were moderately, markedly, or severely ill, as compared to 53%, 20%, and 20% of patients, respectively, in Study 005. Patients enrolled in Study 005 tended to have a slightly longer mean duration of disease (10.0 ± 5.1 years versus 8.2 ± 4.6 years in Study 004). Mean disease duration for patients enrolled at Baylor was 7.2 ± 8.3 (Non-chorea) to 7.9 ± 7.7 (Chorea) years.

5.2.2 Exposure Data

A total of 259 subjects were exposed to TBZ during their participation in a Clinical Pharmacology study. Exposure to TBZ in the clinical studies into which patients were enrolled is presented in Table 29. Patients enrolled in Study 007 were rolled over from Study 004, as were patients in Study 006 from Study 005, therefore there is overlap in patient numbers.

Across these clinical studies, 402 unique patients were treated with TBZ for more than 12 weeks, 332 were treated for more than 24 weeks, 273 were treated for

more than one year (48 weeks), 163 were treated for more than 104 weeks, 70 were treated for more than 5 years, and 20 were treated for more than 10 years.

Table 31 below summarizes the range of "best dose" across the 2 Prestwick-sponsored double-blind trials in patients with chorea associated with HD (Study 004; Study 005), the 2 Prestwick-sponsored open-label extension studies (Study 006; Study 007), and for the open-label studies performed at Baylor. Across these studies, mean "best dose" was approximately 70 mg/day. The range of "best doses" of TBZ in patients enrolled in the Prestwick-sponsored studies of patients with HD chorea were similar to those among patients with chorea (associated with HD or associated with other diseases) and in patients with hyperkinetic movement disorders other than chorea who were enrolled at Baylor.

Table 31. "Best Dose" in the Efficacy Studies, Number (%) of Patients) *

TBZ Dosage (mg/day)	TBZ 103,004 N=54 N (%)	TBZ 103,005 N=30 N (%)	TBZ 103,006 N=24 N (%)	TBZ 103,007 N=66 N (%)	Baylor Chorea N=142 † N (%)	Baylor Non-Chorea N=237 ‡ N (%)
6.25	NA	NA	NA	NA	NA	4 (2%)
12.5	1 (2%)	1 (3%)	1 (4%)	2 (3%)	4 (3%)	11 (5%)
18.75 §	0	0	0	0	1 (1%)	1 (<1%)
25.0	2 (4%)	4 (13%)	3 (13%)	4 (6%)	18 (13%)	35 (15%)
37.5	8 (15%)	9 (30%)	2 (8%)	7 (11%)	25 (18%)	43 (18%)
50.0	11 (20%)	5 (17%)	4 (17%)	18 (27%)	23 (16%)	41 (17%)
62.5	2 (4%)	0	1 (4%)	5 (8%)	7 (5%)	14 (6%)
75.0	2 (4%)	9 (30%)	2 (8%)	8 (12%)	41 (29%)	56 (24%)
87.5	6 (11%)	0	4 (17%)	8 (12%)	0	2 (1%)
100.0	22 (41%)	0	3 (13%)	1 (2%)	3 (2%)	12 (5%)
112.5	NA	1 (3%)	2 (8%)	1 (2%)	5 (4%)	3 (1%)
125.0	NA	0	2 (8%)	3 (5%)	2 (1%)	5 (2%)
150.0	NA	1 (3%)	0	8 (12%)	9 (6%)	8 (3%)
200.0	NA	NA	NA	1 (2%)	2 (1%)	1 (<1%)
225.0	NA	NA	NA	NA	1 (1%)	1 (<1%)
300.0	NA	NA	NA	NA	1 (1%)	0

* "Best dose" was defined as the dose that was efficacious and tolerable for Studies 004 at the End-of-Week 12 visit; Study 005 at entry (patients enrolled in the study had to be on stable TBZ dose for 2 months); Study 006 at the End-of-Week 24 visit; and Study 007 at the End-of-Week 24 visit. "Best dose" was set as equal to "standard dose" for Baylor chorea patients. "Best dose" was set as equal to last dose at the time of the 2002 cut-off for the Baylor Non-Chorea patients.

† Two of 145 (1%) patients had unknown doses.

‡ Among the Baylor Non-Chorea patients, 43 of 280 (15%) patients had unknown last dose data.

§ 18.75 mg = ¾ of a 25 mg tablet

NA = Not applicable, TBZ=tetrabenazine.

5.3 Adverse Events in Clinical Pharmacology Studies

Four hundred thirty-five AEs were reported in the 12 clinical pharmacology studies. Of these reported AEs, 66.2% (288 of 435) occurred with TBZ. The

most common AEs reported were somnolence, headache, asthenia, restlessness, and nausea.

AEs judged by the investigator to be related to TBZ (whether the association was considered probable or possible versus unrelated) totaled 75.4% (217 of 288) of the AEs reported on TBZ.

There was one TBZ-related AE that was considered to be "severe" in intensity; 77.4% (223 of 288) were judged to be "mild" in intensity, and 22.2% (64 of 288) were judged to be "moderate" in intensity.

5.4 Adverse Events in Study 004

In Study 004, AEs were more common in the TBZ group than in the placebo group. Forty-nine of 54 (91%) patients who received TBZ experienced 1 or more AEs at any time during the study as compared to 70% (21/30) of placebo patients. The most commonly reported AEs that were at least 5% and greater than placebo were sedation/somnolence (31%), fatigue (22%), insomnia (22%), depression (15%), restlessness aggravated (13%), and nausea (13%). The number and percentage of the most commonly reported AEs (i.e., reported by ≥ 5% of patients) are presented by body system and preferred term in Table 32, in decreasing order of frequency within body system for the TBZ group.

Table 32. Treatment Emergent Adverse Events Reported in ≥ 5% of Patients in Study 004

Body System	AE Preferred Term	TBZ (N=54) N (%)	Placebo (N=30) N (%)
PSYCHIATRIC DISORDERS	Sedation/Somnolence	17 (31%)	-
	Insomnia	12 (22%)	-
	Depression	8 (15%)	-
	Restlessness Aggravated	7 (13%)	-
	Irritability	5 (9%)	1 (3%)
	Anxiety	4 (7%)	1 (3%)
	Anxiety Aggravated	4 (7%)	-
	Drowsiness	3 (6%)	-
CENTRAL & PERIPHERAL NERVOUS SYSTEM	Akathisia	5 (9%)	-
	Balance Difficulty	5 (9%)	-
	Parkinsonism/Bradykinesia	5 (9%)	-
GASTROINTESTINAL SYSTEM DISORDERS	Nausea	7 (13%)	2 (7%)
	Diarrhea	3 (6%)	3 (10%)
	Vomiting	3 (6%)	1 (3%)
BODY AS A WHOLE – GENERAL	Fatigue	12 (22%)	4 (13%)
SECONDARY TERMS	Fall	8 (15%)	4 (13%)
	Inflicted Injury	3 (6%)	-
RESPIRATORY SYSTEM DISORDERS	Upper Respiratory Tract Infection	6 (11%)	2 (7%)
	Coughing	3 (6%)	3 (10%)
PLATELET, BLEEDING & CLOTTING	Bruise	4 (7%)	2 (7%)
	Ecchymosis	3 (6%)	-

5.5 Adverse Events in Study 007

The safety of TBZ also was evaluated in Study 007, an 80-week, long-term, open-label study of patients who completed Study 004. Of 84 patients (54 TBZ and 30 placebo) enrolled in Study 004, 75 rolled over into Study 007 after completing a washout period of at least 1 week following Study 004.

The most commonly observed AEs were sedation/somnolence (43%), depression (32%), fall (31%), insomnia (28%), anxiety (25%), akathisia (20%), chorea (19%), fatigue (16%), and sleepiness (11%) (Table 33). In most cases, AEs were mild to moderate. In 26 patients (35%), AEs were severe. Severe AEs occurred in the psychiatric disorders (13/75, 17%) and in the central and peripheral nervous system disorders (7/75, 9%). The most frequently reported severe AEs consisted of anxiety (5/75, 7%), akathisia (4/75; 5%), depression (4/75, 5%), and sedation (3/75, 4%).

Although the incidence of AEs in Study 007 is higher than reported in Study 004, it is important to note that the duration of follow up was 80 weeks and 12 weeks, respectively, for the 2 studies. Adverse event rates normalized for patient

exposure are summarized in Section 5.13 for AEs of interest, including depressive symptoms, akathisia, parkinsonism, dysphagia, and sedation.

Table 33. Treatment Emergent Adverse Event Reported in ≥ 5% of Patients in Tetrabenazine-Treated Patients in 80-Week, Long-Term, Open-Label Study 007

Body System	AE Preferred Term	TBZ (N=75) N (%)
PSYCHIATRIC DISORDERS	Sedation/Somnolence	32 (43%)
	Depression	24 (32%)
	Insomnia	21 (28%)
	Anxiety	19 (25%)
	Sleepiness	8 (11%)
	Agitation	5 (7%)
	Drowsiness	4 (5%)
	Lethargy	4 (5%)
	Obsessive Reaction	4 (5%)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	Akathisia	15 (20%)
	Chorea	14 (19%)
	Dystonia	6 (8%)
	Dizziness	4 (5%)
	Dysarthria	4 (5%)
SECONDARY TERMS	Fall	23 (31%)
	Inflicted Injury	4 (5%)
GASTRO-INTESTINAL SYSTEM DISORDERS	Diarrhea	7 (9%)
	Constipation	4 (5%)
BODY AS A WHOLE – GENERAL	Fatigue	12 (16%)
RESPIRATORY SYSTEM DISORDERS	Upper Respiratory Tract Infection	5 (7%)
	Pneumonia	4 (5%)

5.6 Adverse Events: Titration vs. Maintenance

As previously noted, the dose of TBZ was titrated upward during the first 7 weeks of Study 004 and the first 11 weeks of Study 007.

As shown in Table 34, the majority of AEs reported by patients randomized to TBZ in Study 004 occurred during Weeks 0-9 (up to the first visit following the final titration step) as opposed to Weeks 9-12 (corresponding to the maintenance phase) of the 12-week study treatment period (91%, 49/54 vs. 35%, 19/54, respectively). This trend is noteworthy in AEs in the psychiatric disorders and central and peripheral nervous system disorders body systems. AEs such as sedation/somnolence, drowsiness, akathisia, parkinsonism/bradykinesia, nausea, and diarrhea occurred only during the upward dose titration period. Other AEs, such as depression (7 versus 1), restlessness aggravated (6 versus 1), irritability (4

versus 1), balance difficulty (4 versus 1), fatigue (11 versus 1), and fall (7 versus 3), occurred mainly, but not exclusively, during the upward dose titration.

Table 34. Treatment Emergent Adverse Events (> 2 Patients) in TBZ-Treated Patients (N=54) by Dose Titration Period in Study 004

Body System	AE Preferred Term	Titration Period (Weeks 0 to 9) N (%)	Maintenance Period (Weeks 9 to 12) N (%)
PSYCHIATRIC DISORDERS	Sedation/Somnolence *	17 (31%)	0 (0%)
	Insomnia	7 (13%)	5 (9%)
	Depression	7 (13%)	1 (2%)
	Restlessness Aggravated	6 (11%)	1 (2%)
	Irritability	4 (7%)	1 (2%)
	Anxiety	1 (2%)	3 (6%)
	Anxiety Aggravated	2 (4%)	2 (4%)
CENTRAL & PERIPHERAL NERVOUS SYSTEM	Akathisia	5 (9%)	0 (0%)
	Balance Difficulty	4 (7%)	1 (2%)
	Parkinsonism/Bradykinesia	5 (9%)	0 (0%)
GASTROINTESTINAL SYSTEM DISORDERS	Nausea	7 (13%)	0 (0%)
	Diarrhea	3 (6%)	0 (0%)
BODY AS A WHOLE – GENERAL	Fatigue	11 (20%)	1 (2%)
SECONDARY TERMS	Fall	7 (13%)	3 (6%)
RESPIRATORY SYSTEM DISORDERS	Upper Respiratory Tract Infection	3 (6%)	4 (7%)
PLATELET, BLEEDING & CLOTTING	Bruise	4 (7%)	0 (0%)
	Ecchymosis	3 (6%)	0 (0%)

* Sedation/somnolence includes drowsiness and sleepiness

A similar trend was observed in Study 007, where the incidence of AEs was lower during the maintenance period for AEs coded to sedation/somnolence, depression, insomnia, anxiety, and akathisia. As the reporting periods (0-12, 13-24 weeks) are congruent in Study 007 (versus Study 004), the comparison of AE incidence has greater validity (Table 35).

Table 35. Treatment Emergent Adverse Events (≥ 5%) in TBZ-Treated Patients (N=74) by Dose Titration Period in Study 007

Body System	AE WHO Term	Weeks 0-12 (N=75) N (%)	Weeks 13-24 (N=73) N (%)
PSYCHIATRIC DISORDERS	Sedation/Somnolence	23 (31%)	9 (12%)
	Depression	15 (20%)	6 (8%)
	Insomnia	15 (20%)	1 (1%)
	Anxiety	8 (11%)	3 (4%)
	Sleepiness	7 (9%)	1 (1%)
	Agitation	1 (1%)	2 (3%)
	Drowsiness	4 (5%)	1 (1%)
	Lethargy	4 (5%)	--
	Obsessive Reaction	2 (3%)	1 (1%)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	Akathisia	8 (11%)	5 (7%)
	Chorea	1 (1%)	2 (3%)
	Dystonia	3 (4%)	--
	Dizziness	3 (4%)	--
	Dysarthria	3 (4%)	--
SECONDARY TERMS	Fall	7 (9%)	4 (5%)
	Inflicted Injury	3 (4%)	--
GASTRO-INTESTINAL SYSTEM DISORDERS	Diarrhea	6 (8%)	1 (1%)
	Constipation	1 (1%)	1 (1%)
BODY AS A WHOLE – GENERAL	Fatigue	11 (15%)	--
RESPIRATORY SYSTEM DISORDERS	Upper Respiratory Tract Infection	3 (4%)	--
	Pneumonia	1 (1%)	1 (1%)

5.7 Adverse Events in Study 006

In Study 006, the open-label, 48-week follow-on study to Study 005, 27 of 29 (93%) of patients reported 1 or more AEs during their participation in the study. As shown in Table 36, the most commonly observed AEs were depression (31%), anxiety (24%), insomnia (17%), sedation/somnolence (17%), urinary tract infection (14%), dysphagia/ swallowing difficulty (10%), parkinsonism (10%), and agitation, restlessness marked, appetite decreased, nausea, and increased salivation, each at 7%. In most cases, AEs were mild to moderate in severity. Severe AEs were reported in 4 patients, including psychiatric disorders (depression n=1; thoughts of self harm n=1) the gastrointestinal system (nausea n=1; diarrhea n=1) and the respiratory system (pneumonia, pleural effusion, pneumothorax each at n=1).

Table 36. Treatment Emergent Adverse Events Reported in ≥ 5% of Patients in the 48-Week, Open-Label Study 006

Body System	AE WHO Term	TBZ (N=29) N (%)
PSYCHIATRIC DISORDERS	Depression	9 (31%)
	Anxiety	7 (24%)
	Insomnia	5 (17%)
	Sedation/Somnolence	5 (17%)
	Agitation	2 (7%)
	Appetite decreased	2 (7%)
	Emotional lability	2 (7%)
	Restlessness marked	2 (7%)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	Parkinsonism	3 (10%)
GASTRO-INTESTINAL SYSTEM DISORDERS	Dysphagia/ swallowing difficulty	3 (10%)
	Nausea	2 (7%)
	Saliva increased	2 (7%)
URINARY SYSTEM DISORDERS	Urinary tract infection	4 (14%)
SKIN AND APPENDAGES DISORDERS	Skin discoloration	2 (7%)
METABOLIC AND NUTRITIONAL DISORDERS	Dehydration	2 (7%)
SECONDARY TERMS	Fall	3 (10%)
	Inflicted injury	3 (10%)

5.8 Reversibility of Adverse Events

As TBZ is to be titrated to the desired effect or until side effects emerge that are not well tolerated, individual patients with important AEs during the clinical studies were examined to assess the reversibility of these events. The events analyzed include sedation/somnolence, which was the most common adverse event across studies, as well as depressive symptoms/depression, akathisia, parkinsonism, and dysphagia. The latter events are considered important because they were anticipated during the clinical trials due to the pharmacology of tetrabenazine and because they are clinically significant AEs. As indicated in Table 37, these AEs resolved in some cases with either discontinuation of therapy or with continued treatment at the same dose. More commonly, dose reduction was employed to manage these AEs, and in the majority of cases, this maneuver led to resolution or improvement of the event.

Table 37. Reversibility of Important AEs with or without Tetrabenazine Dose Reduction

Adverse Event Study	Total No. of Patients	Resolved with		Dose Reduction			
		D/C TBZ	No Dose Change	No. with Dose Reduction	AE Outcome With Dose Reduction		
					Resolved	Improved	No Change
Sedation							
004	17	2	5	10	9	1[1]	–
006	5[2]	–	1	2	2	–	–
007	32[3]	5	3	23[4]	19	–	2
Depression							
004	8	3	2	3	3	–	–
006	9[5]	–	4	1	–	1[6]	–
007	24[7]	–	5	13	8	4[8]	1[9]
Akathisia							
004	5	3	–	2	2	–	–
006	0	–	–	–	–	–	–
007	15[10]	4	3	7	7	–	–
Parkinsonism							
004	5	1	1	3	2	–	1[11]
006	3[12]	–	–	1	1	–	–
007	2	–	–	2	1[13]	1[14]	–
Dysphagia							
004	1	–	–	1	1[16]	–	–
006	3[15]	–	–	1	1	–	–
007	3[17]	–	–	2	2	–	–

Data in each column are number of patients. Some patients also had a change in concomitant medications.

[1] AE ongoing with improvement in ESS.

[2] Includes 2 patients who were managed with changes in concomitant medication (starting or increasing dose of Provigil) without dose reduction and the AE persisted.

[3] Includes 1 patient with no dose reduction and the AE persisted.

[4] Includes 2 patients with an unknown outcome.

[5] Includes 3 patients who were managed with changes in concomitant medication without dose reduction and the AE persisted (1 with comparable HAM-D score to baseline and 2 with HAM-D scores of 13 and 16). In addition, includes 1 patient who had no medical intervention and the AE persisted with a normal HAM-D score.

[6] Severity decreased for 2 months after dose reduction and then increased thereafter. Final HAM-D on therapy was 7 (normal).

[7] Includes 6 patients managed with changes in concomitant medication but the AE persisted, however 5 of the patients had normal HAM-D scores and the other patient had an ongoing AE with an improved HAM-D score.

[8] Ongoing AE with either normal or improved HAM-D score.

[9] AE persisted on TBZ 150 mg/day with improved HAM-D score.

[10] Includes 1 patient who prematurely discontinued from treatment due to depression and akathisia and was lost to follow up. The AE was ongoing at patient withdrawal.

[11] The patient's AE was ongoing upon enrollment into Study 007, however, the patient was lost to follow-up after 7 days due to skilled nursing home placement.

[12] Includes 2 patients who had no dose reduction and the AE persisted, yet both had UHDRS Parkinsonism scores that were improved as compared to study entry.

[13] Patient had second episode and outcome was unknown as patient died due to metastatic breast cancer.

[14] At end of study participation, AE ongoing but UHDRS Parkinsonism score at baseline level.

[15] Includes 2 patients with no intervention but ongoing dysphagia at study end. One of these patients reported the AE on the last treatment day. The other patient had a UPDRS dysphagia score of 1 consistent with rare choking.

[16] The dose was reduced, however the AE resolved before down titration for protocol washout.

[17] Includes 1 patient with dysphagia at baseline who developed severe dysphagia requiring feeding tube placement. The patient also required nursing home placement. Dysphagia was present approximately 6 months following study participation.

AE=adverse event; D/C=discontinue; TBZ=tetrabenazine; ESS = Epworth Sleepiness Scale; HAM-D = Hamilton Depression Scale; UHDRS = Unified Huntington's Disease Rating Scale

In summary, an analysis of individual patients with AEs of sedation, depression, akathisia, parkinsonism, and dysphagia revealed that these events were detected throughout the course of therapy and were effectively managed with dose reduction of TBZ. In some cases, AEs resolved without intervention. Adverse events coded to akathisia or depression were also managed with changes in concomitant medication, with or without TBZ dose adjustment, as is summarized in Section 5.13. Each of these maneuvers was effective in ameliorating these AEs, indicating that TBZ can be safely used in clinical practice.

5.9 Adverse Events in Withdrawal Study 005

Study 005 was a placebo-controlled study into which patients were randomized to withdrawal of TBZ after their morning dose on Day 1 (Group 1, n=12) or Day 3 (Group 2, n=12) or to continuation of study drug (Group 3, n=6). Of 30 enrolled patients, 6 (20%) who received TBZ experienced 1 or more AEs at any time during the study, including 4 patients in Group 1 and 1 patient each in Groups 2 and 3. Anxiety and dysphagia were the most common AEs, each reported by 2 patients following withdrawal of TBZ. One patient reported multiple AEs (i.e., anxiety, decreased appetite, mood swings, restlessness aggravated, and difficulty swallowing, inflicted injury [tongue laceration]). The number and percentage of treatment-emergent AEs are presented by body system and preferred term in Table 38, in decreasing order of frequency within body system for Group 1.

Table 38. Treatment Emergent Adverse Events in Study 005, in Decreasing Order of Frequency for Group 1

Body System	AE Preferred Term	Group 1 N=12 N (%)	Group 2 N=12 N (%)	Group 3 N=6 N (%)
PSYCHIATRIC DISORDERS	Anxiety	2 (17%)	-	-
	Appetite decreased	1 (8%)	-	1 (17%)
	Hallucination	1 (8%)	-	-
	Insomnia	1 (8%)	-	-
	Mood swings	1 (8%)	-	-
	Obsessive reaction	-	-	1 (17%)
	Restlessness aggravated	1 (8%)	-	-
	Sleep decreased	-	-	1 (17%)
GASTROINTESTINAL SYSTEM DISORDERS	Diarrhea	-	1 (8%)	-
	Dysphagia/swallowing difficult	2 (17%)	-	-
SECONDARY TERMS	Inflicted injury *	1 (8%)	-	

* Tongue laceration

5.10 Adverse Events in Investigator-Initiated Studies

Tetrabenazine has been studied in an open-label, long-term, compassionate use trial for the treatment of incapacitating dyskinesias. The protocols have been reviewed and approved annually by the Baylor College of Medicine Institutional Review Board. The safety analyses presented in the NDA included 280 patients with hyperkinetic movement disorders and 145 chorea patients.

The assessments of AEs included all voluntary complaints of patients at each follow-up visit and at each telephone contact. AEs were evaluated and recorded every 3 to 6 months during clinic visits as well as during periodic telephone contacts. Patients were instructed to inform the primary investigator or a member of the study staff of any AEs that occurred at any time during the study.

5.10.1 Baylor Chorea Patients

A total of 145 chorea patients were enrolled at Baylor, including 98 with HD and 47 without HD. Syndenham's chorea (n=7), tardive chorea (n=7), and hemi-chorea (n=6) were the most common non-HD diagnoses. The most frequently reported AEs (≥ 5% of chorea patients) are presented in Table 39.

Table 39. Treatment Emergent Adverse Events Reported in ≥ 5% of Baylor Chorea Patients

COSTART Body System	COSTART Preferred Term	TBZ N = 145 N (%)
NERVOUS SYSTEM	Somnolence	65 (45%)
	Depression *	44 (30%)
	Insomnia	41 (28%)
	Extrapyramidal syndrome/Parkinsonism †	20 (14%)
	Increased salivation	19 (13%)
	Akathisia	17 (12%)
	Nervousness	16 (11%)
	Anxiety	15 (10%)
	Dizziness	10 (7%)
	Agitation	9 (6%)
	Ataxia	9 (6%)
	Amnesia	8 (6%)
	Dysarthria	8 (6%)
	Speech disorder	8 (6%)
BODY AS A WHOLE	Accidental injury	30 (21%)
	Asthenia	15 (10%)
	Pain	12 (8%)
	Headache	9 (6%)
DIGESTIVE SYSTEM	Dysphagia	22 (15%)
	Diarrhea	13 (9%)
	Nausea	13 (9%)
	Constipation	11 (8%)
	Fecal incontinence	7 (5%)
	Gastrointestinal disorder	7 (5%)
METABOLIC & NUTRITIONAL DISORDERS	Weight loss	21 (14%)
UROGENITAL SYSTEM	Urinary incontinence	10 (7%)

* Four of these 44 patients had "suicidal ideation" as an AE. The COSTART dictionary codes suicidal ideation as "depression" for the preferred term. Of the 4 patients who had suicidal ideation, 2 were reported to have depression, and 2 were not reported to have depression as separate AEs.

† The COSTART dictionary codes parkinsonism to extrapyramidal syndrome; all 20 AEs of extrapyramidal syndrome were parkinsonism.

Over the evaluation period, the most commonly reported AEs in the chorea patients were somnolence (45%), depression (30%) insomnia (28%), accidental injury (21%), and dysphagia (15%). As compared to the Prestwick-sponsored studies, the AE profile in the Baylor chorea patients is similar. Although the rates are generally higher, it is important to note that duration of follow-up is considerably longer than in the Prestwick studies.

5.10.2 Baylor Non-Chorea Patients

A total of 280 patients with hyperkinetic movement disorders were enrolled at Baylor. The most common diagnoses were: tardive dyskinesia (n=87), Tourette's syndrome (n=66), cranial dystonia (n=26), and cervical dystonia (torticollis) (n=20).

The most frequently reported AEs (≥ 5% of patients) are presented in Table 40 for patients with non-chorea, hyperkinetic movement disorders.

Table 40. Treatment Emergent Adverse Events Reported in ≥ 5% of Baylor Non-Chorea Patients

Body System	AE Term	TBZ N = 280 N (%)
NERVOUS SYSTEM	Drowsiness/fatigue	74 (26%)
	Parkinsonism	54 (19%)
	Depression	26 (9%)
	Akathisia	21 (8%)
	Nervousness/anxiety	18 (6%)
	Insomnia	15 (5%)
DIGESTIVE SYSTEM	Nausea/vomiting	21 (8%)

Note: AEs are verbatim term per Baylor.

The profile of AEs reported in the non-chorea patients is similar to that observed in patients with chorea associated with HD in the Prestwick-sponsored studies and to that observed in the Baylor chorea patients. Drowsiness/fatigue (26%), parkinsonism (19%), depression (9%), akathisia (8%), nausea/vomiting (8%), nervousness/anxiety (6%), and insomnia (5%) were the most frequent AEs.

5.11 Discontinuations due to Adverse Events

Among the 259 subjects enrolled in the Clinical Pharmacology studies, 6 prematurely discontinued study drug due to an AE, including: 1 due to probably-related, mild rash; 1 due to probably-related, restlessness and nausea; 1 due to possibly-related junctional rhythm in a subject with a history of palpitations; 1 due to unrelated positive fecal hemacult test in a subject with a history of possible inflammatory/irritable bowel disease; 1 due to unrelated ALT elevation; and 1 due to possibly-related restlessness.

In the Prestwick-sponsored clinical trials in HD patients, 14 of 111 (13%) TBZ-treated patients were withdrawn due to 1 or more AEs. Akathisia and depression

led to discontinuation of TBZ and withdrawal from the study in 2 and 1 case, respectively; 1 additional patient prematurely discontinued due to both akathisia and depression. Suicidal ideation was reported as the reason for withdrawal in 2 patients. All other AEs that led to study drug discontinuation were each reported in 1 patient. Other AEs that led to study drug discontinuation included: disabling tics in 1 patient; abnormal coordination, unsteady gait and balance difficulty in 1 patient; fall in 1 patient; breast cancer in 2 patients; suicide leading to death in 1 patient; and nausea/dehydration in 1 patient. Abnormal laboratory values were associated with withdrawal in 2 patients (increased LFTs less than 5 times normal and mildly increased bilirubin). In both cases, the abnormal laboratory values returned to normal values within a few weeks following discontinuation of TBZ. The profile of reasons for withdrawal in these patients revealed no particular pattern, both in terms of the nature of the AE and the dose and duration of treatment with TBZ.

Among 145 patients with chorea treated at Baylor, AEs were reported at the time of withdrawal in 29% patients. However, the case report forms (CRFs) did not always specify which AE led to withdrawal. For this reason, all AEs at the time of withdrawal are reported. Most of the AEs were in the psychiatric, central and peripheral nervous system, gastrointestinal, and respiratory body systems. The most commonly reported AEs at the time of withdrawal were depression (6%) and somnolence (5%). Other AEs such as parkinsonism and akathisia were reported at the time of discontinuation in smaller numbers of patients. Discontinuation in such patients occurred after a wide range of treatment durations (6 to >100 months) and at a wide range of doses (12.5 to 150 mg per day), and the majority were described as “not severe.”

Among 280 non-chorea patients treated at Baylor, AEs were reported at the time of withdrawal in 18% of patients. The profile of these AEs is also consistent with the safety profile of TBZ in published reports and in the Prestwick-sponsored clinical studies.

5.12 Serious Adverse Events and Deaths

5.12.1 Serious Adverse Events

No SAEs were reported in any of the Clinical Pharmacology studies.

In the Prestwick-sponsored double-blind clinical trials in HD patients submitted in the NDA, 4 TBZ-treated patients experienced 1 or more SAEs, although only 2 of

these events were judged possibly related to TBZ. One of these SAEs was a death attributed to suicide in a 40-year-old male with no known history of depression but a past history of suicidal ideation, and no evidence of depression observed by the investigator and family just 2 weeks prior to the event. The other SAE judged possibly related to TBZ was reported in a patient with a history of falling episodes prior to enrollment who experienced a fall complicated by subarachnoid hemorrhage and confusion, and the patient was withdrawn from the study. Of the other SAEs judged unrelated to TBZ, 1 patient was hospitalized initially for persistent restlessness later determined to be due to prostatitis. This patient was subsequently hospitalized for suicidal ideation after his chorea worsened as a result of a downward titration of TBZ after the initial SAE. He responded to antidepressant medication and resumed TBZ, but then developed psychosis and paranoia that resolved quickly with antipsychotic medication. The patient was then withdrawn from the study. One patient had a pre-existing breast mass diagnosed during the study as breast cancer, and she was withdrawn from the study, but later was granted a waiver and resumed taking TBZ in the open-label follow on study after it was determined that the breast cancer was prolactin-insensitive. There were no SAEs reported in the double-blind withdrawal Study 005.

Among HD patients initially enrolled in the double-blind studies and then enrolled in 1 of 2 open-label, long-term extension studies, 16 patients had 1 or more SAEs. One of these SAEs was metastatic breast cancer that resulted in death (note: this patient is different from the patient who was diagnosed with breast cancer in Study 004 and granted a waiver to continue treatment in the open-label extension study). Among the 15 non-fatal SAEs, there were 2 events of pneumonia (1 with dysphagia), 1 report of a fall and pneumonia, and 2 reports of falls; both pneumonia and falls are known complications of HD. Two of the cases of pneumonia was judged possibly related to TBZ. All 5 patients continued on TBZ, and the SAEs resolved. One patient was reported with increased depression, akathisia, anxiety, and agitation judged related to TBZ. This patient responded to antidepressant treatment, but elected to discontinue TBZ treatment. One patient who had stopped taking her antidepressant medication developed suicidal ideation, which resolved after resumption of her antidepressant; this patient continued TBZ treatment. Another patient with a history of depression attempted suicide (unwitnessed swallowing of Windex®), which the investigator classified as not related to TBZ. Seven (7) additional patients experienced SAEs judged to be unrelated to TBZ. These events included diarrhea and depression,

nausea, urinary tract infection, chest pain, prostate cancer, recurrent breast cancer, and elective hip replacement for arthritis.

Among the 145 Baylor chorea patients, 31 patients experienced SAEs, the vast majority of which were judged unrelated to TBZ. The profile of these SAEs is consistent with the types of events expected in patients with HD such as pneumonia. Furthermore, most of these SAEs were each reported in 1 patient, such that no particular pattern emerged.

A comparison of the SAEs across all studies submitted in the NDA reveals no particular pattern of SAEs. Furthermore, these SAEs occurred over a range of doses and at different timepoints in each study.

5.12.2 Deaths

Table 41 lists all deaths across the studies reported in the NDA.

Table 41. Deaths across the Tetrabenazine Clinical Trials

Study	Number of Subjects/ Patients Enrolled	Number of Subjects/Patients Treated with		Number of Patients Who Died	Cause of Death
		TBZ	Placebo		
Clinical Pharmacology Studies	261	259	0	0	NA
004	84	54	30	1	Completed Suicide
005	30	30	24	0	NA
006	29	29	0	0	NA
007	75	75	0	1	Metastatic Breast Cancer
Baylor Chorea	145	145	0	9	End Stage HD
				2	Cardiovascular Disease
				3	Pneumonia/Pulmonary Disease
				1	Peptic Ulcer & GI Hemorrhage
				1	Metastatic Lung Carcinoma
				2	Unknown
Baylor Non-Chorea	280	280	0	3	Cardiovascular Disease

NA = not available, HD=Huntington's disease, TBZ = tetrabenazine.

Across all studies submitted in the NDA, 23 deaths were reported. No deaths were reported in the 10 Clinical Pharmacology studies.

In the controlled and open-label studies in HD patients there were 2 deaths. One death was a result of metastatic breast cancer and was considered unrelated to treatment (Study 007). The other study was a result of suicide (Study 004). It

cannot be excluded that suicide may have been related to treatment with TBZ; however, suicide is the third leading cause of death in HD.

A total of 18 Baylor chorea patients died, many having end-stage HD. The causes of death were: end-stage HD including choreoathetosis (n=9), aspiration pneumonia or pneumonitis/respiratory failure (n=3), MI (n=2), not specified (n=2), peptic ulcer disease complicated by a gastrointestinal hemorrhage (n=1), metastatic lung carcinoma (n=1). Three patients who were administered TBZ died during their participation in the Baylor non-chorea open-label study. All deaths were due to cardiovascular disease and were judged by the investigator to be unrelated to TBZ treatment. These deaths occurred several months to 3 years after the last study evaluation.

In summary, in 773 unique patients/subjects enrolled in the TBZ clinical development program, there was only 1 death that could possibly be related to TBZ (i.e., suicide in Study 004). Across all studies submitted in the NDA, the majority of deaths were due to end-stage HD and its associated complications, as would be expected in this patient population. Furthermore, there did not appear to be any particular pattern of occurrence of the deaths in terms of the duration of treatment, nor the dose of TBZ. Among patients treated at Baylor, patient deaths were primarily related to aspiration pneumonia and other causes common to advanced neurological disease, as well as diseases not uncommon in the general population such as cardiovascular disease. Although detailed information in many cases is limited, the causes of death in these cases were generally reported as unrelated to TBZ.

5.13 Adverse Events of Interest

As TBZ has been shown in pre-clinical experiments to reduce brain dopamine (DA) and to a lesser extent norepinephrine (NE) and serotonin (5-HT) through inhibition of VMAT2, it was anticipated that dose-limiting toxicity could potentially result from this pharmacological action. The clinical trials were, therefore, designed to monitor for AEs associated with monoamine depletion. Thus, in addition to routine monitoring for AEs of depression, akathisia, parkinsonism, dysphagia, and sedation, instruments to monitor for these events, such as the HAM-D, Barnes Akathisia Rating Scale, Unified Parkinson's Disease Rating Scale (UPDRS) for dysarthria and dysphagia, and the Epworth Sleepiness Scale were employed in the clinical development program. In following sections, the safety data for the aforementioned AEs of interest are reviewed.

5.13.1 Depressive Symptoms

Depressive symptoms or depression are potential AEs of concern for TBZ because there is a high background rate of depression in HD and because TBZ depletes monoamines pre-synaptically.

The background rate of these symptoms was high in the Prestwick-sponsored studies. In Study 004, almost 60% of patients had a past history of depression and a similar proportion was taking an antidepressant drug at baseline. Patients with overt depression, as indicated by a HAM-D score ≥15, were excluded from participation.

There were no reports of a treatment-emergent AE of depression in the clinical pharmacology studies.

During the placebo-controlled Study 004, AEs coded to depression were reported in 8 of 54 (15%) TBZ-treated patients and none of the placebo patients. All 8 patients had a past history of depression, and in 7 of 8 subjects the AE was mild to moderate in severity. According to the Study 004 protocol, the HAM-D was performed at Baseline and at Weeks 1, 3, 5, 7, 9 and 12. Mean change from baseline for TBZ- and placebo-treated subjects is summarized in Figure 18.

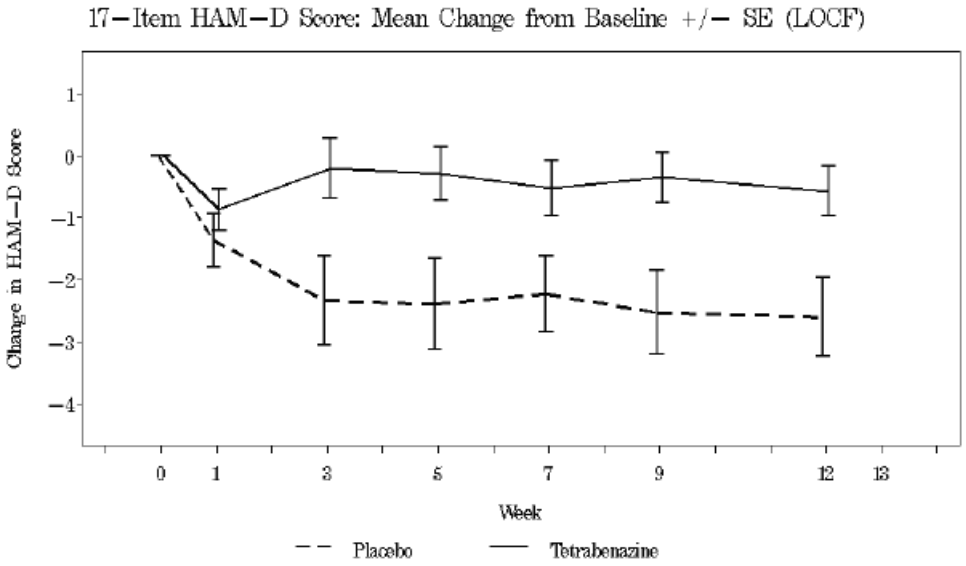


Figure 18. Mean Change* HAM-D Scores Throughout the Study in 84 HD Patients

* Note: Negative changes reflect improvement.

Although both placebo and TBZ groups had declines in HAM-D over the course of the study, consistent with improvement, the placebo group declined to a greater extent. A by-item analysis of the HAM-D at Week 12 showed that the between group difference was largely explained by relatively higher scores on insomnia, agitation, and anxiety in the TBZ group compared to placebo. There were no between-group differences in depressed mood, feelings of guilt, or suicide (thoughts/gestures).

Seven of the 8 patients from Study 004 with an AE of depression completed the trial and enrolled in the long-term extension Study 007. The AE of depression resolved in 6 of these patients and was ongoing at the end of Study 004 in 1 patient. One of the 8 patients withdrew due to an accidental fall associated with a subarachnoid hemorrhage.

The number of patients with a treatment-emergent AE of depression in the long-term studies is presented in Table 42. The data indicate that the majority of events were mild to moderate in severity and a past medical history of depression was common. The event rate for AEs coded to depression ranged from 24.8 to 35.3 per 100 patient-years in the Prestwick-sponsored studies and were lower in the studies conducted at Baylor (3.8 to 9.9 per 100 patient-years). As noted in Section 5.6, AEs of depression are more common during titration than during maintenance treatment and, accordingly, lower event rates could be expected in trials of longer duration. In addition, the rate of depression in Baylor Non-chorea patients was considerably lower than in the long-term studies in HD patients, consistent with a higher background rate of depression in the HD population.

Table 42. Number of Patients with an AE of Depression and Event Rates in Long Term Studies

Study Treatment Duration	No. of Patients	Population	Events			PMH Depression
			Total	Mild to Moderate	Total Per 100 Pat-Yrs	
006 *48 weeks*	29	HD	9	8	35.3	6
007 *Up to 80 weeks*	75	HD	24	20	24.8	20
Baylor Chorea *Up to several years*	98	HD	30	24	9.9	13
	47	Non-HD Chorea	10	9	8.5	
Baylor Non-Chorea *Up to several years*	280*	HMD	26	16	3.8	10

HD=Huntington's disease, HMD=hyperkinetic movement disorders other than chorea, Pat-Yrs=patient years, PMH=past medical history.
* 33 of the 280 study patients were lost to follow-up; event rate based on data from 247 patients.

5.13.1.1 Clinical Significance of Events Reported as Depression

Table 43 below displays the number of patients who were withdrawn from the Prestwick-sponsored and investigator-initiated studies because of an AE of depression.

Depression did not lead to withdrawal in Studies 004, 005, or 006. In Study 007 there were 2 withdrawals for depression. There were 8 Baylor Chorea patients who withdrew with an associated AE of depression.

Table 43. Number of Patients Withdrawn from Prestwick-Sponsored and Investigator-Initiated Studies due to an AE of Depression

Study	Number of Patients	Indication	Patients Withdrawn for an AE of Depression N
004	84	Chorea in HD	0
005	30	Chorea in HD	0
006	29	Chorea in HD	0
007	75	Chorea in HD	2*
Baylor Chorea	98	Chorea in HD	4
	47	Non-HD chorea	4
Baylor Non-Chorea	280	HMD	10

* One patient reported in the NDA for Study 007. The second patient (ID 747-262) was withdrawn prematurely due to suicide ideation.

AE=adverse event, HD=Huntington's disease, HMD=hyperkinetic movement disorders other than chorea.

5.13.1.2 Suicide and Suicidal Ideation

Suicide rates for symptomatic HD patients have been reported to be 7- to 10-fold higher than the general US population (Bird, 1999; Paulsen et al., 2005). Impaired impulse control is thought to contribute to the increased rate of suicide in HD patients. As summarized in Table 44, suicide-related AEs were uncommon during Prestwick studies as well as the investigator-initiated studies at Baylor. Any additional risk for suicidality associated with the use of TBZ is believed to be low, however controlled data to address this issue are limited.

Table 44. Number of Patients (Event Rate per 100 Patient-Years) With an AE of Suicide Ideation, Suicide Attempt or Completed Suicide

Study	No. of Treated Patients	Suicidal Ideation	Suicide Attempt	Completed Suicide
004 *12 weeks*	54	1 (8.2)	0 (0)	1 (8.2)
005 *5 days*	30	0 (0)	0 (0)	0 (0)
006 *48 weeks*	29	1 (3.9)	0 (0)	0 (0)
007 *Up to 80 weeks*	75	1 (1.0)	1 (1.0)	0 (0)
Baylor Chorea	98	3 (0.99)	0 (0)	0 (0)
Up to several years	47	1 (0.85)	0 (0)	0 (0)
Baylor Non-Chorea *Up to several years*	280	1 (0.15)	0 (0)	0 (0)

One subject in the development program committed suicide. He was 40 years old, had HD for 9 years, was unmarried and had no children. There was no history of depression although the participant had reported suicidal ideation in the past. The subject's sister, who also had HD, had committed suicide previously. The subject was receiving TBZ in Study 004. According to the family, the subject became withdrawn after he decided to stop work due to HD disability. The participant did not appear for his last scheduled day of work and the family subsequently informed the study site that the subject had drowned. Two weeks prior to the subject's death, a HAM-D score of 1 was recorded at the week 7 visit. The investigator judged that this AE was possibly related to study drug.

5.13.1.3 Reversibility of Depressive Symptoms with Reduction in Tetrabenazine Dose

The reversibility of depression-related AEs is summarized in Table 45.

Table 45. Reversibility of AEs of Depression With or Without Tetrabenazine Dose Reduction

Study	Total No. of Patients	Resolved with D/C TBZ	Resolved with No Dose Change	Dose Reduction: No. With Dose Reduction	AE Outcome With Dose Reduction: Resolved	AE Outcome With Dose Reduction: Improved	AE Outcome With Dose Reduction: No Change
004	8	3	2	3	3	–	–
006	9[*]	–	4	1	–	1[†]	–
007	24[‡]	–	5	13	8	4[§]	1[¶]

Data in each column are number of patients. Some patients also had a change in concomitant medications.

[*] Includes 3 patients who were managed with changes in concomitant medication without dose reduction and the AE persisted (1 with comparable HAM-D score to baseline and 2 with HAM-D scores of 13 and 16). In addition, includes 1 patient who had no medical intervention and the AE persisted with a normal HAM-D score.

[†] Severity decreased for 2 months after dose reduction and then increased thereafter. Final HAM-D on therapy was 7 (normal).

[‡] Includes 6 patients managed with changes in concomitant medication but the AE persisted, however 5 of the patients had normal HAM-D scores and the other patient had an ongoing AE with an improved HAM-D score.

[§] Ongoing AE with either normal or improved HAM-D score.

[¶] AE persisted on TBZ 150 mg/day with improved HAM-D score.

AE=adverse event, TBZ=tetrabenazine.

In Study 004, 8 patients experienced AEs coded to depression: 2 had no dose reduction, 3 were managed with dose reduction (including 1 with a change in concomitant medication), and 3 were managed with changes in concomitant medications alone. All events resolved: 5 during therapy and 3 following discontinuation of TBZ.

In Study 006, 9 patients experienced AEs coded to depression: 4 had no dose reduction, 4 were managed with changes in concomitant medication alone, and 1 was managed with a combination of dose reduction and concomitant medication change. The 4 patients without dose reduction had events that were generally mild and recovered or were ongoing with a normal HAM-D at study end. The 4 patients with changes in concomitant medications had events that were moderate in severity. Of these 4 patients, 1 recovered, 1 was ongoing with a comparable HAM-D score to baseline (12 and 13, respectively), and 2 were ongoing with HAM-D scores of 13 and 16.

Of the 24 subjects in Study 007 who experienced AEs coded to depression, 4 were managed with dose reduction alone, 9 were managed with dose reduction and change in concomitant medications, and 11 were managed with changes in concomitant medications. The AEs in patients managed with dose reduction only tended to be mild in severity and events in all 4 patients resolved with this intervention. The AEs in the 11 patients managed with changes in concomitant medications were generally moderate in severity and of these patients: 5 events

resolved, 5 had an ongoing AE but a normal HAM-D score, and 1 patient had an ongoing AE with an improved HAM-D. The 9 patients managed with a combination of dose reduction and change in concomitant medication had events that were moderate to severe and of these patients: 4 resolved with management, 2 had an ongoing event with a normal HAM-D, and 3 had an ongoing event with a HAM-D score that improved from the time of the event but was still elevated.

5.13.2 Akathisia

During Study 004, akathisia was reported as an AE in 5 of 54 (9%) TBZ-treated patients and none of the placebo patients. All 5 events were mild to moderate in severity and occurred during the titration phase. According to the study protocol, the BARNES was performed at Baseline and at Weeks 7 and 12, and mean change from baseline for TBZ and placebo-treated subjects is shown in Figure 19.

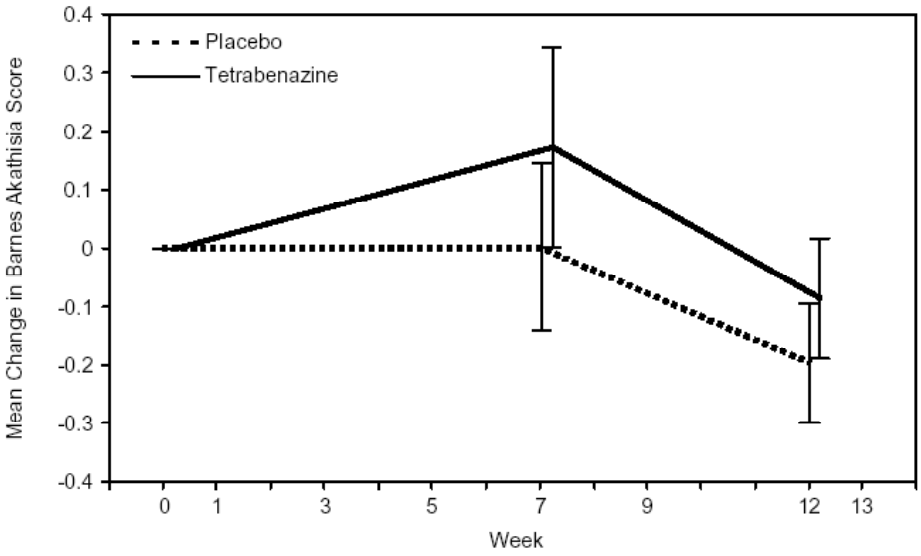


Figure 19. Mean (±SE) Change in BARNES Scores Throughout Study 004 in 84 HD Patients

The data in Figure 19 suggest a trend toward increased akathisia at Week 7 for TBZ-treated patients, however there was no significant difference from placebo at this timepoint. Furthermore, the mean change from baseline to Week 12 was negative, consistent with improvement in both groups. In the TBZ group, this finding suggests that the dose reduction employed to manage this AE was successful.

The number of patients with a treatment-emergent AE coded to akathisia in the long-term studies is presented in Table 46. There were no reports of akathisia in the long-term Study 006. There were 15 cases of akathisia in Study 007, with 8 having occurred in the titration phase of dosing. The event rate for akathisia in long-term study 007 was 15.5 cases per 100 patient-years and was lower in the studies conducted at Baylor (3.1 to 4.2 over 100 patient-years).

Table 46. Number of Patients with an AE of Akathisia and Event Rate in Long-Term Studies

Study Treatment Duration	No. of Patients	Population	Events		
			Total	Mild to Moderate	Total Per 100 Pat-Yrs
006 *48 weeks*	29	HD	0	–	0
007 *Up to 80 weeks*	75	HD	15	11	15.5
Baylor Chorea *Up to several years*	98	HD	12*	10	3.9
	47	Non-HD Chorea	5*	5	4.2
Baylor Non-Chorea *Up to several years*	280†	Hyperkinetic movement disorders other than chorea	21	19	3.1

* 17 events were reported in the NDA, although the distribution of events in the NDA was 10 and 7 in HD and non-HD chorea patients, respectively
† 33 of the 280 study patients were lost to follow-up; event rate based on data from 247 patients
AE=adverse event, HD=Huntington's disease, Pat-Yrs=patient years.

5.13.2.1 Clinical Significance of Events Reported as Akathisia

One patient in the long-term extension study 007 with akathisia, anxiety, agitation, and increased depression had an event that met the regulatory definition of serious. He was hospitalized for 24 hours and discharged after improving with medical therapy.

The number of patients who were withdrawn from the Prestwick-sponsored and investigator-initiated studies because of an AE of akathisia is presented in Table 47.

Table 47. Number of Patients Withdrawn from Prestwick-Sponsored or Investigator-Initiated Studies due to an AE of Akathisia

Study	Number of Patients	Indication	Patients Withdrawn for AE of Akathisia N
004	54	Chorea in HD	1
005	30	Chorea in HD	0
006	29	Chorea in HD	0
007	75	Chorea in HD	2
Baylor Chorea	98	Chorea in HD	1
	47	Non-HD chorea	2
Baylor Non-Chorea	280	HMD	6

AE=adverse event, HD=Huntington's disease, HMD=hyperkinetic movement disorders other than chorea.

Akathisia did not lead to withdrawal in Studies 005 and 006. In Studies 004 and 007 there were 1 and 2 withdrawals, respectively, for akathisia. Among patients treated at Baylor (chorea and non-chorea), akathisia was reported in 9 patients at the time of withdrawal.

5.13.2.2 Reversibility of Akathisia with Reduction in Tetrabenazine Dose

The reversibility of akathisia is summarized in Table 48.

Table 48. Reversibility of AEs of Akathisia With or Without Tetrabenazine Dose Reduction

Study	Total No. of Patients	Resolved with		Dose Reduction			
		D/C TBZ	No Dose Change	No. with Dose Reduction	AE Outcome With Dose Reduction		
					Resolved	Improved	No Change
004	5	3	–	2	2	–	–
006	0	–	–	–	–	–	–
007	15 *	4	3	7	7	–	–

* Includes 1 patient who prematurely discontinued from treatment due to depression and akathisia and was lost to follow up. The AE was ongoing at patient withdrawal.

AE=adverse event, TBZ=tetrabenazine.

In Study 004, 5 patients developed AEs coded to akathisia that were mild to moderate in severity. Of these 5 patients, 1 was managed with dose reduction, 2 were managed with dose reduction/discontinuation and medical therapy, and 2 patients had no intervention. All events resolved: 2 during therapy and 3 following discontinuation of therapy.

In Study 007, 15 patients reported AEs coded to akathisia: 9 were managed with dose reduction/discontinuation, 3 were managed with a combination of dose reduction and medical management, and 3 had no intervention. Of the 3 patients without intervention, the events were mild to moderate and all recovered with continued therapy. Of the 9 patients with akathisia managed with dose reduction or discontinuation, the events ranged from mild to severe in intensity. Of these 9 events, 5 resolved at a reduced dose and 3 recovered following withdrawal of therapy. One patient had mild akathisia when the patient prematurely discontinued from treatment and was lost to follow up. Of the 3 patients with akathisia managed with dose reduction/medical management, events were moderate to severe and resolved with continued therapy (n=2) or following withdrawal (n=1).

5.13.3 Parkinsonism

The antichorea efficacy of TBZ is thought to be mediated by DA depletion in the striatum. Since DA depletion in the striatum causes parkinsonism, it is not surprising that parkinsonism was reported across clinical trials in HD patients, although there were no reports of parkinsonism in healthy volunteers treated with TBZ.

During Study 004, parkinsonism (including AEs coded to bradykinesia, parkinsonism, or extrapyramidal disorder) was reported as an AE in 5 of 54 (9%) TBZ-treated patients and none of the placebo patients. All 5 events occurred during the titration phase. According to the Study 004 protocol, the UHDRS score for parkinsonism (including sum of finger taps, pronation/supination, rigidity arms, bradykinesia body, gait, tandem walking, and retropulsion pull test) was performed at Baseline and at Weeks 1, 3, 5, 7, 9, and 12, and mean change from baseline for TBZ and placebo-treated subjects is shown in Figure 20.

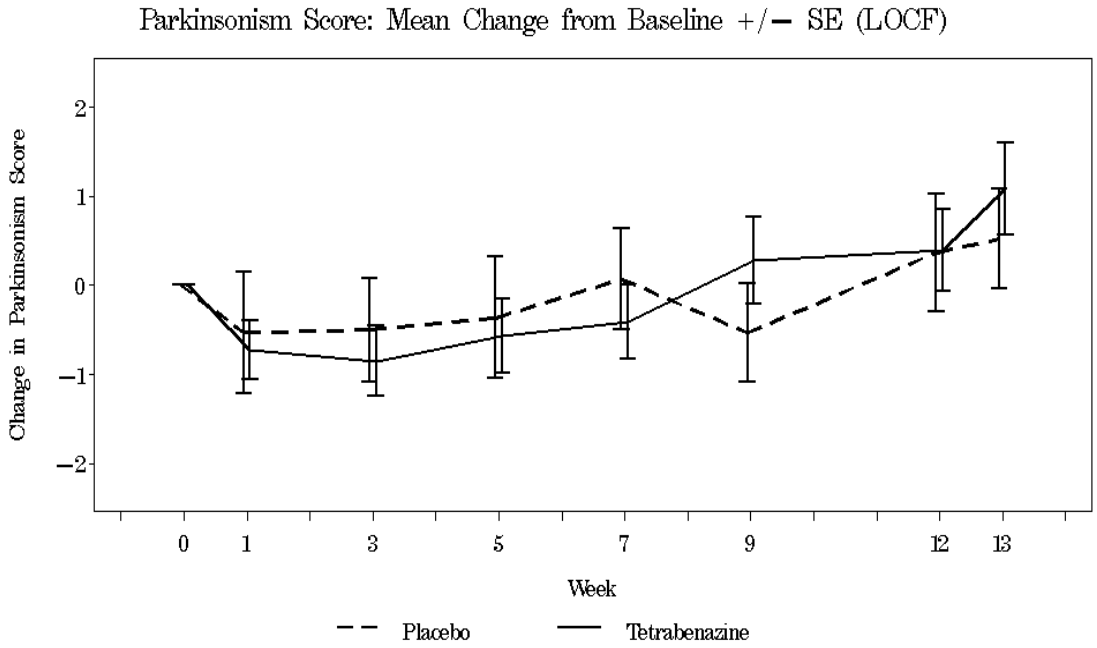


Figure 20. Mean Change in UHDRS Score for Parkinsonism throughout Study 004 in 84 HD Patients

Data presented as mean ± SE.

As shown in Figure 20, there were no meaningful between-group differences in the mean change from baseline in parkinsonism scores.

The number of patients with a treatment-emergent AE of parkinsonism (AE coded to coded as bradykinesia, parkinsonism, or extrapyramidal disorder) in the long-term studies is presented in Table 49.

For the 3 cases of parkinsonism reported in Study 006, 1 was present at study entry and 2 developed during therapy: 1 at 169 days after study enrollment and another after 375 days of therapy. There were 2 events coded to parkinsonism in Study 007; 1 patient developed the AE during titration. The event rate in the long-term studies ranged from 2.1 to 11.8 cases per 100 patient-years.

Table 49. Number of Patients with an AE of Parkinsonism and Event Rate in Long-Term Studies

Study Treatment Duration	No. of Patients	Population	Events		
			Total	Mild to Moderate	Total Per 100 Pat-Yrs
006 *48 weeks*	29	HD	3	3	11.8
007 *Up to 80 weeks*	75	HD	2	2	2.1
Baylor Chorea* *Up to several years*	98	HD	11	11	3.6
	47	Non-HD Chorea	9	8	7.6
Baylor Non-Chorea† *Up to several years*	280†	HMD	55	52	8.0

* Parkinsonism coded as extrapyramidal symptom in COSTART.
† 33 of the 280 study patients were lost to follow-up; event rate based on data from 247 patients.
AE=adverse event, HD=Huntington's disease, HMD=hyperkinetic movement disorders other than chorea, Pat-Yrs=patient years.

5.13.3.1 Clinical Significance of the Events Suggesting Parkinsonism

There were no parkinsonism events that met the regulatory definition of serious. Across the Prestwick-sponsored studies, no patient was withdrawn for parkinsonism. Parkinsonism was reported in 3 Baylor Chorea and 13 Baylor Non-Chorea patients who discontinued TBZ treatment as a result of the AE.

5.13.3.2 Reversibility of Parkinsonism with Reduction in Tetrabenazine Dose

The reversibility of parkinsonism is summarized in Table 50.

Table 50. Reversibility of AEs of Parkinsonism With or Without Tetrabenazine Dose Reduction

Study	Total No. of Patients	Resolved with		Dose Reduction			
		D/C TBZ	No Dose Change	No. with Dose Reduction	AE Outcome With Dose Reduction		
					Resolved	Improved	No Change
004	5	1	1	3	2	–	1*
006	3†	–	–	1	1	–	–
007	2	–	–	2	1‡	1§	–

Data in each column are number of patients. Some patients also had a change in concomitant medications.
* The patient's AE was ongoing upon enrollment into Study 007, however, the patient was lost to follow-up after 7 days due to skilled nursing home placement.
† Includes 2 patients who had no dose reduction and the AE persisted, yet both had UHDRS Parkinsonism scores that were improved as compared to study entry.
‡ Patient had second episode and outcome was unknown as patient died due to metastatic breast cancer.
§ At end of study participation, AE ongoing but UHDRS Parkinsonism score at baseline level.
AE=adverse event, DC=discontinuation.

In Study 004, 5 patients developed AEs of parkinsonism. Four of the events were managed with dose reduction, and 1 patient had no intervention. The patient

managed without medical intervention had resolution of the AE with continued therapy. Of the 4 patients managed with dose reduction: 2 recovered, 1 improved with dose reduction and ultimately resolved at washout, and 1 was ongoing at the time of rollover into Study 007. This latter patient was lost to follow up after nursing home placement.

In Study 006, there were 3 patients who experienced an AE of parkinsonism. One patient was managed with dose reduction and had resolution of the event with continued therapy. Two patients had no medical intervention: Both patients had events that were ongoing at study end yet both patients had UHDRS Parkinsonism scores that were improved as compared to study entry.

In Study 007, 2 patients experienced AEs of parkinsonism, both of which were managed with dose reduction. One patient had 2 episodes, 1 of which recovered with dose reduction and 1 with unknown status as the patient died due to metastatic breast cancer after discontinuation of study drug. The second patient had an ongoing event when study participation ended but the UHDRS Parkinsonism score at that time was comparable to the score at baseline.

These findings suggest that parkinsonism is reversible following dose reduction and/or discontinuation of TBZ.

5.13.4 Dysphagia

Dysphagia is a symptom of HD, particularly late-stage disease, and may be complicated by aspiration pneumonia (Leopold and Kagel 1985; Hunt and Walker 1989; Kagel and Leopold 1992). In HD, chorea of lingual, respiratory, and laryngeal muscles contribute to dysphagia (Kagel and Leopold 1992). Other factors such as swallowing incoordination, repetitive swallows, prolonged laryngeal elevation, inability to stop respiration, and frequent eructations are also involved.

During Study 004, dysphagia was reported as an AE in 1 of 54 (2%) TBZ-treated patients and 1 of 30 (3%) placebo patients. The event reported with TBZ was mild in intensity and occurred during titration. According to the study protocol, the UPDRS for dysphagia score was recorded at Baseline and at Weeks 1, 2, 3, 5, 7, 9, and 12. The UPDRS dysphagia score rates dysphagia as follows: 0=normal; 1=rare choking; 2=occasional choking; 3=requires soft food; 4=requires nasogastric tube or gastrostomy feeding. Small declines from baseline in UPDRS

dysphagia score (≤ 8% of maximum score), reflecting improvement, were observed over the course of the study, with no meaningful between-group differences (Figure 21).

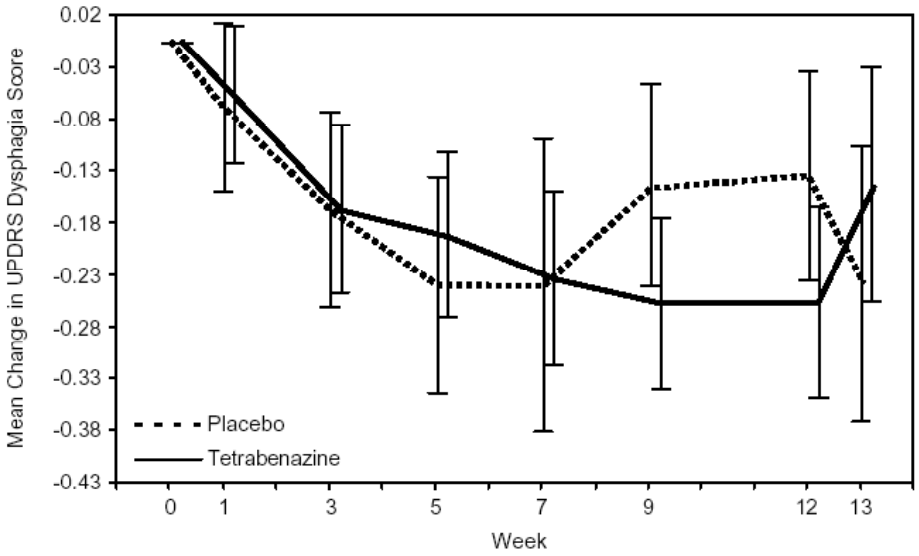


Figure 21. Mean (±SE) Change in Unified Parkinson's Disease Rating Scale (UPDRS) for Dysphagia Throughout Study 004 in 84 HD Patients

The number of patients with a treatment-emergent AE of dysphagia in the long-term studies is presented in Table 51.

Table 51. Number of Patients with an AE of Dysphagia and Event Rate in Long-Term Studies

Study Treatment Duration	No. of Patients	Population	Events		
			Total	Mild to Moderate	Total Per 100 Pat-Yrs
006 *48 weeks*	29	HD	3*†	3	11.8
007 *Up to 80 weeks*	75	HD	3*	2	3.1
Baylor Chorea *Up to several years*	98	HD	19	12	6.2
	47	Non-HD Chorea	3	2	2.5
Baylor Non-Chorea *Up to several years*	280‡	HMD	2	2	0.3

* 2 patients reported in the ISS.
† AE onset was 10 days after discontinuation of study drug in 1 patient.
‡ 33 of the 280 study patients were lost to follow-up; event rate based on data from 247 patients.
AE=adverse event, HD=Huntington's disease, HMD= Hyperkinetic movement disorders other than chorea, Pat-Yrs=patient years.

The event rate of dysphagia for the Prestwick studies ranged from 3.1 to 11.8 cases per 100 patient-years. The event rate for the HD chorea patients at Baylor was comparable at 6.2 cases per 100 patient-years, whereas the rate for hyperkinetic movement disorders other than chorea was considerably lower at 0.3 cases per 100 patient-years. The latter finding is not unexpected given the background rate of dysphagia in HD. In Study 005, which was the 5-day withdrawal study, 2 patients developed dysphagia 1 to 2 days after discontinuing TBZ.

5.13.4.1 Clinical Significance of Dysphagia Occurring in the Prestwick-sponsored Studies

There was 1 case of dysphagia that was classified as serious across the Prestwick-sponsored studies. This Study 007 patient had an SAE of dysphagia (characterized as severe) and pneumonia.

There were no withdrawals in the Prestwick-sponsored studies or the Baylor non-chorea patients due to an AE of dysphagia. One Baylor Chorea patient withdrew prematurely after 203 days of treatment due to dysphagia (and somnolence, tremor, and increased cough). At that time, the patient was also receiving neuroleptics (i.e. pimozide 1 mg tid and Prolixin [fluphenazine] 4 mg).

5.13.4.2 Reversibility of Dysphagia with Reduction in Tetrabenazine Dose

The reversibility of dysphagia is summarized in Table 52.

Table 52. Reversibility of AEs of Dysphagia With or Without Tetrabenazine Dose Reduction

Study	Total No. of Patients	Resolved with		Dose Reduction			
		D/C TBZ	No Dose Change	No. with Dose Reduction	AE Outcome With Dose Reduction		
					Resolved	Improved	No Change
004	1	–	–	1	1*	–	–
006	3†	–	–	1	1	–	–
007	3‡	–	–	2	2	–	–

Data in each column are number of patients. Some patients also had a change in concomitant medications.
* The dose was reduced, however the AE resolved before down titration for protocol washout began.
† Includes 2 patients with no intervention but ongoing dysphagia at study end. One of these patients reported the AE on the last treatment day. The other patient had a UPDRS dysphagia score of 1 consistent with rare choking.
‡ Includes 1 patient with dysphagia at baseline who developed severe dysphagia requiring feeding tube placement. The patient also required nursing home placement. Dysphagia was present approximately 6 months following study participation.
AE=adverse event, DC=discontinuation.

In Study 004, 1 TBZ-treated patient had an AE of dysphagia that was mild in severity. This patient was managed with dose reduction but the event resolved before down titration began. Another patient receiving placebo had an AE of dysphagia that resolved on the day it was reported.

In Study 006, 3 patients had AEs of dysphagia of mild to moderate in severity. One subject was managed with dose reduction and had resolution of the event with continued therapy. Two subjects had no intervention and were noted to have ongoing dysphagia at study end, with UPDRS dysphagia scores consistent with rare to occasional choking.

In Study 007, 3 patients had AEs of dysphagia that were moderate to severe in severity. Two patients were managed with dose reduction and had resolution of their events with continued TBZ therapy. One patient with dysphagia at baseline developed severe dysphagia requiring feeding tube placement. The patient also required nursing home placement. Dysphagia was present approximately 6 months following study participation, suggesting it is likely a component of underlying disease.

5.13.5 Sedation

During Study 004, sedation (including AEs that coded to sedation or somnolence) was reported as an AE in 17 of 54 (31%) TBZ-treated patients and 1 placebo patient. All events in the TBZ group occurred during titration. According to the study protocol, the Epworth Sleepiness Scale (ESS) was recorded at Baseline and at Weeks 7 and 12, and mean change from baseline for TBZ and placebo-treated subjects is shown in Figure 22.

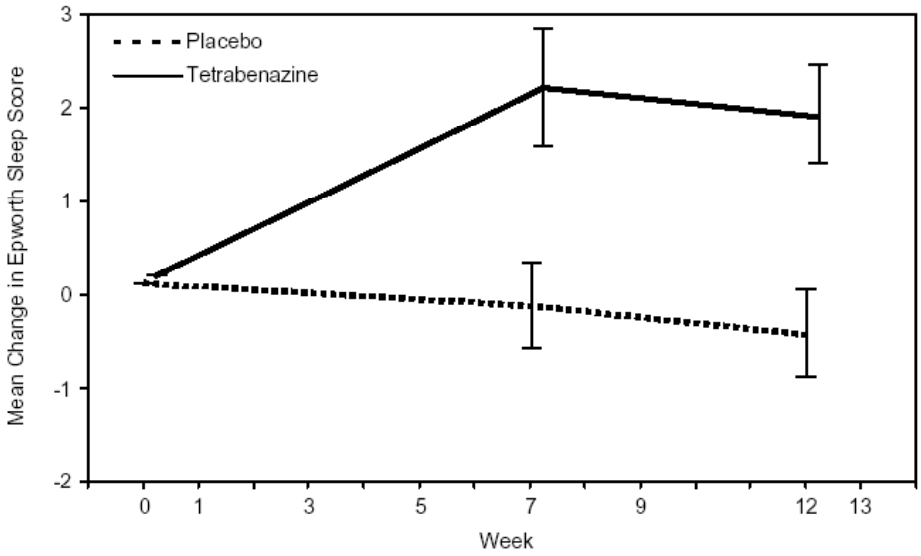


Figure 22. Mean (±SE) Change in Epworth Sleepiness Scale Throughout Study 004 in 84 HD Patients

As indicated in Figure 22, the TBZ-treated patients showed a mean increase from baseline to Week 7 in ESS, consistent with increased somnolence, which was significantly different from placebo. This effect persisted at Week 12, but was somewhat smaller than at Week 7.

The number of patients with a treatment-emergent AE of sedation in the long-term studies is presented in Table 53.

Table 53. Number of Patients with Sedation/Somnolence and Event Rate in Long-Term Studies

Study Treatment Duration	No. of Patients	Population	Events		
			Total	Mild to Moderate	Total Per 100 Pat-Yrs
006 *48 weeks*	29	HD	5	5	19.6
007 *Up to 80 weeks*	75	HD	32	29	33.1
Baylor Chorea *Up to several years*	98	HD	38	37	12.2
	47	Non-HD Chorea	27	27	23.7
Baylor Non-Chorea *Up to several years*	280*	HMD	74*	69	10.8

* Sedation is listed as drowsiness/fatigue.
AE=adverse event, HD=Huntington's disease, HMD= Hyperkinetic movement disorders other than chorea, Pat-Yrs=patient years.

5.13.5.1 Clinical Significance of Sedation Occurring in the Prestwick-sponsored Studies

There were no SAEs in the Prestwick-sponsored or investigator-initiated studies due to sedation. Similarly, there were no withdrawals in the Prestwick-sponsored studies due to sedation.

Seven Baylor Chorea and 20 Baylor Non-Chorea patients who withdrew experienced an AE of sedation/somnolence.

5.13.5.2 Reversibility of Sedation with Reduction in Tetrabenazine Dose

The reversibility of sedation is summarized in Table 54.

Table 54. Reversibility of AEs of Sedation With or Without Tetrabenazine Dose Reduction

Study	Total No. of Patients	Resolved with		Dose Reduction			
		D/C TBZ	No Dose Change	No. with Dose Reduction	AE Outcome With Dose Reduction		
					Resolved	Improved	No Change
004	17	2	5	10	9	1[*]	–
006	5[†]	–	1	2	2	–	–
007	32[‡]	5	3	23[§]	19	–	2

Data in each column are number of patients. Some patients also had a change in concomitant medications.
[*] AE ongoing with improvement in ESS.
[†] Includes 2 patients who were managed with changes in concomitant medication (starting or increasing dose of Provigil) without dose reduction and the AE persisted.
[‡] Includes 1 patient with no dose reduction and the AE persisted.
[§] Includes 2 patients with an unknown outcome.
AE=adverse event, DC=discontinuation.

In Study 004, 17 TBZ-treated patients and 1 placebo-treated patient had an AE of sedation/somnolence. Of the 17 TBZ-treated patients, 5 were managed without intervention and all resolved with ongoing therapy. Of the 12 managed with dose reduction, 9 recovered with continued therapy at a reduced dose, 2 resolved following washout, and 1 was ongoing at study end with an improvement in ESS compared to when the AE occurred.

In Study 006, there were 5 patients who experienced sedation/somnolence that was mild to moderate in severity. One was managed without intervention and 2 with dose reduction; sedation in these 3 patients resolved with continued therapy. Two subjects were managed with changes in concomitant medication (starting or increasing dose of Provigil) without dose reduction and both AEs were ongoing at study end.

In Study 007, there were 32 patients who experienced sedation/somnolence. All but 3 events were mild to moderate in severity and the 3 severe events resolved with dose reduction or withdrawal of therapy. Six patients with mild sedation were managed without intervention and 5 of these patients recovered with continued therapy. Of the 28 patients managed with dose reduction or discontinuation, 19 recovered with continued therapy, 5 recovered following discontinuation of TBZ, 2 had ongoing sedation, and 2 patients had an unknown outcome.

5.13.6 Summary: AEs of Interest

In the development program, akathisia, parkinsonism, sedation, and depression-related AEs were observed during titration and maintenance therapy, although rates for these AEs were generally higher during titration of TBZ. Since AEs were reported both during titration and after prolonged therapy, the data suggest that treating physicians can identify AEs as distinct from underlying disease progression, even during long-term treatment.

While some AEs resolved without dose reduction, other AEs generally resolved or symptomatically improved when TBZ was dose reduced, as reflected by a reduction in scoring on validated measures such as the BARNES and the Parkinson subscale of the UHDRS.

There was no signal of concern regarding dysphagia in the double-blind trials or the long-term studies. Across the development program, dysphagia event rates adjusted for person-time indicated that dysphagia was reported at similar rates across studies among HD patients treated with TBZ, including the investigator initiated studies.

An analysis of individual patients with AEs of akathisia, parkinsonism, depressive symptoms, dysphagia, and sedation revealed that these events were appropriately detected throughout the course of therapy and were effectively managed with dose reduction of TBZ, changes in concomitant medication, a combination of both interventions or, in some cases, no intervention. Each of these maneuvers was effective in ameliorating the AEs of interest, indicating TBZ can be safely used in clinical practice.

Because AEs were more frequent during the titration period of dosing than during maintenance therapy, Prestwick believes that targeted risk management strategies

can be employed to enhance monitoring for the occurrence of these events during titration. In addition, these strategies will guide the treating physicians regarding the appropriate management of these events, including dose reduction, should they occur. Accordingly, Prestwick is planning to work with the FDA to develop a comprehensive Risk Minimization Action Plan to mitigate the potential risks associated with TBZ use.

5.14 Vital Signs, Laboratory Values, and ECGs

5.14.1 Vital Signs

In controlled clinical trials, TBZ did not affect blood pressure, pulse, or body weight.

5.14.2 Laboratory Values

In the Clinical Studies submitted in the NDA, no consistent pattern of changes in laboratory values were observed with TBZ, confirming published reports that TBZ does not affect laboratory parameters.

No subjects in the Clinical Pharmacology or short-term treatment Study 005 developed liver enzyme abnormalities considered Possibly Clinically Significant. There were 5 TBZ patients in the 12-week Study 004 and in the long-term treatment Studies 006 and 007 who developed ALT abnormalities classified as Possibly Clinically Significant. Of these increases in ALT, 4 of 158 (2.5%) were greater than 3 times the upper limit of normal and 1 of 158 (0.6%) was greater than 10 times the upper limit of normal. No subject had clinical symptoms of hepatitis and no subject had a concomitant increase in bilirubin outside the normal range. Furthermore, ALT abnormalities promptly resolved with discontinuation of TBZ. Of note, the subject who developed an increase in ALT greater than 10 times the upper limit of normal entered the trial with an abnormal ALT (1.3 x ULN) and reported binge drinking around the time of his abnormal liver enzymes.

In summary, the liver test data from the clinical trial database suggest a sporadic observation of possibly clinically significant elevations in liver enzymes, although it is unclear if these changes are treatment-related. The changes were not associated with clinical symptoms or abnormal bilirubin values and did not appear with re-challenge for up to 7.5 months.

5.14.3 Effect of Tetrabenazine on ECGs

Regarding the qualitative analysis, there was no meaningful change in incidence of normal/abnormal ECGs in either the clinical pharmacology or patient studies. Furthermore, there were no treatment-emergent ECG findings deemed "abnormal, clinically significant" in any of the studies. Within the ECG database, there were no reports of prolonged QT interval, ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

5.15 Summary of Non-Clinical Safety Information

The toxicology program for TBZ included Good Laboratory Practices (GLP) repeated-dose studies in mice (13 weeks), rats (26 weeks), and dogs (9 months). The studies in mice were a 15-day non-GLP study and a 90-day GLP study. The studies in rats included a 26-week toxicity study with a 13-week interim sacrifice. The studies in dogs were a 15-day non-GLP study and a 9-month GLP study. A full battery of GLP genetic toxicity studies on TBZ was also conducted. Additional *in vitro* mutagenicity and clastogenicity genetic toxicity GLP studies of TBZ and the 2 primary metabolites, α-HTBZ and β-HTBZ, were performed. Reproductive toxicity studies included developmental toxicity studies, a GLP rat developmental and perinatal/postnatal study, a rabbit range-finding, and a definitive developmental study.

Orally administered TBZ was generally well tolerated across all animal species tested (i.e., mice, rats, rabbits, dogs). Most effects observed were related to the pharmacological properties of the drug and reflect reduced dopaminergic neurotransmission. Tremor and hypoactivity were observed in the 9-month dog study at 3 and 10 mg/kg. These findings were generally present between 1 and 7 hours post-dose and resolved before administration of the subsequent dose. Similarly, in the 26-week rat study, lethargy was reported up to 7 hours post-dose. However, permanent deficits in locomotion were not observed in either the 9-month dog or the 26-week rat study.

Across all animal species tested, dose-dependent sedation was the dose-limiting and principal adverse effect following oral administration of TBZ. The no adverse effect levels (NOAELs) measured in these repeated dose toxicity studies were all based on clinical signs that represented exaggerated pharmacological effects of the drug. In the dogs, these effects occurred at lower doses than in other

species and were more pronounced, often including disruptions in normal behavior such as stereotypic behaviors (e.g. chewing) and panting.

Organ toxicity was not observed in any species except that related to exaggerated pharmacology (e.g., histopathological changes in rat female reproductive tissues from elevation of prolactin). Across all species, a target organ of toxicity was not identified. No adverse effects were observed that would not be predicted based on the pharmacological effects of TBZ.

When administered during the period of organogenesis, TBZ had no clear effects on embryo-fetal development when administered to pregnant rats (up to 30 mg/kg/day).

When TBZ was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in offspring perinatal mortality was observed at 15 and 30 mg/kg/day, and delayed pup maturation was observed at all doses.

Taken together, TBZ was evaluated in a comprehensive toxicology program, which included appropriate genetic, reproductive/developmental, and chronic toxicology studies. In studies evaluating doses of up to 100 mg/kg/day, there was no evidence of pathology in any organ system, and specifically no neuropathology.

5.16 Overdose

There were no reports of overdose in the clinical pharmacology studies or in the controlled and open-label studies sponsored by Prestwick; however, in the Baylor Non-chorea Report, 1 overdose was reported. A patient with Tourette's syndrome took an overdose of TBZ tablets (36 × 25-mg tablets [total dose 900 mg TBZ]). The patient was a 40-year-old man treated for a total of 3.5 months. The dose recorded was 125 mg/day at initial and last evaluation periods. Disease severity was assessed as moderate with no change over time. The patient suffered no life-threatening or persistent AEs.

5.17 Abuse and Dependence Liability

Drugs that block DAergic transmission, such as TBZ, are not known to have abuse potential in humans. Results of preclinical studies indicate that TBZ should not have abuse potential in humans. In a rat model of re-enforcement, TBZ was

found to suppress intracranial self-stimulation and to antagonize the effects of d-amphetamine in the test. Similarly, TBZ (4 mg/kg) was found to decrease the rate of response in rats trained to press a lever to obtain water re-enforcement. In the same experimental conditions, d-amphetamine and methylphenidate increased the rate of response. However, TBZ has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. There have been no reports of misuse of the drug outside the US in the countries where it is registered, and Prestwick-sponsored clinical trials did not reveal any tendency for drug-seeking behavior, but these observations were not systematic.

5.18 Post-marketing Surveillance

Tetrabenazine first became available as a pharmaceutical product in Europe during the late 1950s. The precise date of first marketing is unclear because no European country, at that time, had legislation controlling the access of medicinal products onto their markets. The first reports of its use in the treatment of HD were published in the 1960s.

As summarized in Table 2, tetrabenazine is currently approved for use in the treatment of hyperkinetic movement disorders, including chorea associated with HD, in various countries outside of the U.S.

Also, tetrabenazine has been provided in the past on a “humanitarian use” basis to patients in various countries including: Vatican City, Spain, Sweden, Argentina, Brazil, Hong Kong, Singapore, South Korea, Taiwan, and Iceland.

As shown in Table 55, TBZ has been used by patients outside of the US, and the use is currently estimated at 7,000 based on 2006 data.

Table 55. Global Sales of Tetrabenazine since 1974 with Estimates of the Sales of Defined Daily Doses (DDDs)

Year	No of packs (25 mg x 112)	Sales (kg)	DDDs (100mgs) 1,000s	DDDs (75 mgs) 1,000s	Estimated Patients per Annum*
1974	14,643	41	410	547	1,464
1975	17,500	49	490	653	1,750
1976	18,214	51	510	680	1,821
1977	18,571	52	520	693	1,857
1978	22,143	62	620	26	2,214
1979	24,643	69	690	920	2,464
1980	33,214	93	930	1,240	3,321
1981	36,071	101	1,010	1,347	3,607
1982	41,429	116	1,160	1,547	4,143
1983	43,929	123	1,230	1,640	4,393
1984	46,071	129	1,290	1,720	4,607
1985	52,500	147	1,470	1,960	5,250
1986	50,000	140	1,400	1,867	5,000
1987	55,000	154	1,540	2,053	5,500
1988	47,143	132	1,320	1,760	4,714
1989	50,357	141	1,410	1,880	5,036
1990	50,000	140	1,400	1,867	5,000
1991	52,500	147	1,470	1,960	5,250
1992	52,857	148	1,480	1,973	5,286
1993	56,071	157	1,570	2,093	5,607
1994	57,857	162	1,620	2,160	5,786
1995	51,786	145	1,450	1,933	5,179
1996	65,000	182	1,820	2,427	6,500
1997	52,916	148	1,482	1,976	5,292
1998	67,816	190	1,899	2,532	6,782
1999	49,682	139	1,391	1,855	4,968
2000	58,673	164	1,643	2,190	5,867
2001	62,812	176	1,759	2,345	6,281
2002	57,061	160	1,598	2,130	5,706
2003	69,365	194	1,942	2,590	6,937
2004	56,063	157	1,570	2,093	5,606
2005	85,412	239	2,392	3,189	8,541
2006	66,931	187	1,874	2,499	6,693

* Based on 10 packs/pt/annum.

5.18.1 Adverse Events in Post-marketing Surveillance Database

The adverse drug event (ADE) profile of TBZ from post-marketing surveillance reporting is summarized in Table 56. In spontaneous AE reporting, the majority of AEs with TBZ relate to the nervous system, psychiatric disorders, or the gastrointestinal system. This profile is consistent with the AE profile of TBZ in the clinical trials. In addition to the AEs reported in Table 56, significant AEs including sudden death (N=1), suicide (N=2), suicidal ideation (N=1), and coma (N=1) were reported.

Table 56. Distribution of Postmarketing Adverse Drug Events (≥ 3 patients/ event) by Body System

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	4
	Paresthesia	4
	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	7
Psychiatric Disorders	Depression	12
	Confusion	7
	Agitation	4
	Apathy	4
	Suicide Attempt	5
	Hallucination	3
	Irritability	3
Respiratory System Disorders	Pneumonia	10
	Aspiration	3
Skin and Appendages Disorders	Rash Erythematous	4
	Hair loss	3
Urinary System Disorders	Urinary Tract Infection	3
Vascular Disorders	Hypotension	6
	Hypotension Postural	4
	CVA	3
Vision Disorders	Vision Disturbance	3

5.19 Safety Summary

The results summarized in this document show that TBZ can be safely administered to HD patients for the treatment of chorea. Across all the studies submitted in the NDA, AEs occurred mainly in the Psychiatric System Disorders and in the CNS Disorders. This is, in keeping with the mechanism of action of TBZ, a drug that selectively inhibits VMAT-2, a protein found nearly exclusively in the brain.

In a double-blind, placebo controlled, 12-week treatment study (Study 004), the most commonly reported AEs at any time during the study for TBZ-treated patients were sedation/somnolence (31%), fatigue (22%), insomnia (22%), depression (15%), fall (15%). For placebo-treated patients, fatigue (13%), fall (13%), coughing (10%), and diarrhea (10%) were the most common. Noteworthy differences between the TBZ-treated group and the placebo-treated group included sedation, insomnia, depression, and restlessness aggravated. The majority of AEs with TBZ was of mild to moderate intensity and occurred mainly during the upward dose titration. The profile of AEs observed in the placebo-controlled Study 004 is similar to that reported in the literature, and to that observed in other Prestwick-sponsored studies.

Across all studies submitted in the NDA, the dose of TBZ was titrated upward by 12.5 mg increments to "best dose," defined as a dose that is efficacious and well-tolerated. The literature has shown, and Prestwick has confirmed, that anti-chorea efficacy is achieved at doses that are only slightly lower than the maximum tolerated dose. Thus, a typical treatment paradigm is to titrate the dose of TBZ upward by 12.5 mg/day until dose-limiting AEs occur, and then down-titrate by 12.5 or 25 mg/day until dose-limiting AEs resolved without loss of efficacy.

The need for upward titration of TBZ is justified by published results showing wide inter-individual differences in the dose of TBZ that causes dose-limiting AEs (and attending efficacy), ranging from 25 mg/day to 200 mg/day. The wide inter-individual difference in maximum tolerated dose was confirmed in Prestwick-sponsored studies. For example, in Study TBZ 103,007, conducted in 75 HD patients, there was a 20-fold difference among patients in maximum tolerated dose. It is not possible to predict the dose level at which patients will experience dose-limiting AEs. Thus, upward titration is justified to safely achieve "best dose."

The analysis of AEs associated with TBZ showed a higher incidence of AEs during upward dose-titration than during maintenance. For example, in the double-blind, placebo-controlled Study 004, the majority of AEs reported by patients randomized to TBZ occurred during Weeks 0-9 (corresponding to the titration phase) as opposed to Weeks 9-12 (corresponding to the maintenance phase) of the 12-week treatment period (91%, 49/54 vs. 35%, 19/54, respectively). In this double-blind study, AEs such as sedation/somnolence, drowsiness, akathisia, parkinsonism/bradykinesia, diarrhea, and nausea occurred only during the upward dose titration period. Other AEs such as depression (13% versus 2%), restlessness aggravated (11% versus 2%), irritability (7% versus 2%), balance difficulty (7% versus 2%), and fatigue (20% versus 2%), occurred mainly, but not exclusively, during the upward dose-titration period as opposed to during the maintenance period. The incidence of insomnia was a slightly higher during dose titration than during dose maintenance (13% versus 9%).

Prestwick has also confirmed published reports that dose adjustment with downward titration allows most patients to reach a dose at which the dose-limiting AE is no longer present or is tolerable, but at which efficacy is maintained.

Throughout the study, the incidence of falls was comparable in the TBZ and in the placebo groups (15% versus 13%), showing that TBZ treatment is not associated with an increased incidence of falls. Falls complicate HD and are thought to be precipitated by chorea. Interestingly, in the TBZ-treatment group, the incidence of falls was reduced by 50% (13% versus 6%) during the dose maintenance period, at a time when chorea was maximally reduced. This result suggests that TBZ-induced reduction in chorea may be associated with a reduction in the incidence of falls.

In the development program, akathisia, parkinsonism, sedation, and depression-related AEs were observed during titration and maintenance therapy, although rates for these AEs were generally higher during titration of TBZ. Since AEs were reported both during titration and after prolonged therapy, the data suggest that treating physicians can identify AEs as distinct from underlying disease progression, even during long-term treatment.

While some AEs resolved without dose reduction, other AEs generally resolved or symptomatically improved when TBZ was dose reduced, as reflected by a reduction in scoring on validated measures such as the BARNES and the Parkinson subscale of the UHDRS.

There was no signal of concern regarding dysphagia in the double-blind trials or the long-term studies. Across the development program, dysphagia event rates adjusted for person-time indicated that dysphagia was reported at similar rates across studies among HD patients treated with TBZ, including the investigator initiated studies.

An analysis of individual patients with AEs of akathisia, parkinsonism, depressive symptoms, dysphagia, and sedation revealed that these events were appropriately detected throughout the course of therapy and were effectively managed with dose reduction of TBZ, changes in concomitant medication, a combination of both interventions or, in some cases, no intervention. Each of these maneuvers was effective in ameliorating the AEs of interest, indicating TBZ can be safely used in clinical practice.

The literature indicates that suicidal ideation and completed suicides occur commonly in HD patients (e.g., Paulsen et al., 2005). The data presented demonstrate that the risks of suicidal ideation and suicide associated with use of TBZ are low. The caudate dysfunction of HD is associated with impaired impulse control, such that some patients can have difficulty controlling emotions or impulses. In a small study of suicide risk factors in HD, the most important risk factor for completed suicide was having no offspring (Lipe et al., 1993). Furthermore, patients with a family history of suicide have been shown to have greater impulsivity (Roy, 2006).

To reduce the risk of depressive symptoms and associated negative outcomes (e.g., suicide), depression and suicide have been listed in the warning section of the Draft Labeling. In addition, Prestwick is planning to work with the FDA to develop a comprehensive Risk Minimization Action Plan to mitigate the potential risks of these potential adverse events.

Overall, clinically significant changes in laboratory values were not observed. While 5 of 158 (2.5%) patients had a transient, possibly clinically significant increase in ALT, no subject had symptoms of hepatitis and no subject had a concomitant increase in bilirubin outside the normal range. One patient with elevated ALT was withdrawn. One patient with an isolated increase in total bilirubin was withdrawn. The other subjects continued treatment with TBZ and liver enzyme abnormalities resolved and did not occur again. No clinically significant changes in vital signs or ECG were reported with TBZ.

Taken together, data from the TBZ development program indicate that TBZ was well tolerated by patients; the most commonly reported AEs occurred mainly during the upward dose titration and were of mild to moderate intensity. Furthermore, AEs associated with TBZ were appropriately detected throughout the course of therapy and were effectively managed with dose reduction, discontinuation of therapy, or other medical intervention.

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7 APPENDIX

APPENDIX 1. RATING SCALES IN TETRABENAZINE TRIALS AND UTILIZED IN BRIEFING DOCUMENT

- Unified Huntington's Disease Rating Scale (UHDRS)
- Clinical Global Impression – Improvement
- Functional Impact Scale (FIS)
- 17-Item Hamilton Depression Scale (HAM-D)
- Barnes Akathisia Rating Scale (BARNES)
- Unified Parkinson's Disease Rating Scale (UPDRS) – Dysphagia and Dysarthria Score
- Epworth Sleepiness Scale

UNIFIED HUNTINGTON'S DISEASE RATING SCALE (UHDRS)

TETRA-HD (00)

UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99

Page 1 of 11

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

PARTICIPANT NO. ☐☐☐ SITE NO. ☐☐☐ VISIT NO. ☐☐

INITIALS ☐☐☐ VISIT DATE ☐☐ MM ☐☐ DD ☐☐☐☐ YEAR

I. MOTOR ASSESSMENT

1. OCULAR PURSUIT — Horizontal 1a. ☐ Vertical 1b. ☐
   - 0 = complete (normal)
   - 1 = jerky movement
   - 2 = interrupted pursuits/full range
   - 3 = incomplete range
   - 4 = cannot pursue

2. SACCADE INITIATION — Horizontal 2a. ☐ Vertical 2b. ☐
   - 0 = normal
   - 1 = increased latency only
   - 2 = suppressible blinks or head movements to initiate
   - 3 = unsuppressable head movements
   - 4 = cannot initiate saccades

3. SACCADE VELOCITY — Horizontal 3a. ☐ Vertical 3b. ☐
   - 0 = normal
   - 1 = mild slowing
   - 2 = moderate slowing
   - 3 = severely slow, full range
   - 4 = incomplete range

4. DYSARTHRIA 4. ☐
   - 0 = normal
   - 1 = unclear, no need to repeat
   - 2 = must repeat to be understood
   - 3 = mostly incomprehensible
   - 4 = anarthria

5. TONGUE PROTRUSION 5. ☐
   - 0 = can hold tongue fully protruded for 10 seconds
   - 1 = cannot keep fully protruded for 10 seconds
   - 2 = cannot keep fully protruded for 5 seconds
   - 3 = cannot fully protrude tongue
   - 4 = cannot protrude tongue beyond lips

6. FINGER TAPS — Right 6a. ☐ Left 6b. ☐
   - 0 = normal (≥ 15/5 sec.)
   - 1 = mild slowing and or reduction in amplitude (11-14/5 sec.)
   - 2 = moderately impaired. Definite and early fatiguing. May have occasional arrests in movement (7-10/5sec.)
   - 3 = severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements (3-6/5 sec.)
   - 4 = can barely perform the task (0-2/5 sec.)

7. PRONATE/SUPINATE-HANDS — Right 7a. ☐ Left 7b. ☐
   - 0 = normal
   - 1 = mild slowing and/or irregular
   - 2 = moderate slowing and irregular
   - 3 = severe slowing and irregular
   - 4 = cannot perform

8. LURIA (fist-hand-palm test) 8. ☐
   - 0 = ≥ 4 in 10 seconds, no cue
   - 1 = < 4 in 10 seconds, no cue
   - 2 = ≥ 4 in 10 seconds with cues
   - 3 = < 4 in 10 seconds with cues
   - 4 = cannot perform

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ___ SITE # ___ VISIT # ___ (00) Page 2 of 11

	Right	Left
9. RIGIDITY-ARMS 0 = absent 1 = slight or present only with activation 2 = mild to moderate 3 = severe, full range of motion 4 = severe with limited range	9a.	9b.
10. BRADYKINESIA-BODY 0 = normal 1 = minimally slow (? normal) 2 = mildly but clearly slow 3 = moderately slow, some hesitation 4 = markedly slow, long delays in initiation		10.
11. MAXIMAL DYSTONIA 0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	11a. TRUNK	
	11b. RUE	
	11c. LUE	
	11d. RLE	
	11e. LLE	
12. MAXIMAL CHOREA 0 = absent 1 = slight/intermittent 2 = mild/common or moderate/intermittent 3 = moderate/common 4 = marked/prolonged	12a. FACE	
	12b. BOL	
	12c. TRUNK	
	12d. RUE	
	12e. LUE	
	12f. RLE	
	12g. LLE	

13. GAIT 13. ___
0 = normal gait, narrow base
1 = wide base and/or slow
2 = wide base and walks with difficulty
3 = walks only with assistance
4 = cannot attempt

14. TANDEM WALKING 14. ___
0 = normal for 10 steps
1 = 1 to 3 deviations from straight line
2 = > 3 deviations
3 = cannot complete
4 = cannot attempt

15. RETROPULSION PULL TEST 15. ___
0 = normal
1 = recovers spontaneously
2 = would fall if not caught
3 = tends to fall spontaneously
4 = cannot stand

16. WEIGHT (kg) 16. ___ . ___

17. DIAGNOSIS CONFIDENCE LEVEL 17. ___
To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a participant at risk for HD?
0 = normal (no abnormalities)
1 = non-specific motor abnormalities (less than 50% confidence)
2 = motor abnormalities that may be signs of HD (50 - 89% confidence)
3 = motor abnormalities that are likely signs of HD (90 - 98% confidence)
4 = motor abnormalities that are unequivocal signs of HD (≥ 99% confidence)

18. **Motor Examiner** 18. ___ STAFF CODE

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ☐☐☐ SITE # ☐☐☐ VISIT # ☐☐ 00 Page 3 of 11

II. COGNITIVE ASSESSMENT

19. **VERBAL FLUENCY TEST** (raw score) 19. ☐☐

20. **SYMBOL DIGIT MODALITIES TEST** (raw score) 20. ☐☐

STROOP INTERFERENCE TEST

21. Color Naming (number correct) 21. ☐☐☐

22. Word Reading (number correct) 22. ☐☐☐

23. Interference (number correct) 23. ☐☐☐

24. **Cognitive Examiner** 24. ☐☐☐☐ STAFF CODE

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ___ SITE # ___ VISIT # ___ (00) Page 4 of 11

III. BEHAVIORAL ASSESSMENT

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

DEPRESSED MOOD

25a. Frequency 25a. ☐

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

25b. Severity 25b. ☐

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

LOW SELF-ESTEEM/GUILT

26a. Frequency 26a. ☐

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

26b. Severity 26b. ☐

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

ANXIETY

27a. Frequency 27a. ☐

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

27b. Severity 27b. ☐

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

 1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ___ SITE # ___ VISIT # ___ (00)

SUICIDAL THOUGHTS

28a. Frequency 28a. ☐

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

28b. Severity 28b. ☐

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

DISRUPTIVE OR AGGRESSIVE BEHAVIOR

29a. Frequency 29a. ☐

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

29b. Severity 29b. ☐

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

IRRITABLE BEHAVIOR

30a. Frequency 30a. ☐

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

30b. Severity 30b. ☐

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

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ☐☐☐ SITE # ☐☐☐ VISIT # ☐☐ 00 Page 6 of 11

PERSEVERATIVE/OBSESSIONAL THINKING

31a. Frequency 31a. ☐

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

31b. Severity 31b. ☐

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

COMPULSIVE BEHAVIOR

32a. Frequency 32a. ☐

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

32b. Severity 32b. ☐

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

DELUSIONS

33a. Frequency 33a. ☐

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

33b. Severity 33b. ☐

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

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ☐☐☐ SITE # ☐☐☐ VISIT # ☐☐ (00) Page 7 of 11

HALLUCINATIONS

34a. Frequency 34a. ☐

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

34b. Severity 34b. ☐

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

APATHY

35a. Frequency 35a. ☐

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

35b. Severity 35b. ☐

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

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

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

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

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

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

INFORMATION SOURCES

41. Was the Behavioral Assessment information obtained from: 41. ☐

1 = Participant only
2 = Participant and family/companion

42. **Behavioral Examiner** 42. ☐☐☐☐ STAFF CODE

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ☐☐☐ SITE # ☐☐☐ VISIT # ☐☐ (00)

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

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

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ☐☐☐ SITE # ☐☐☐ VISIT # ☐☐ (00)

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

60. Could participant walk to places in his/her neighorhood without help? 60. ☐

61. Could participant walk without falling? 61. ☐

62. Could participant walk without help? 62. ☐

63. Could participant comb hair without help? 63. ☐

64. Could participant transfer between chairs without help? 64. ☐

65. Could participant get in and out of bed without help? 65. ☐

66. Could participant use toilet/commode without help? 66. ☐

67. Could participant's care still be provided at home? 67. ☐

INFORMATION SOURCES

68. Was the Functional Assessment information obtained from: 68. ☐
    1 = Participant only
    2 = Participant and family/companion

V. INDEPENDENCE SCALE

Please indicate the most accurate current level of participant's independence 69. ☐☐☐
(only increments of 5 are acceptable)

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

1/24/03

UHDRS (Continued)

TETRA-HD UHDRS '99 PT # ___ SITE # ___ VISIT # ___ (00)

VI. FUNCTIONAL CAPACITY

70. OCCUPATION 70. ☐
- 0 = unable
- 1 = marginal work only
- 2 = reduced capacity for usual job
- 3 = normal

71. FINANCES 71. ☐
- 0 = unable
- 1 = major assistance
- 2 = slight assistance
- 3 = normal

72. DOMESTIC CHORES 72. ☐
- 0 = unable
- 1 = impaired
- 2 = normal

73. ADL 73. ☐
- 0 = total care
- 1 = gross tasks only
- 2 = minimal impairment
- 3 = normal

74. CARE LEVEL 74. ☐
- 0 = full time skilled nursing
- 1 = home or chronic care
- 2 = home

INFORMATION SOURCES

75. Was the Functional Capacity information obtained from: 75. ☐
- 1 = participant only
- 2 = participant and family/companion

76. **Functional Examiner** 76. ☐☐☐☐ STAFF CODE

VII. CLINICAL SUMMARY

77. What was the purpose of this visit? 77. ☐
- 1 = Participant in an at risk study
- 2 = Participant in a manifest HD study
- 3 = Presymptomatic genetic testing
- 4 = Determine if person is symptomatic
- 5 = Known manifest HD
- 6 = Other (please specify) _____

78. Since your last assessment of the participant, in your opinion, has the participant: 78. ☐
- 1 = improved
- 2 = worsened
- 3 = stayed about the same
- 4 = not applicable (never seen before)

79. Since your last assessment does the participant feel: 79. ☐
- 1 = improved
- 2 = worsened
- 3 = about the same
- 4 = not aplicable (never seen before)

1/24/03

CLINICAL GLOBAL IMPRESSION - IMPROVEMENT

Part 2 (Global Improvement) of the Clinical Global Impression (CGI)

Compared to baseline, rate total improvement whether or not, in your judgment, it is due entirely to drug.

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

FUNCTIONAL IMPACT SCALE (FIS)

TETRA - HD

FUNCTIONAL IMPACT SCALE IN HD (FIS)

30

Page 1 of 1

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

PARTICIPANT NO **447-** ☐☐☐ SITE NO. ☐☐☐ VISIT NO. **0 0**

INITIALS ☐☐☐ VISIT DATE: ☐☐ (MM) ☐☐ (DD) ☐☐☐☐ (YEAR)

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

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

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

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

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

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

HAMILTON DEPRESSION (HAM-D) SCALE

HAM-D Please CIRCLE THE NUMERIC CODE which best describes the patient.
1. DEPRESSED MOOD: (Sadness, hopeless, helpless, worthless) 0 = Absent 1 = These feelings are indicated only on questioning 2 = These feelings are spontaneously reported verbally 3 = These feelings are communicated non-verbally - i.e. through facial expression, posture, voice, and tendency to weep 4 = Patient reports VIRTUALLY ONLY these feelings in his spontaneous verbal and non-verbal communication
2. FEELINGS OF GUILT 0 = Absent 1 = Self-reproach, feels he has let people down 2 = Ideas of guilt or rumination over past errors or sinful deeds 3 = Present illness is a punishment. Delusions of guilt 4 = Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. SUICIDE 0 = Absent 1 = Feels life is not worth living 2 = Wishes he were dead or any thoughts of possible death to self 3 = Suicidal ideas or gesture 4 = Attempts at suicide (any serious attempt rates 4)
4. INSOMNIA EARLY 0 = No difficulty falling asleep 1 = Complains of occasional difficulty falling asleep, i.e. more than ½ hour 2 = Complains of nightly difficulty falling asleep
5. INSOMNIA MIDDLE 0 = No difficulty 1 = Patient complains of being restless and disturbed during the night 2 = Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)
6. INSOMNIA LATE 0 = No difficulty 1 = Waking in early hours of the morning but goes back to sleep 2 = Unable to fall asleep again if gets out of bed
7. WORK AND ACTIVITIES 0 = No difficulty 1 = Thoughts and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies 2 = Loss of interest in activity, hobbies, or work – either directly reported by patient, or indirectly in listlessness, indecision and vacillation (feels he has to push self to work or join activities) 3 = Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours per day in activities (hospital job or hobbies) exclusive of ward chores 4 = Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores; or if the patient fails to perform ward chores unassisted
8. RETARDATION: *Slowness of thought and speech; impaired ability to concentrate; decreased motor activity* 0 = Normal speech and thought 1 = Slight retardation at interview 2 = Obvious retardation at interview 3 = Interview difficult 4 = Complete stupor
9. AGITATION 0 = None 1 = Fidgetiness 2 = "Playing with" hands, hair, etc. 3 = Moving about, can't sit still 4 = Hand-wringing, nail-biting, hair-pulling, biting of lips

HAM-D SCALE (Continued)

HAM-D Please CIRCLE THE NUMERIC CODE which best describes the patient.
10. ANXIETY/PSYCHIC 0 = No difficulty 1 = Subjective tension and irritability 2 = Worrying about minor matters 3 = Apprehensive attitude apparent in face or speech 4 = Fears expressed without questioning
11. ANXIETY (SOMATIC): *Physiological concomitants of anxiety, such as: Gastro-intestinal– dry mouth, wind, indigestion, diarrhea, cramps, belching; Cardio-vascular–palpitations, headaches; Respiratory–hyperventilation, sighing; Urinary frequency; Sweating.* 0 = Absent 1 = Mild 2 = Moderate 3 = Severe 4 = Incapacitating
12. SOMATIC SYMPTOMS/GASTRO-INTESTINAL 0 = None 1 = Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen 2 = Difficulty eating without staff urging.
13. SOMATIC SYMPTOMS/GENERAL 0 = None 1 = Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability 2 = Any clear-cut symptom rates 2
14. GENITAL SYMPTOMS: *Loss of libido, menstrual disturbances* 0 = Absent 1 = Mild 2 = Severe
15. HYPOCHONDRIASIS 0 = Not present 1 = Self-absorption (bodily) 2 = Preoccupation with health 3 = Frequent complaints, requests for help, etc. 4 = Hypochondrial delusions
16. LOSS OF WEIGHT 0 = No weight loss or weight loss NOT caused by present illnesses 1 = Weight loss probably caused by present illness 2 = Definite (according to patient) weight loss caused by present illness
17. INSIGHT 0 = Acknowledges being depressed and ill 1 = Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. 2 = Denies being ill at all

BARNES AKATHISIA SCALE (BARNES)

Instructions for Assessment

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

Objective

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

Subjective

Awareness of restlessness

0 Absence of inner restlessness.
1 Non-specific sense of inner restlessness.
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs and/or complains of inner restlessness aggravated specifically by being required to stand or sit still
3 Awareness of an intense compulsion to move most of the time and/or reports a strong desire to walk or pace most of the time.

Reported distress related to restlessness

0 No distress.
1 Mild.
2 Moderate.
3 Severe

BARNES (Continued)

Global Clinical Rating of Akathisia

0 *Absent*. No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move legs should be classified as pseudoakathisia.

1 *Questionable*. Non-specific inner tension and fidgety movements

2 *Mild akathisia*. Awareness of restlessness in the legs and/or inner restlessness worse when required to stand or sit still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress.

3 *Moderate akathisia*. Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing.

4 *Marked akathisia*. Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing.

5 *Severe akathisia*. The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. The patient experiences constant restlessness, which is associated with intense distress and insomnia.

UNIFIED PARKINSON'S DISEASE RATING SCALE (UPDRS)

(DYSPHAGIA)

Swallowing:

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

(DYARTHRIA)

Speech:

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

EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to
choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____