CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209885Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA 505(b)(2)
Application Number(s)	209885
Priority or Standard	Priority
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Division/Office	Division of Psychiatric Products, ODE 1. OND, CDER
Reviewer Name(s)	Anand Mattai M.D.
Review Completion Date	2017 July 29
Established Name	Deutetrabenazine (SD-809)
(Proposed) Trade Name	Austedo
Applicant	Teva Pharmaceuticals, Inc.
Formulation(s)	Oral tablets: 6 mg, 9 mg, and 12 mg
Dosing Regimen	Titrated by clinical response up to 24 mg BID
Applicant Proposed Indication(s)/Population(s)	Treatment of Tardive Dyskinesia
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CDQ	Craniocervical Dystonia Questionnaire
CFR	Code of Federal Regulations
CGI-C	Clincial Global Impression-Change
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EPS	extrapyramidal symptoms
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGI-C	Patient's Global Impression of Change
PI	prescribing information
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RLD	Reference Listed Drug
SAE	serious adverse event
SAP	statistical analysis plan
SDQ	Swallowing Disturbance Questionnaire
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TQT	Thorough QT Study
VMAT	Vesicular Monoamine Transporter

1 Executive Summary

1.1. Product Introduction

Deutetrabenazine (developed as SD-809; proposed proprietary name: Austedo) is a compound developed by the Applicant for the treatment of tardive dyskinesia (TD). TD is an iatrogenic hyperkinetic movement disorder that can manifest following the sustained use of drugs which block dopaminergic receptors, most notably antipsychotics. TD is distinct from acute extrapyramidal symptoms associated with antipsychotic use in that its onset is delayed for months to years. Signs and symptoms of TD can include involuntary movements of the orofacial region, trunk, and extremities. These abnormal movements can be disabling and disruptive to patients and frequently persist even after tapering or discontinuing antipsychotic medications. There is currently only one FDA-indicated treatment for TD (valbenazine).

Deutetrabenazine is an inhibitor of vesicular monoamine transporter 2 (VMAT2); VMAT2 is an integral membrane transporter that transports monoamines, including dopamine, from the cytosol into synaptic vesicles. Inhibiting VMAT2 decreases the quantity of neurotransmitter molecules released by presynaptic neurons during synaptic transmission. The Applicant hypothesizes that modulating dopaminergic tone in the striatum by inhibiting VMAT2 will reduce the signs and symptoms of TD. The proposed dosage forms for deutetrabenazine are 6 mg, 9 mg, and 12 mg capsules, to be titrated to the recommended daily dose of 12 mg to 48 mg a day administered in divided doses (i.e., 6 mg twice daily to 24 mg twice daily).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of deutetrabenazine for the treatment of tardive dyskinesia was demonstrated in two multi-center randomized controlled trials (Studies C-18 and C-23). The primary endpoint in both studies was the change from baseline to the end of Week 12 on the Abnormal Involuntary Movement Scale (AIMS) total dyskinesia score, which is used in clinical and research settings for rating the severity of involuntary movements across multiple body regions. The AIMS was scored by central video raters who were blind to study treatment and visit sequence. In both studies, deutetrabenazine was statistically superior to placebo on the primary efficacy endpoint of the AIMS total dyskinesia score change from baseline at the end of Week 12. Based on Study C-23, the effect does not appear to be dose dependent as the 24 mg/day treatment cohort performed similarly to 36 mg/day cohort. Study C-20 which re-randomized of subjects initially treated with placebo to receive deutetrabenazine, provided additional evidence of continued drug effect.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Deutetrabenazine (to be marketed as Austedo) is a vesicular monoamine transporter 2 (VMAT2) inhibitor developed as a treatment for tardive dyskinesia (TD). TD is characterized by involuntary athetoid or choreiform movements that develop in association with long-term neuroleptic (D_2 dopamine receptor antagonist) use. The intended patient population is adults with moderate to severe TD. Furthermore, given the iatrogenic nature of TD, patients will have current or prior conditions that were treated with neuroleptics (e.g., psychotic disorders, mood disorders) or other dopamine receptor antagonists use for medical illness (e.g., gastric motility disorders, etc.). The purported nature of benefit from deutetrabenazine is a reduction in involuntary movements. From a clinical perspective, I recommend that deutetrabenazine be approved for this indication.

While not life threatening, TD has the potential to be a very severe illness that may adversely affect all aspects of one's life. The involuntary movements can cause a sense of shame and make it challenging for individuals to establish relationships or successfully integrate into the community or workplace. There is currently one FDA-approved treatment indicated for TD. Treatment guidelines generally emphasize prevention, early detection, and modification or discontinuation of the causative neuroleptic agent. However, given the persistence of many psychiatric symptoms, this approach is seldom practical. Furthermore, there is limited evidence that off-label treatments for TD are effective. Given the dearth of FDA approved treatments for this condition, deutetrabenazine has strong potential to help address this unmet medical need.

Evidence from two pivotal studies (C-18 and C-23) has demonstrated the effectiveness of deutetrabenazine in reducing the severity of abnormal involuntary movements associated with TD. The primary efficacy endpoint was the change in the Abnormal Involuntary Movement Scale total dyskinesia score from baseline to the end of Week 12, as assessed by central video raters who were blind to treatment and visit sequence. It is anticipated that the majority of individuals with TD who take deutetrabenazine 24 mg/day or higher will experience a reduction in abnormal involuntary movement severity. While the key secondary endpoints in both studies were not met primarily due to the statistical analysis hierarchy, it is self-evident that a tangible reduction in involuntary movements will be clinically meaningful to patients.

An overall review of the safety results from the clinical developmental program for TD supports the idea that deutetrabenazine is well tolerated over the range of designated therapeutic doses (12 mg to 48 mg). Additional supportive information comes from HD safety data as well as experience with its close relative, tetrabenazine. Compared to tetrabenazine, no unusual side effects were seen with deutetrabenazine treatment. The most common drug reactions were diarrhea, nasopharyngitis, and insomnia which were distinctly different compared to those

seen in the HD population. Suicidal ideation/behavior and depression did not show any clear association with deutetrabenazine treatment in the development program, as supported by a lack of worsening of instruments measuring suicidality (C-SSRS) and depression (HADS). Similarly, there were no additional safety concerns with respect to sedation, parkinsonism, and akathisia that were found to lead to tolerability issues in the parent compound. The most paramount safety concern involves the potential for deutetrabenazine to cause QT prolongation. While the Applicant purported that the QT prolongation associated with use of the drug was not clinically significant, the aggregate safety data does not support this especially in subgroups (e.g., CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitors). This concern can be mitigated by labeling and a patient package insert. Furthermore, deutetrabenazine will be subject to continuing pharmacovigilance by the Applicant and regular analysis of post-marketing safety reports.

In summary, upon comparative analysis of the apparent risks and benefits associated with deutetrabenazine, it is clear that marketing approval should be recommended from a clinical perspective. This compound will be the second agent approved to treat TD and consequently offer another viable treatment option for this unmet medical need. Safety findings and assessment of subject disposition in clinical trials suggests deutetrabenazine is reasonably well-tolerated and in some respects differentially safer compared to the parent compound. One important remaining uncertainty involves the persistence of effect upon cessation of medication among stable patients. As a result, we will propose the Applicant conduct a post-marketing randomized withdrawal study to further characterize this aspect of the compound.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	TD is characterized by involuntary athetoid or choreiform movements (generally of the tongue, lower face and jaw, extremities, and/or trunk) that develop in association with long term use of D_2 dopamine receptor antagonist medications. Abnormal movements associated with TD may	While not a life threatening condition, TD can adversely impact the quality of life for those experiencing it. The movements can be disruptive and disfiguring leading to challenges

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cause functional impairments and stigmatization due to their disfiguring appearance. Risk factors for developing TD include older age, the use of first-generation/typical antipsychotics, and the development of acute extrapyramidal symptoms early in neuroleptic treatment. The clinical course of TD is variable; if identified early and the causative drug is withdrawn, it is can be reversible over the course of several months. However, TD is frequently a chronic condition that is intractable in the context of exposure to continued neuroleptic treatment. While several pathophysiologic mechanisms for TD have been proposed, the etiology is unclear.	in trying to successfully integrate into the community or workplace. The development of TD can impede treatment of the underlying condition (i.e., schizophrenia, bipolar disorder, etc.), as discontinuation or modification of neuroleptic medications could lead to psychiatric destabilization.
Current Treatment Options	There is currently only one FDA-approved treatment (Valbenazine) indicated to treat TD. Prior to this approval, the primary treatment recommendations from treatment guidelines consist of early detection and modification of the neuroleptic regimen (e.g., lowering the dose, switching to an antipsychotic with a lower propensity for causing TD such as clozapine, or discontinuing the neuroleptic if clinically feasible). A number of off-label treatments for TD have been utilized with marginal success. As a result, there is little evidence supporting these approaches.	Given the dearth of FDA approved treatments for the TD, there is clear and pressing need for alternative therapies to help alleviate this potentially disabling condition. Off-label use of various medications has been largely successful. Furthermore, discontinuing or changing antipsychotic treatments are frequently not feasible clinically and, furthermore, are not considered to be widely effective for resolving TD symptoms.
Benefit	Evidence for the effective of deutetrabenazine was provided by two pivotal studies. Study C-18 and C-23 sufficiently provide this evidence (Section 6.1 and Section 6.2). The choice and methodology involving in assessing the primary efficacy measure (i.e., central video raters who were blind to visit number, subject identification, and treatment), reduced inter-rater variability and expectancy bias associated with on-	The evidence submitted with the sNDA is assessed as meeting the evidentiary standard for approval. The majority of individuals with TD who take deutetrabenazine greater than 24 mg/day are expected to experience an appreciable reduction in abnormal involuntary

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	site raters. In both studies, deutetrabenazine was statistically superior to placebo on the primary efficacy endpoint of the AIMS total dyskinesia score change from baseline at the end of Week 12. Study C-20 which re-randomized of subjects initially treated with placebo to receive deutetrabenazine, provided additional evidence of continued drug effect The findings from the pivotal efficacy studies are anticipated to be fairly generalizable to the indicated patient population. There was no gross variability in efficacy across subpopulations.	movement severity. There were insufficient numbers of subjects in examined subpopulations to make firm conclusions as to who may experience greater or lesser benefit. There are some limitations in the evidence that warrant discussion. Study C-18 did not provide much support identifying a range of potentially therapeutic doses. Most subjects were on daily doses of 36 mg and higher limiting the generalizability of the deutetrabenazine separation versus placebo. Similarly, while higher doses were found to be in effective in Study C-18, a 48 mg cohort was not investigated as part of Study C-23. While the proposed label suggests dosing up to 48 mg a day, there was limited data to support this from Study C-18. Nonetheless, based on C-20, it appears that dosing up to 48 mg has been reasonably well tolerated and effective. A PMC has been suggested to help determine the persistence of drug effect in the context of a randomized withdrawal trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	The safety database was adequate and consisted subjects representing a wide variety of ages, medication use, and concurrent diagnoses. Many of the clinical sites were in the US, allowing for risks to be generalized to the US population. Suicidal ideation/behavior and depression did not show a clear association with deutetrabenazine treatment in the development program, as supported by a lack of worsening of instruments measuring suicidality (C-SSRS) and depression (CDSS, HADS). While the rates of sedation appear lower in the TD population compared to the HD population, it does seem likely that deutetrabenazine has the potential to cause or exacerbate sedation. Similarly, there were no additional safety concerns with respect to parkinsonism, and akathisia that were found to lead to tolerability issues in the parent compound. The totality of the cardiac safety evidence supports the idea that deutetrabenazine may prolong the QT interval and warnings should be instituted to those patients that are CYP2D6 PM, take CYP2D6 inhibitors, or are co-administered that can prolong the QT interval.	The clinical developmental program for TD supports the idea that deutetrabenazine is well tolerated over the range of designated therapeutic doses (12 mg to 48 mg). Safety issues related to the RLD such as suicidality do not appear applicable to the TD indication. Labeling should be modified to reflect this. To inform clinicians of risks associated with QT prolongation in certain sub-populations, deutetrabenazine will be labeled with a Warning & Precaution (similar to the RLD), in addition to specific language in labeling directing clinicians to assess the QT interval prior to increases in dosage in sub-populations at increased risk. Guidelines regarding the use of other QT prolonging medications will also be addressed in the labeling.
Risk Management	The product will be labeled to describe adverse reactions and laboratory abnormalities due to deutetrabenazine occurring in the safety population. Additionally, adverse reactions will be summarized in a patient package insert in order to better inform patients.	These risk mitigation strategies will clearly communicate the risks to clinicians and patients. Additionally, a PMR will address undefined

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The applicant did not adequately assess withdrawal, dependence, and tolerance in valbenazine. Therefore, the agency will require these to be assessed in a PMR, with a recommendation that these assessments be added to ongoing studies.	risks of withdrawal, dependence, and tolerance.

2 Therapeutic Context

2.1. Analysis of Condition

Tardive dyskinesia (TD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as "involuntary athetoid or choreiform movements (lasting at least a few weeks) generally of the tongue, lower face and jaw, and extremities (but sometimes involving the pharyngeal, diaphragmatic, or trunk muscles) developing in association with the use of a neuroleptic medication for at least a few months" (Association, 2013). This condition is differentiated from other medication-induced movement disorders by the time of onset. The term "tardive dyskinesia" was first introduced in 1964 by Faurbye, highlighting the delay between the initiation of treatment with the offending drug and the onset of the abnormal movements (hence, the name "tardive"). TD tends to occur months or years after initiation of a psychotropic as compared to other movements disorders that can present shortly after starting medication. Until recently, it was suggested that only antipsychotic agents cause TD; however, today it is known that medications from a variety of chemical groups and classes with a variety of therapeutic purposes may also induce these disturbances, including clozapine (Lerner P, 2015). These agents include antidepressants, calcium channel blockers, antiemetic, antiepileptic, anti-parkinsonian, anticholinergic medications, and mood stabilizers. In addition to drugs used as antipsychotics, the dopamine receptor antagonist metoclopramide, which is used as a treatment for gastrointestinal symptoms, is also a known cause of TD that is reflected as a boxed warning in its product labeling.

The pathophysiology of TD complex and remains unclear. However, some of the leading hypotheses include: supersensitivity of postsynaptic dopamine receptors following prolonged blockade, an imbalance of dopamine D1 vs. D2 receptor-mediated output from the striatum, and/or an excitotoxic loss of striatal interneurons (GABAergic, serotonergic, or peptidergic) which regulate dopaminergic neurons (Lerner P, 2015). As most patients taking antipsychotic (dopamine blocking) medications for years do not develop TD, the condition might be explained by individual and possibly genetic susceptibility (Waln O, 2013).

Clinically, TD typically manifests insidiously as a mixture of oro-buccal-lingual dyskinesias, limb movements and trunk movements. Less commonly, irregular breathing rhythms or grunting may emerge as in association with respiratory muscle involvement. The diagnosis of TD is made clinically based on the development of involuntary dyskinetic movements in association with neuroleptic treatment. The DSM-5 specifies "at least a few months" of neuroleptic treatment in the diagnostic criteria but also notes that TD may develop after a shorter period in older persons (Association, 2013). When diagnosing TD, it is important to rule out other causes of involuntary movements such as neuroleptic withdrawal-emergent dyskinesia, Huntington or

Wilson disease, stereotypic movements associated with the underlying mental illness, other acute extrapyramidal syndromes (EPS) associated with antipsychotic treatment, and other medical illnesses.

Current epidemiologic studies have suggested that the annual incidence of TD associated with typical antipsychotic exposure is ~5% (Waln O, 2013). Risk factors found to be predictive of TD development include older age, higher antipsychotic drug dosage, and the development of extra-pyramidal symptoms (EPS) early in antipsychotic treatment. Subsequently introduced "atypical" antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone, etc.) have differences in pharmacological activity from typical antipsychotics that generally confer a lower risk for causing acute EPS as well as TD. However, this risk is non-negligible, as evidenced by a review of 12 trials published between 2004-2007 (Correll C, 2008). This study showed that the difference in TD incidence between the first-generation antipsychotics (5.5%) and second generation antipsychotics (3.9%) was smaller than previously reported.

The clinical course of TD is variable. If identified early and the causative drug is withdrawn, particularly in younger patients, it is often reversible over the course of several months. However, TD is frequently persistent or may improve only partially, in conjunction with changing the neuroleptic medication type or dose (Vijayakumar D, 2016). Though a significant proportion of patients with TD may have little to no awareness of their movement disorder, its symptoms can be functionally disabling (Emsley, 2011). TD can make eating more difficult, impair speech intelligibility, increase the risk of falls, and increase a sense of shame, which may make it more difficult for individuals to successfully integrate into society (Margolese, 2005).

Overall, TD is assessed to have a significant functional impact on patients. Its onset may affect the ability to adequately treat the underlying psychiatric condition (i.e., the discontinuation or modification of antipsychotic medications could lead to psychiatric destabilization). TD can affect the ability of patients to perform activities of daily living as well as make it more difficult for them to engage in the community or workplace, given the visibility of involuntary movements and the unfortunate societal stigma related to mental illness.

2.2. Analysis of Current Treatment Options

There is currently one FDA-approved product for the treatment of TD. Valbenazine was approved on April 11, 2017, for the treatment of adults with TD. The compound is an inhibitor of vesicular monoamine transporter 2 (VMAT2), which is an integral membrane transporter that transports monoamines, including dopamine, from the cytosol into synaptic vesicles. The proposed dosage form for valbenazine is a 40 mg capsule, to be titrated to the recommended dose of two capsules (80 mg), by mouth, once daily.

Prior to valbenazine, the immediate suggested treatment options for treating TD included

switching treatment from a typical to an atypical antipsychotic or reducing the antipsychotic dose (Association, 2013). Clozapine and/or quetiapine are the preferred atypical antipsychotics for patients with TD, given their lack of propensity for worsening TD. However, these treatments require frequent blood testing and their use is not always practical. The 2004 APA practice guideline lists several treatments that have been studied (e.g., benzodiazepines, anticholinergic agents, calcium channel blockers, γ-amino butyric acid receptor agonists, essential fatty acids, estrogen, and insulin), noting that at the time of publication, there were no convincing data suggesting any of these treatments may be effective (Association, 2013).

More recently, the American Academy of Neurology published an evidence-based guideline on the treatment of tardive syndromes, including TD (Neurology, 2013). Their conclusions and recommendations were that there is some evidence supporting the use of off-label clonazepam, ginkgo biloba, amantadine, and tetrabenazine for the treatment of TD (Table 1: **Off-Label Treatments with Limited Supportive Evidence for Treating TD** There were insufficient data to support or refute either antipsychotic withdrawal or switching from a typical to an atypical antipsychotic as a treatment for TD. There was also insufficient evidence to support or refute the use of the following treatments for TD: acetazolamide, bromocriptine, thiamine, baclofen, vitamin E, vitamin B6, selegiline, clozapine, olanzapine, melatonin, nifedipine, fluperlapine, sulpiride, flupenthixol, thiopropazate, haloperidol, levetiracetam, quetiapine, ziprasidone, sertindole, aripiprazole, buspirone, yi-gan san, biperiden discontinuation, botulinum toxin type A, electroconvulsive therapy, α-methyldopa, reserpine, and pallidal deep brain stimulation (Neurology, 2013).

Overall, the current treatment armamentarium is quite limited for meeting the needs of patients diagnosed with TD. Discontinuing or changing antipsychotic treatments is frequently not feasible clinically and, furthermore, is not widely effective for resolving TD symptoms. Consequently, there is a pressing need for novel therapeutic agents to alleviate this serious condition.

Table 1: Off-Label Treatments with Limited Supportive Evidence for Treating TD

Product Name	Dosing/ Administration	Efficacy Information	Comments	References
Clonazepam	0.5-4.5 mg PO daily, titrated every 3-4 days according to tolerability and efficacy	Maryland Psychiatric Research Center Movement Disorder Scale improvement by ~37%, as compared to placebo, after 4 weeks treatment ($p < 0.001$).	Single crossover-design study (N=19) with adults with TD and continued antipsychotic treatment. In 5 patients who continued open-label clonazepam for up to 9 months, antidyskinetic effects were absent after 5-8 months of treatment, suggesting efficacy may be short-term.	(Thaker GK, 1990)
Ginkgo biloba	EGb-761 (standardized Ginkgo biloba extract) 240 mg PO daily	AIMS total score significantly improved in EGb-761 group as compared to placebo (-2.13 ± 1.75 vs. +0.10 ± 1.69; $p < 0.0001$) at week 12.	Single randomized, double-blind study (N=157) in China. Subjects were inpatients with schizophrenia and TD.	(Zhang WF, 2011)
Tetrabenazine	75-150 mg PO daily; titrated from 12.5 mg daily every few days according to tolerability and efficacy	Measures of TD (AIMS; frequency of oral dyskinetic movements) significantly improved in tetrabenazine groups, as compared to placebo, after 2-14 weeks treatment.	Two small controlled studies have been conducted (N=6, N=24), as well as several uncontrolled studies and reports.	(Kenney C, 2010)

Source: Adapted from Valbenazine Clinical Review (Davis)

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Deutetrabenazine is the deuterated form of tetrabenazine, an orphandesignated drug approved in April, 2017, for the treatment of Huntington's disease chorea. The Applicant has an additional sNDA application for the treatment of TD. Deutetrabenazine was granted breakthrough therapy designation in November 2015 and has a priority review designation.

As the compound was recently reviewed by the Division of Neurological Products (DNP), it is

instructive to review the salient regulatory history related to that application. Deutetrabenazine for the treatment of chorea associated with HD was submitted on 29 May 2015. A Complete Response Letter was issued on 27 May 2016 requesting additional clinical pharmacology and nonclinical data for specific metabolites of deutetrabenazine. A Type A Meeting occurred on 20 September 2016 in which the FDA requested that the calculations of the percentage of total drug-related material represented by M1 and M4 be presented using both AUC_{inf} and AUC_{last} as well as a justification for no further nonclinical assessments of M1 be added to the complete response. Furthermore, FDA confirmed that exposure information for M4 in rodents and M1 in rabbits appeared adequate. Consequently, the application was resubmitted 03 October 2016 in SN 0026 and eventually approved in April 2017.

Approved in 2008, tetrabenazine (RLD) was subject to a Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of the drug outweigh the risks of depression and suicidality. This programming completed in August 2015 after it a determination that the approved REMS had ensured that the benefits of the drug outweigh the risks. However, it is important to note that tetrabenazine (Xenazine) has a medication guide which highlights the following risks: 1) warns about the serious side effects of depression, suicidal thoughts and suicidal actions in the context of the HD population 2) warns about drugs that interact with CYP2D6, a major route of metabolism for tetrabenazine and poor CYP2D6 metabolizers.

3.2. Summary of Presubmission/Submission Regulatory Activity

Deutetrabenazine development has been conducted under IND 120631 opened in March, 2014. Highlights of the interactions with the Sponsor in regards to the clinical development plan follow are noted below (verbatim communications found in the DPP meeting minutes are italicized). As noted previously, the original Sponsor, Auspex Pharmaceuticals, has since transferred rights and responsibilities to Teva Pharma.

Pre-IND Type C Meeting, (February 18, 2014)

Key FDA feedback from this meeting related to concerns about the proposed clinical pharmacology plan. The Division requested additional clinical pharmacology of the parent and major circulating metabolites of deutetrabenazine. With respect to the study design for SD-809-C-18, it was determined that only the Clinical Global Impression of Change (CGIC) endpoint would be accepted by the Agency as a valid key secondary endpoint. The Patient Global Impression of Change (PGIC) and the modified Craniocervical Dystonia Questionnaire 24 (CDQ 24) endpoints were changed to exploratory. Furthermore, agreement was reached on the need to conduct a fixed-dose Phase 3 study (C-23) and that the design of Study C-23 could be modified after review of the Phase 2/3 flexible-dose study.

(b) (4)

Breakthrough Therapy Designation (November 3, 2015)

deutetrabenazine under IND 120631 for the treatment of moderate to severe tardive dyskinesia was granted breakthrough therapy designation on 03 November 2015 based on results from Study SD-809-C-18, which demonstrated a significant reduction in AIMS score at the end of 12 weeks

In early 2016, FDA provided feedback regarding protocol amendments and the statistical analysis plan for Study SD-809-C-23. (b) (4)

(b) (4)

Initial Multidisciplinary Breakthrough Status Meeting (March 16, 2016)

As documented in the meeting minutes, FDA concluded that the total exposure of patients with TD and HD to deutetrabenazine should be sufficient to the meet International Conference on Harmonization exposure recommendations; (b) (4) There was acknowledgment of Protocol Amendment 3 and the statistical analysis plan for Study SD-809-C-23 (b) (4)

(b) (4)

Pre-NDA Meeting (November 3, 2016)

As documented in the meeting minutes, the meeting focused on the NDA organization, cross-referencing to previously submitted information in Original-1 NDA, and a discussion on the efficacy/safety data for the second pivotal Phase 3 trial. Agreement was reached on the proposed plan for the TD NDA content. In addition, the ISE and ISS will contain only tables,

figures, listings, and datasets supporting the integrated safety and efficacy summaries and are provided in Original-2 NDA 209885. DPP agreed to referencing safety data from the HD program in the TD NDA as long as the data are presented separately. Lastly, it was determined that a Risk Evaluation Mitigation Strategy (REMS) was not necessary.

Other salient decisions/agreements include the following:

- Pediatric Research Equity Act (PREA) waiver request was filed on October 26, 2016. The prevalence (<1%) and incidence of TD among pediatric patients was listed as the primary justification for the waiver.
- A Proprietary Name Review (PNR) request for AUSTEDO was granted conditional acceptance. The proprietary name request was resubmitted in SN 0027 for Original-1 NDA 208082 and will be resubmitted in SN 0032 for Original-2 NDA 209885. A Proprietary Name Request was also submitted to IND 120631 (TD IND) on October 4, 2016. The Office of Surveillance and
  Epidemiology provided a target date of January 02, 2017 for the submission to IND 120631.
- Approved by DNP on April 11, 2017

3.3. Foreign Regulatory Actions and Marketing History

Austedo is not currently marketed in other countries

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI was consulted to request clinical inspections. Specifically, the following clinical sites (see Table 2) from Studies C-18 and C-23 were to be audited to verify the primary (AIMS dyskinesia total score) and key secondary (CGI-TD) endpoints. These sites were chosen based on enrollment of a relatively large number of study subjects, no prior inspections, geographic clustering and impact on the overall efficacy of Study C-18.

Table 2: List of Site Inspections

Establishment(s) for Inspection	**Site # Protocol # # of Subjects**	**Inspection Dates**
Steven Macina, D.O. Advanced Research Center 1020 S. Anaheim Boulevard, Suite 316 Anaheim, CA 92805	Site #108 SD-809-C-18 10 randomized SD-809-C-23 30 randomized	3/15/2017 to 3/31 2017
Michael McManus, M.D. PCSD-Feighner Research 1550 Hotel Circle North, Suite 450 San Diego, CA 92108	Site #110 SD-809-C-18 7 randomized SD-809-C-23 1 randomized	3/22/2017 to 3/24/2017
Lili Meisamy, D.O. North Texas Clinical Trials, LLC 200 W. Magnolia, Suite 102 Fort Worth, TX 76104	Site #151 SD-809-C-18 5 randomized SD-809-C-23 6 randomized	3/6/2017 to 3/10/2017

Inspectional Findings:

1. Lili Meisamy, D.O. (Site #151): One subject was enrolled and treated in the study C-18 even though met exclusion criteria (intermittent use of Marijuana and amphetamine abuse), only 5 randomized total.

2. Videos and AIMS scores (source documents for efficacy) assessed by blinded independent physicians were not available at sites of Drs. Steven Macina and Michael McManus. PDF files (non-certified copies) sent to field inspectors to verify

Biometrics conducted efficacy analyses both including and omitting subject data from Site 151. It was noted that excluding all 5 subjects that were randomized as part of Study C-18 would have impacted the overall efficacy results of the study. However, the study results remained statistically significant when only excluding the previously mentioned subject inappropriately randomized.

The remaining inspection results were not remarkable. Each site had a few deviations from GCP that were considered minor by the inspector.

4.2. Product Quality

No issues were identified as part of the clinical review

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

There were no new findings identified by the nonclinical reviewer.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Please review Section 4.0 of Dr Bergmann's review (Bergmann) for further information.

4.5.2. Pharmacodynamics

Please review Section 4.0 of Dr Bergmann's review (Bergmann) for further information.

4.5.3. Pharmacokinetics

Please review Section 4.0 of Dr Bergmann's review (Bergmann) for further information.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3: Listing of Clinical Trials Relevant to this sNDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Study SD-809-C-18 (ARM-TD)	Randomized, double-blind, placebo-controlled, flexible-dose, parallel-group study	Screening period of up to 4 weeks 6-week titration period 6-week maintenance period, and a 1-week washout deutetrabenazine at 12 mg/day titrated based on dyskinesia control and tolerability up to a maximum dose of 48 mg/day or matching placebo	Change in AIMS score from baseline; proportion of subjects who are a treatment success at the end of the end of therapy, based on the Clinical Global Impression of Change (CGI-C).	6-week titration to optimal dose, 6-week maintenance (12-week total treatment duration)	117 patients deutetrabenazine (n=58) and placebo (n=59)	Patients between 18 and 75 years of age with a clinical diagnosis of TD. Patients were required to have moderate or severe abnormal movements based on Item 8 of the (AIMS) and a total motor AIMS score of ≥6 (based on Items 1 through 7) and to have used a dopamine receptor antagonist for at least 3 months (or 1 month in patients 60 years of age and older).	USA 29 POL 7 CZE 2 SVK 3
Study SD-809-C-23	Randomized, double-blind, placebo-controlled, fixed-dose, parallel-group, multicenter study	Screening period, a dose-escalation period (4 weeks), a maintenance period (8 weeks), and a post-treatment safety follow-up period.	Change in AIMS score from baseline; proportion of subjects who are	4 week dose escalation period followed by an 8 week	298 patients were randomized and	Patients between 18 and 75 years of age with a clinical diagnosis of TD.	USA 38 POL 19 CZE 6 HUN 7 SVK 3

		Randomization was stratified by baseline use of dopamine receptor antagonist. The overall treatment period was 12 weeks in duration, followed by a 1-week washout.	a treatment success at the end of the end of therapy, based on the Clinical Global Impression of Change (CGI-C).	maintenance period.	distributed evenly between the deutetrabenazine 12, 24, and 36 mg/day and placebo	The mean duration of TD was 5.57 years and the mean AIMS score was 9.6; 73% of patients were using a DRA and 18% had impaired cytochrome P450 2D6 (CYP2D6) function.	DEU 2
Studies to Support Safety							
Study SD-809-C-20	Open-label, single-arm, multicenter, long-term, extension study	Screening period, a titration period (up to 6 weeks), a long-term treatment period (up to 2 years), and a post-treatment safety follow-up period	Change in AIMS Analysis of adverse events	Titration period (up to 6 weeks) followed by a long-term treatment period of up to 2 yrs.	A total of 304 patients received deutetrabenazine in this study: 202 patients who had received deutetrabenazine parent study treatment and 102 patients who had received placebo in the parent study	Patients at least 18 years of age with a diagnosis of TD were included in this study. Male and female adult patients with TD who successfully completed one of the parent efficacy studies (Study C-18 or Study C-23) and met eligibility criteria were enrolled	75 sites in US and Europe
- SD-809-C-15	Randomized, Double-blind,	deutetrabenazine 6 mg, 9 mg, or 12 mg	Change in Total Maximal Chorea	8-week titration to	90 enrolled	Adult patients with	34 sites in US

(First-HD)	Placebo controlled, Parallel group, Multi-center	Placebo QD to BID dosing with meals, about 10 hours apart (BID) PO dosing started at 6 mg/day and titrated weekly in 6 mg/day increments to maximum 48 mg/day (24 mg BID) or 36 mg/day (18 mg BID) if receiving CYP2D6 inhibitor	Score from baseline; proportion of subjects who are a treatment success at the end of the end of therapy, based on the Patient Global Impression of Change and Clinical Global Impression of Change.	optimal dose, 4-week maintenance (12-week total treatment duration)	and in ITT, mITT, and Safety Population 45 deutetrabenazine 45 placebo 81 in Per-Protocol Population 41 deutetrabenazine 40 placebo	chorea of Huntington's disease (CAG repeats ≥ 37) with a Total Maximal Chorea score ≥8	and Canada
SD-809-C-16 (ARC-HD	Open-label, 2-cohort, multi-center, Long-term safety	ARC-Rollover cohort: deutetrabenazine 6 mg, 9 mg, or 12 mg QD to BID dosing with meals, about 10 hours apart (BID) ARC-Switch cohort: subjects started on a regimen of deutetrabenazine providing comparable AUC to incoming Xenazine regimen	Safety; Comparison to tetrabenazine in switch study	After titration period, patients receive long term maintenance therapy	Rollover: 75 Switch: 37 Total: 112	Rollover: Patients who completed Study deutetrabenazine-C-15 Switch: HD patients on stable doses of Xenazine	37 sites in US, Canada and Australia

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5.2. Review Strategy

The two placebo controlled studies (C-18 and C-23) were used in the efficacy review of deutetrabenazine as a treatment for TD. The primary safety review involved evaluating both of the previously mentioned placebo controlled studies in addition to Study C-20. However, the HD clinical studies (C-15 and C-16) were also reviewed as to help identify any salient safety signals or specific safety issues that might be applicable to the TD application.

My approach to this review of efficacy and safety was relatively straightforward. In addition to presenting and confirming the efficacy and reviewing the safety findings of the double blind trials, the rollover cohort of the open study (C-20) also provides support for safe longer term use of deutetrabenazine. The Thorough QTc (TQT) Study is presented in synopsis form in Section 8.4.9 QT in the Review of Safety with a summary of the consultative review by the Interdisciplinary Review Team.

I performed many of the tabulations and calculations in this review using JMP 12.1.0 and JMP Clinical 11.2 software on the Applicant-supplied datasets conforming to CDISC SDTM and ADaM standards. Biomedical informatics output created by Douglas Warfield, Ph.D., was used to assist with adverse event analysis. Any table or figure taken from the Applicant's reports is referenced as such in the table or figure caption. Applicant's analyses were periodically used as part of the review. In these instances, the biostatistician (Semhar Ogbagaber, Ph.D.) confirmed the reported results.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study C-18: Randomized (1:1) double-blind placebo-controlled flexible dose study of deutetrabenazine for the treatment of TD

6.1.1. Study Design

Trial Design

This is a randomized, double-blind, placebo-controlled, parallel-group study in which subjects with moderate to severe TD were invited to participate. The overall treatment period was 12 weeks in duration (6 week titration period, 6 week maintenance period), followed by a 1-week washout period. Subjects were randomly assigned in a 1:1 ratio to receive either deutetrabenazine or placebo. The randomization was stratified by baseline use of dopamine receptor antagonists (currently taking versus not currently taking a dopamine receptor

antagonist). Subjects underwent dose adjustment over the initial 6 weeks of treatment to identify a dose of study drug that controls dyskinesias and is well tolerated (i.e., optimal dose) followed by maintenance therapy at that dose.

Reviewer Comment: This appeared to be an appropriate design for a relatively small dose exploration study. The duration of the study was appropriate and twice as long as some of the valbenazine registration studies. Stratification by dopamine receptor antagonist (DRA) enhanced the process of randomization and helped ensure treatment groups were comparable to one another. It might have been helpful to further stratify by dosage equivalents of DRA's; however this was not likely practical given the size of the study.

The trial was performed in the patient population intended for marketing deutetrabenazine. To participate, subjects had to have a clinical diagnosis of TD and had symptoms for at least 3 months prior to screening. The subjects TD symptoms must have been bothersome and/or cause functional impairment. The inclusion and exclusion criteria were appropriate given the objectives of the trial. Salient criteria are listed below.

Inclusion Criteria:

- Subject is between 18 and 80 years of age, inclusive.
- Subject has a history of using a dopamine receptor antagonist for at least 3 months (or 1 month in subjects 60 years of age and older). See Appendix 15.
- Subject has a clinical diagnosis of TD, and has had symptoms for at least 3 months prior to Screening.
- The subject's TD symptoms are bothersome to the subject or cause functional impairment.
- At the Screening and Baseline visits, the subject has:
    - Moderate or severe abnormal movements as judged by the Investigator based on Item 8 of the AIMS AND
    - A total motor AIMS score of ≥6 (based on Items 1 through 7) as assessed by the Principal Investigator. Note: A video recording of the AIMS assessment at Screening will be reviewed by a blinded central rater to confirm eligibility prior to randomization.
- For subjects with underlying psychiatric illness:
    - Subject is psychiatrically stable and has had no change in psychoactive medications (including, but not limited to neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before Screening (45 days for antidepressants).
- Subjects on long-acting (depot) medications have been on stable therapy (dose, frequency) for ≥3 months before Screening.

- Subject has a mental health provider who is aware of the subject's participation in the trial, and does not anticipate any changes to the subject's treatment regimen (drug, dose and frequency) over the next 3 months

Exclusion Criterion:

- Subject has received any of the following medications within 30 days of Screening or Baseline:
    - Tetrabenazine, reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Screening), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
    - Metoclopramide, promethazine, and prochlorperazine
    - Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc.), or monoamine oxidase inhibitors (MAOIs) Levodopa or dopamine agonists
- Subject has participated in any previous study of deutetrabenazine in which they received deutetrabenazine.
- Subject has a neurological condition other than TD that may interfere with assessing the severity of dyskinesias.
- Subject has a serious untreated or undertreated psychiatric illness at Screening or Baseline.
- Subject has active suicidal ideation at Screening or Baseline.
- Subject has history of any of the following within 6 months of Screening:
    - Previous intent to act on suicidal ideation with a specific plan (positive answer
    - to question 5 on C-SSRS), irrespective of level of ambivalence at the time of
    - suicidal thought
    - Previous preparatory acts to commit suicide or suicidal behavior
    - A previous actual, interrupted or aborted suicide attempt
- Subject has a score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at Screening or Baseline.
- Subject is developmentally disabled or has evidence of dementia.
- Subject has an unstable or serious medical illness at Screening or Baseline.
- Subject has history (within 3 months) or presence of violent behavior.
- Subject has a QTcF value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block [RBBB]) on 12-lead ECG at Screening.
- Subject has a positive urine drug screen (for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, or opiates) at Screening or Baseline, except if subject is receiving a stable dose of a benzodiazepine.

As noted previously, the dose range of the investigational product, (deutetrabenazine) was estimated using pK measurements of the reference listed product, Xenazine (tetrabenazine). Xenazine is labeled for an initial starting dose of 12.5 mg/d, increasing by 12.5 mg weekly based upon clinical response. The maximum recommended daily dose is 50 mg/d given in divided doses. The starting dose of 6 mg of deutetrabenazine provides an AUC of total (α+β)-HTBZ that is comparable to 12.5 mg of tetrabenazine (the approved starting dose for the treatment of chorea associated with HD), but with a lower peak concentration and reduced plasma fluctuation.

Deutetrabenazine and placebo tablets have been manufactured according to current Good Manufacturing Practices regulations. Deutetrabenazine tablets or placebo were supplied as 6, 9, 12, 15, and 18 mg tablets and were packaged in blister packs and labeled according to applicable regulatory guidelines. Placebo tablets contained the same excipients as deutetrabenazine.

The study treatments dose levels for titration were as follows:

Table 4 Study C-18 Dose Titration Steps

Dose Level	Total Daily Dose	Morning Dose	Evening Dose
1	12 mg	6 mg	6 mg
	Tablets	1 x 6 mg	1 x 6 mg
2	18 mg	9 mg	9 mg
	Tablets	1 x 9 mg	1 x 9 mg
3	24 mg	12 mg	12 mg
	Tablets	1 x 12 mg	1 x 12 mg
4	30 mg	15 mg	15 mg
	Tablets	1 x 15 mg	1 x 15 mg
5	36 mg	18 mg	18 mg
	Tablets	1 x 18 mg	1 x 18 mg
6	42 mg	21 mg	21 mg
	Tablets	1 x 12 mg and 1 x 9 mg	1 x 12 mg and 1 x 9 mg
7	48 mg	24 mg	24 mg
	Tablets	2 x 12 mg	2 x 12 mg

Note: deutetrabenazine dosage strengths include 6, 9, 12, 15, and 18 mg tablets.
Source: Clinical Study Report (C-18), page 35

Assignment to treatment was based upon 1:1 randomization ratio through a web-based automated system. Patients were initially dosed at Visit 2 (Baseline).

During the treatment period the Applicant, investigators and their site personnel, and patients were blinded to treatment assignment. The active and placebo investigational product were identical in appearance and packaged in investigational product kits by an independent vendor according to the randomization code. The randomization was stratified by baseline use of dopamine receptor antagonists (currently taking versus not currently taking a dopamine receptor antagonist). As noted previously, randomization and stratification were performed through the Interactive Web Response System (IWRS).

Dose modifications were pre-specified for patients receiving a potent CYP2D6 inhibitor with a limit of 36 mg/d. The maximum dose was otherwise 48 mg/d. The goal of titration was to achieve an optimal level of dyskinesia control in which the patient is tolerating the treatment regimen or until the maximum permitted dose is reached. The dose of deutetrabenazine was increased on a weekly basis until there was adequate control of dyskinesia, the subject experienced a protocol defined clinically significant AE (defined as related to study drug and either moderate or severe in intensity or meets the criteria for a SAE).

If a subject experiences a clinically significant AE, the Investigator used his or her judgment to determine if a dose reduction or suspension is necessary. Dose adjustments were made based on all available information including the subject's and caregiver's (if required) reports of AEs and dyskinesia control, the clinical assessment of safety and efficacy by the Investigator, and information from rating scales.
A dose reduction of 6 mg/day was allowed at a time. Discontinuations were reviewed by the study's medical monitor.

An Independent Data Monitoring Committee (IDMC) was established prior to study start, with an appropriate charter to direct decisions and communications, maintain a firewall to preserve the blinding and integrity of the study, and monitor the trial safety results at intervals throughout the study. The IDMC as comprised of at least two clinicians and a statistician not otherwise associated with the trial.

Please refer to Table 5 for a schedule of events during the placebo-controlled period.

Table 5-Schedule of Events

	Screening		Titration						Maintenance			Follow Up		Uns
Week	Up to -4	BL[1]	1	2	3	4	5	6	7†	9	12/ ET[2]	13	16[3]	
Visit window (days)			± 1	± 3								± 1	± 3	
Activity														
Clinic Visit[4]	X	X		X		X		X		X	X	X		X
Telephone Contact			X		X		X		X				X	
Evaluate/adjust dose of study drug			X	X	X	X	X	X						
Informed Consent/Assent	X													
Inclusion/Exclusion Criteria	X	X												
Medical History/Demographics	X													
Vital Signs/Weight	X	X[5]		X		X		X[5]		X	X[5]	X		X
Physical Examination	X	X[6]									X			X[6,7]
Complete Neurological Exam	X										X			X[7]
Height	X													
12-lead ECG	X	X		X		X[8]		X[8]		X[8]	X			X[7]
Chemistry/Hematology/UA	X	X						X			X			X[7]
Urine drug screen	X	X												
Randomization via IWRS[9]		X												
Blinded CYP2D6 Genotype		X												
Pregnancy Test/FSH[10]	S	U												
HBsAg/Prothrombin time (INR)	X													
Provide diary card for next visit								X		X				
Blood sampling for deutetrabenazine and metabolites										X[11]	X[11,15]			X[15]
AIMS	X	X		X		X		X		X	X			
Video recording of AIMS[12]	X	X		X		X		X		X	X			
UPDRS – III (motor)	X	X		X		X		X		X	X	X		X[7]
BARS		X		X		X		X		X	X	X		X[7]
HADS	X	X		X		X		X		X	X	X		X

C-SSRS[13]	X	X		X		X		X		X	X	X		X
ESS		X		X		X		X		X	X	X		X[7]
CGIC				X		X		X		X	X			
PGIC						X		X		X	X			
MoCA		X								X	X			
Modified CDQ-24		X									X			
Dispense Study Drug via IWRS[14]		X	X	X	X	X	X	X	X	X				
Assess Study Drug Accountability/Compliance				X		X		X		X	X			
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; ESS Epworth Sleepiness Scale; FSH, follicle stimulating hormone; HADS, Hospital Anxiety and Depression Scale; INR, International Normalized Ratio; IWRS, Interactive Web Response System; MoCA, Montreal Cognitive Assessment; n/a, not applicable; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SAE, serious adverse event; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale.

Source: Study C-18 Clinical Protocol (page 10)

Procedures were in place to evaluate drug accountability, dispensing and return. Treatment compliance was determined by pill count performed during the patient visit. A patient was considered compliant if they had taken over 80%-105% of the expected tablets of study drug.

Patients receiving strong CYP2D6 inhibitors (bupropion, fluoxetine, paroxetine, or quinidine) were limited to a maximum of 36 mg/d of deutetrabenazine. A list of prohibited drugs was provided in the protocol, as was a list of prohibited QTc prolonging drugs.

Subject Completion, Discontinuation, or Withdrawal
Subjects who fully completed the study participated in a screening period, a 12-week placebo-controlled treatment period, and a 1-week washout period before initiation of a 104-week open label extension period. Subjects were free to discontinue participation at any time. Investigators were required to withdraw subjects if the type, frequency, or severity of any AE became unacceptable or intolerable or if a subject exhibited active suicidal ideation with at least some intent to act, or if the subject was lost to follow-up, confirmed to be pregnant, or was unable to tolerate the treatment dose after a one-time dose reduction. If subjects withdrew prematurely from the study, the reason for withdrawal was recorded and subjects underwent early termination assessments (see Procedures and Schedule above). It was considered crucial to obtain follow-up data for subjects withdrawn for safety-related reasons.

Study Endpoints

The primary efficacy assessment was adapted from the AIMS. The AIMS is an assessment tool used to detect and follow the severity of TD over time, and was originally developed by a consortium of clinical psychopharmacology researchers funded by the National Institute of Mental Health's (NIMH) Psychopharmacology Research Branch (Guy, 1976). While the original AIMS is commonly used in clinical practice, the scale does not include detailed descriptors. For the present study, the Applicant utilized AIMS descriptors which are consistent with those utilized in large trials in schizophrenia.

The AIMS is composed of 12 clinician-administered and scored items. Items 1-10 are rated on a 5-point, anchored scale and consist of the following:

- Items 1-4 assess orofacial movements
- Items 5-7 deal with extremity and truncal dyskinesia
- Items 8-10 deal with global severity as judged by the examiner, and the patient's awareness of the movements and the distress associated with them.
- Items 11-12 are yes/no questions concerning problems associated with teeth and/or dentures, as such problems can be mistaken for dyskinesia.

A total score from items 1 through 7 (orofacial, extremity and truncal movements) can be calculated and represents observed movements, with higher scores indicative of more severe dyskinesia. Item 8 can be used as an overall severity index; items 9 and 10 provide additional information with regard to patient incapacitation and awareness; and items 11 and 12 provide information that may be useful in determining lip, jaw, and tongue movements.

To enable a systematic evaluation of the primary endpoint, the AIMS was digitally video-recorded using a standard protocol at Screening, Baseline, and Weeks 2, 4, 6, 9, and 12. The videos from Screening, Baseline, and Weeks 2, 4, 6, 9 and 12 were independently reviewed by a blinded central rater(s) who was an expert in movement disorders. The Screening video was centrally reviewed prior to randomization to ensure subject eligibility based on confirmation of a clinical diagnosis of moderate to severe TD and a total motor AIMS score ≥6 (based on Items 1 through 7). Videos were recorded and submitted to the central rater in a blinded manner with respect to visit number, site and date of recording.

In this reviewer's opinion, the AIMS total score from Items 1 through 7 (orofacial, extremity, and truncal movements) was a reasonable choice for a primary efficacy measure. Please see Table 6 for a complete listing of the scale. Its validity has been established by comparisons to other similar instruments, and it has been widely used in clinical and research settings for the purpose of assessing the presence and severity of TD. Limitations with this measure include the need for a trained and experienced rater (which the Applicant has mitigated by using central AIMS raters) and the lack of consensus as to what would constitute a meaningful change in AIMS score. The use of consensus central AIMS raters is considered to be strength of this study, because it negated inter-rater variability and the sequence/expectation bias that can accompany on-site raters.

Table 6: Primary Efficacy Assessment - Abnormal Involuntary Movement Scale (AIMS)

Score	Descriptors (For items 1-7)
0	No dyskinesia
1	Minimal or slight dyskinesia: Low amplitude, present during some but not most of the exam
2	Mild dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam)
3	Moderate dyskinesia: Moderate amplitude and present during most of exam
4	Severe dyskinesia: Maximal amplitude and present during most of exam

Facial and Oral Movements	None	Minimal	Mild	Moderate	Severe
1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks, include frowning, blinking, smiling, grimacing	0	1	2	3	4
2. Lips and perioral area e.g., puckering, pouting, smacking	0	1	2	3	4
3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0	1	2	3	4
Extremity Movements					
5. Upper *(arms, wrists, hands, fingers)* Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic)	0	1	2	3	4
6. Lower *(legs, knees, ankles, toes)* e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0	1	2	3	4
Trunk Movements					
7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4

Source: Study C-18 Clinical Protocol (page 74)

Secondary Efficacy Endpoints

The Clinical Global Impression of Change (CGI-C) was used as a key secondary outcome measure. Specifically, the key secondary efficacy endpoint was the proportion of subjects who are a treatment success at Week 12 based on the CGI-C. A treatment success was defined as Much or Very Much Improved on the CGI-C at the Week 12 visit. Subjects whose status at Week 12 was not known, as well as subjects who are not Much or Very Much Improved at the Week 12 visit, were considered to be treatment failures for this analysis. The CGI-C is a 7-point Likert

Scale, ranging from Very Much Worse to Very Much Improved**.** This measure was completed at Weeks 2, 4, 6, 9 and 12.

End of Phase 2 meeting minutes (March 4, 2014) and subsequent protocol amendment (May 20, 2014) for Study 18 confirmed the Division agreed on proportion of subjects with treatment success at week 12 based on CGI-C (see Table 7) as the only key secondary endpoint. Limitations with this outcome measure include the variability introduced by potentially different raters across visits and the subjective assessment of improvement, which may vary according to training and clinical experience. Furthermore, this comparison-based assessment necessitates an accurate recall of the subjects' baseline presentations. Unlike the AIMS, this measure was not scored by central raters. Consequently, this efficacy endpoint is considered less-informative than the central-rated AIMS change from baseline.

Table 7: Clinical Global Impression of Change

Appendix 3: Clinical Global Impression of Change (CGIC)

With respect to the subject's tardive dyskinesia, how would you describe the subject now compared to immediately before starting study drug:	
-3	Very Much Worse
-2	Much Worse
-1	Minimally Worse
0	Not Changed
1	Minimally Improved
2	Much Improved
3	Very Much Improved

Source: Study C-18 Clinical Study Protocol Amendment (page 75)

Additional Efficacy Endpoints

Patient Global Impression of Change (PGIC)

The PGIC is single-item questionnaire that asks the patient to assess their TD symptoms at specific visits after initiating therapy. The PGIC uses a 7-point Likert Scale, ranging from very much worse (–3) to very much improved (+3), to assess overall response to therapy. In general, patient-rated global measures of change have face validity and have been shown to correlate with disability for a number of chronic conditions (Kamper, Maher, & Mackay, 2009). This measure was completed by subjects at Weeks 4, 6, 9 and 12.

Modified Craniocervical Dystonia Questionnaire (CDQ-24)

The CDQ-24 is a disease-specific quality of life questionnaire developed for use in patients with craniocervical dystonia, including both cervical dystonia (CD) and blepharospasm (BPS) (Muller, 2004). The CDQ-24 includes domains which are relevant not only to CD and BPS, but to TD. The following domains are evaluated in the CDQ-24: stigma, emotional well-being, pain, activities of daily living, and social/family life. For the present study, the CDQ-24 was modified such that the questions focus more directly on the impact of TD (as opposed to CD/BPS) on quality of life.

Furthermore, there were a variety of other secondary measures (some used as safety assessments) were included in the study. With the exception of the Montreal Cognitive Assessment (MoCA), lower scores are in the direction of improvement or better status

- Swallowing Disturbance Questionnaire (SDQ) is a 15-item questionnaire designed to assess the frequency of swallowing disturbance. It is not disease-specific and is a tool for identifying patients with swallowing disturbances arising from different etiologies. Higher scores indicate greater impairments in swallowing (range 0.5 -44.5).
- Barnes Akathisia Rating Scale (BARS) is used to evaluate drug-induced akathisia (motor restlessness). The scale yields a summary score (comprised of an objective assessment of akathisia and subjective measures including self-awareness and distress); higher scores indicate more akathisia and restlessness.
  - Total Score, range 0-9
  - Global Score, range 0-5
- Hospital Anxiety and Depression Scale (HADS) is a 14-item scale that includes seven items for depression (Depression Subscale [HADS-D]) and seven items for anxiety (Anxiety Subscale [HADS-A]). For both subscales, higher scores reflect greater frequency or severity of symptoms relative to the preceding week.
  - Depression Subscale, range 0-21
  - Anxiety Subscale, range 0-21
- Montreal Cognitive Assessment (MoCA) is a validated, screening instrument for assessing mild cognitive dysfunction; it includes items for visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation. Higher scores indicate better cognitive function, range 0-30.
- Unified Parkinson's Disease Rating Scale (UPDRS) is a four part, multiple item instrument used to assess the signs and symptoms of Parkinson's disease; it includes patient and clinician assessments of motor, cognitive, and behavioral symptoms. In this study, the UPDRS question pertaining to speech/dysarthria is used. Dysarthria item only, range 0-4, higher scores indicate greater impairment.
- Epworth Sleepiness Scale (ESS) is an eight-item scale that provides an assessment of a person's general level of daytime sleepiness. Participants are asked to rate their chances of

falling asleep in various situations or activities; higher scores indicate higher levels of daytime sleepiness (range 0-24).

- Columbia Suicide Severity Rating Scale (C-SSRS) is a questionnaire used to screen for suicidality in clinical studies of compounds that are active in the central nervous system. The scale is based on interviews performed by study personnel who are trained in its use prior to study participation.

Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for this study was dated July 8, 2014. The SAP defined three analysis sets for this study:

1. Intent-to-Treat Population: The Intent-to-Treat (ITT) Population included all randomized subjects. In analyses and summaries based on the ITT Population, subjects were included in the treatment group to which they were randomized, regardless of the treatment that was actually received.

2. Modified Intent-to-Treat Population: The Modified Intent-to-Treat (mITT) Population includes all subjects in the ITT Population who were randomized to treatment, received study drug, and had at least one post-baseline assessment of the AIMS. The primary efficacy analysis was completed in the mITT Population. In analyses and summaries based on the mITT population, subjects were included in the treatment group to which they were randomized regardless of the treatment that was actually received

3. The Per Protocol Population will included subjects with documented compliance with study drug (80-105%) and/or measurable levels of active metabolites at the primary endpoint was assessed and who had no major protocol deviations.

Handling of Missing Data:

The SAP indicated that procedures for handling missing data would depend on the type of endpoint. For endpoints analyzed using MMRM, all available data from the subject were used. For proportion endpoints, subjects with missing data at the time point of interest were classified into the least favorable of the two categories. For CDQ-24, if a subject has missing data at Week 12, the baseline observation for the subject was used (i.e., the subject will be assumed to have no change from baseline).

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint for this study was the change in AIMS (items 1 through 7) as assessed by blinded central video rating from Baseline (defined for each subject as the value from the Day 0 visit) to Week 12 for the mITT population. The primary analysis was carried out

using a linear mixed model for repeated measurements (MMRM) with the change from baseline in AIMS score as the dependent variable. The model included fixed effects for treatment group, time point (five levels: Weeks 2, 4, 6, 9, and 12), the treatment group by time point interaction, and the randomization stratification variable. Baseline AIMS score was included as a covariate. The unstructured covariance model was used and the primary analysis compared the deutetrabenazine and placebo groups at Week 12 using a two-sided test at the 5% level of significance.

Analysis of the Key Secondary Endpoint:

The key secondary efficacy endpoint for this study was the proportion of subjects who are a treatment success at Week 12 based on the CGIC. A treatment success was defined as Much or Very Much Improved on the CGIC at the Week 12 visit. Subjects whose status at Week 12 was not known, as well as subjects who are not Much or Very Much Improved at the Week 12 visit, were considered to be treatment failures for this analysis.

The Applicant noted that if the primary analysis is statistically significant ($p<0.05$), then the key secondary endpoint will be analyzed, also at the 5% level of significance (two-sided). The proportion of subjects who are a treatment success at Week 12 based on the CGIC will be compared between groups using Pearson's chi-square test

Additional Secondary Analyses

The following additional secondary efficacy endpoints were also to be analyzed:

- The change in the modified CDQ-24 score from Baseline to Week 12.
- The proportion of subjects who are a treatment success at Week 12, based on the PGIC.
- The proportion of subjects who have a 50% or greater reduction in AIMS score from Baseline (defined for each subject as the value from the Day 0 visit) to Week 12.
- The percent change in AIMS score from Baseline to Week 12.
- Based on the change in AIMS score from Baseline to Week 12, as assessed by blinded central video rating, the cumulative proportion of responders were displayed for responder definitions ranging from a 10% improvement from Baseline to a 90% improvement from Baseline in steps of 10 percentage points.

No interim analysis of the trial was planned or performed. Please refer to the Biostatistics review for a detailed evaluation of the Applicant's statistical analyses.

Protocol Amendments

The original protocol was finalized on March 24, 2014. Amendment 1 was finalized on May 20, 2014 and contained the following notable changes:

1. To ensure consistency among assessments, all clinic visits should be performed in the morning and, if possible, the same trained assessor should perform all of a single subject's assessments.
2. CDQ-24 endpoint was reclassified as an additional secondary endpoint
3. Addition of video recording of AIMS and CGIC assessment at Week 2
4. Addition of sensitivity analyses was included in SAP

Amendment 2 was finalized on July 18, 2014, and contained the following notable changes:

1. Role of the independent monitoring committee was expanded to include monitoring of all data, including safety data.
2. Exclusion of subjects who have previously not experienced clinical benefit with tetrabenazine may bias the population.
3. Modified to better reflect medications likely to have significant interactions with deutetrabenazine and/or directly oppose the effects of deutetrabenazine based on known mechanism of action. In addition, additional guidance on specific anticholinergics and stimulants considered exclusionary was provided

Data Quality and Integrity: Applicant's Assurance

The Applicant indicated that the study was performed in compliance with Good Clinical Practice (GCP) and FDA regulations and guidelines. Steps to assure the accuracy and reliability of data included the selection of qualified clinical investigators and appropriate study sites, review of protocol procedures with the clinical investigator and associated personnel prior to the study, and periodic monitoring visits by the Applicant. The Applicant (or designee) had plans to review the data accuracy and completeness during and after the study, and any discrepancies will be resolved with the clinical investigator or designee as appropriate. Furthermore, quality control review and quality assurance audit of the clinical study report was performed by the Applicant, checking for consistency, clarity, and accuracy. Overall, the data quality and integrity plan appears to have been adequate.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that this study was conducted in accordance with accepted practices for the protection of human subjects, use of institutional review boards and independent ethics committees, and adherence to Good Clinical Practice (GCP). All clinical studies were performed under the Applicant's IND.

Financial Disclosure

The financial disclosures by clinical investigators (Form 3454) were reviewed for all investigators in all covered clinical studies (C-18, C-20 and C-23). Five investigators (b) (6) participated in financial arrangements or held financial interests that were required to be disclosed. However, the Applicant placed into effect controls (i.e., randomized, double-blind study design) that appropriately mitigated any potential conflict of interest bias.

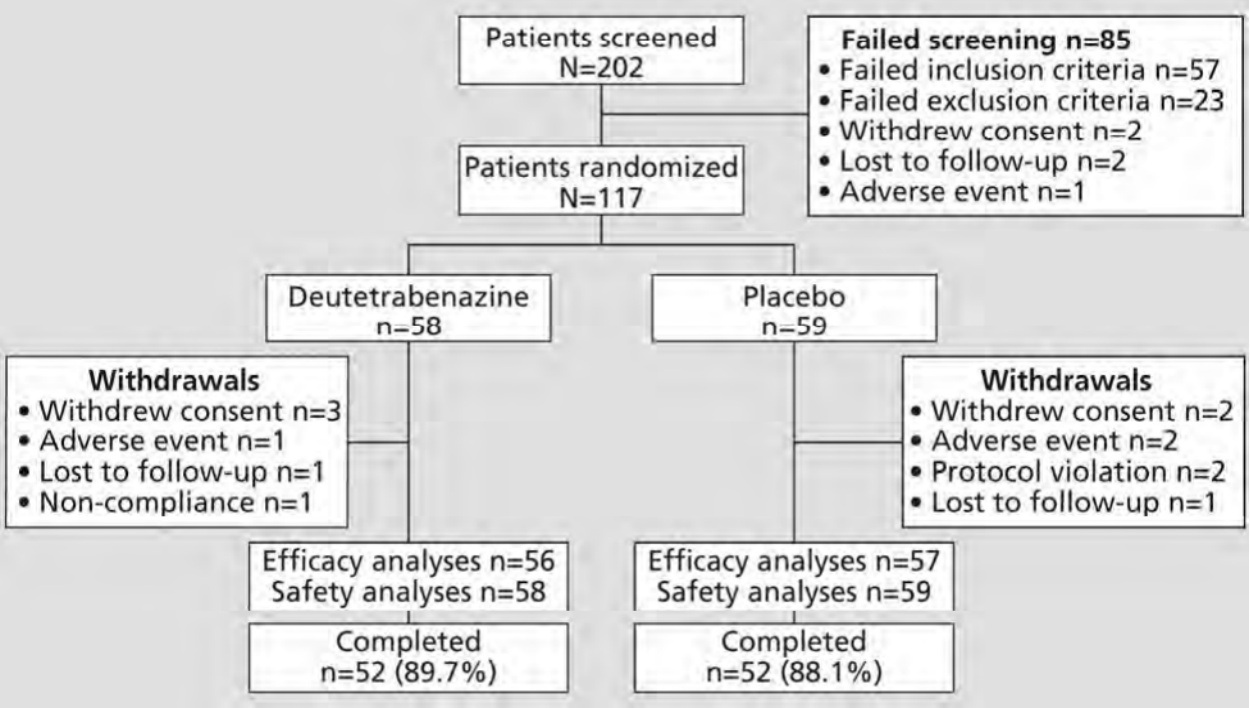
Patient Disposition

A total of 202 patients were screened and gave informed consent to enter the study. Of those patients, 85 (42.1%) were either ineligible for entry into the study or declined study participation. The most common reason for ineligibility (49 patients [24.3%]) was insufficient TD severity as assessed with AIMS.

As a result, a total of 117 patients were randomized between the deutetrabenazine (N=58) and placebo (N=59) treatment groups and consisted of the ITT population (see Table 8). A total of 52 patients (89.7%) in the deutetrabenazine group and 52 patients (88.1%) in the placebo group completed the study. In the deutetrabenazine group, a total of six patients withdrew from the study, including one patient due to an adverse event, one patient lost to follow-up, one patient due to noncompliance, and three patients who withdrew consent. In the placebo group, a total of seven patients withdrew from the study, including two patients due to an adverse event, one patient lost to follow-up, two patients due to protocol violations, and two patients who withdrew consent. About 80% of subjects in each treatment group decided to enroll in the open label extension.

Of the 117 patients in the ITT Population, four patients without at least one centrally-read post-baseline assessment of the AIMS were excluded from the mITT Population (N=113) and the Per-Protocol (PP) Population.

Table 8: Disposition of Patients C-18



Source: Study C-18 CSR Table 14.1.1.1.2 and Listing 16.2.1 (page 61)

Protocol Violations/Deviations

Major protocol violations were not specifically highlighted in the clinical study report. However, I reviewed the complete listing of protocol deviations to acquire this information. The protocol deviations that led to exclusion of patients from the PP population were based on pre-specified criteria in the protocol. Twenty four patients in the deutetrabenazine group and 20 patients in the placebo group were excluded from the PP population due to various protocol deviations including study drug compliance <80% or >105%, not completing 12 weeks of treatment, missing week 12 efficacy assessments, taking a prohibited concomitant medication, altering background CNS medication, or having no measureable levels of active metabolites at the time of the week 12 AIMS assessment (deutetrabenazine group only). Furthermore, approximately 14% of subjects had a centrally read AIMS score <6 but were randomized to treatment based on the local read. Both treatment groups had a similar frequency of these events. It should be noted that the prohibited concomitant medications and background CNS medications were associated with limited use and low occurrence frequencies. Overall, given the relatively even distribution of events between the two treatment groups, it is unlikely that the aforementioned protocol deviations impacted safety or efficacy conclusions.

Table 9: Summary of Characteristics (mITT Population)

Parameter	deutetrabenazine	Placebo (N=57)	Total (N=113)
Age, years			
Mean (SD)	56.9 (8.52)	53.0 (10.67)	54.9 (9.81)
Minimum, maximum	40, 75	25, 70	25, 75
Gender, n (%)			
Female	28 (50.0)	31 (54.4)	59 (52.2)
Male	28 (50.0)	26 (45.6)	54 (47.8)
Race, n (%)			
White	37 (66.1)	42 (73.7)	79 (69.9)
Black or African American	17 (30.4)	14 (24.6)	31 (27.4)
Asian	2 (3.6)	1 (1.8)	3 (2.7)
Ethnicity, n (%)			
Hispanic or Latino	4 (7.1)	10 (17.5)	14 (12.4)
Not Hispanic or Latino	51 (91.1)	46 (80.7)	97 (85.8)
Not reported	1 (1.8)	1 (1.8)	2 (1.8)
Weight, kg			
Mean (SD)	87.31 (24.421)	85.55 (20.883)	86.42 (22.621)
Minimum, maximum	47.3, 182.1	45.1, 166.6	45.1, 182.1
BMI, kg/m^2			
Mean (SD)	30.50 (8.025)	29.63 (6.957)	30.06 (7.484)
Minimum, maximum	16.2, 66.8	18.1, 59.3	16.2, 66.8
Duration of tardive dyskinesia, months			
Mean (SD)	75.0 (82.08)	75.0 (82.52)	75.0 (81.93)
Minimum, maximum	3, 326	3, 436	3, 436
AIMS (Items 1 to 7), centrally read			
Mean	9.7 (4.14)	9.6 (3.78)	9.6 (3.94)
Minimum, maximum	1, 20	3, 18	1, 20
Using a DRA, n (%)	43 (76.8)	48 (84.2)	91 (80.5)
Using a strong CYP2D6 inhibitor, n (%)	9 (16.1)	8 (14.0)	17 (15.0)
CYP2D6 genotype, n (%)			
Poor metabolizer	5 (8.9)	1 (1.8)	6 (5.3)

Not poor metabolizer[a]	51 (91.1)	56 (98.2)	107 (94.7)
Background comorbid illness, n (%)			
Psychiatric disorders	55 (98.2)	56 (98.2)[b]	111 (98.2)
Schizophrenia	30 (54)	32 (56)	62 (55)
Schizoaffective disorder	9 (16)	8 (14)	17 (15)
Bipolar/Depression	13 (23)	15 (26)	28 (25)
Other	4 (7)[c]	1 (2)	5 (4)
Gastrointestinal disorders	2 (3.6)	0	2 (1.8)

Source: Study C-18 CSR page 64

Please see Table 9 for a tabulation of demographic characteristics for the mITT sample. Both sexes were reasonably well represented in small study. The majority of subjects were under 65 years old and the mean age was around 55 year old across all treatment groups. This is representative of the target population given middle aged to elderly patients frequently have a longer duration of total antipsychotic exposure as well as exposure to typical antipsychotics compared to younger patients. Patients of African-American and Caucasian races were well-represented in the study sample.

Table 10: Summary of Baseline Characteristics (mITT Population)

Parameter	deutetra benazin	Placebo (N=57)	Total (N=113)
Duration of tardive dyskinesia, months			
Mean (SD)	75.0 (82.08)	75.0 (82.52)	75.0 (81.93)
Minimum, maximum	3, 326	3, 436	3, 436
AIMS (Items 1 to 7), centrally read			
Mean	9.7 (4.14)	9.6 (3.78)	9.6 (3.94)
Minimum, maximum	1, 20	3, 18	1, 20
Using a DRA, n (%)	43 (76.8)	48 (84.2)	91 (80.5)
Using a strong CYP2D6 inhibitor, n (%)	9 (16.1)	8 (14.0)	17 (15.0)
CYP2D6 genotype, n (%)			
Poor metabolizer	5 (8.9)	1 (1.8)	6 (5.3)
Not poor metabolizer[a]	51 (91.1)	56 (98.2)	107 (94.7)
Background comorbid illness, n (%)			
Psychiatric disorders	55 (98.2)	56 (98.2)[b]	111 (98.2)
Schizophrenia	30 (54)	32 (56)	62 (55)

Schizoaffective disorder	9 (16)	8 (14)	17 (15)
Bipolar/Depression	13 (23)	15 (26)	28 (25)
Other	4 (7)[c]	1 (2)	5 (4)
Gastrointestinal disorders	2 (3.6)	0	2 (1.8)

Please see Table 10 for a summary of subject baseline characteristic. The treatment groups were reasonably well balanced across the examined baseline parameters. One notable exception is the higher prevalence of poor CYP2D6 metabolizers in the deutetrabenazine group (8.9%) compared to placebo (1%). This could potentially affect drug concentrations. There was also a slightly higher percentage of placebo treated patients (84.2%) using DRAs compared to deutetrabenazine treated patients (76.8%). The number of years since initial TD diagnosis had a wide range but was comparable between treatment groups; this is important as the duration of TD may moderate the treatment effect. Background comorbid illnesses were overwhelmingly psychiatric disorders in both treatment groups. As a whole, the baseline characteristics of the mITT analysis were roughly congruent with the expected US target population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
Compliance with treatment was relatively high (~93%) with no difference between the treatment arms. A subject was deemed compliant if the subject took 80%-105% of the expected number of tablets during the given time period.

Concomitant Medication
Fifty-eight patients (100.0%) in the deutetrabenazine group and 57 patients (96.6%) in the placebo group were receiving at least one concomitant medication at baseline (see Table 11). The most common medications at baseline were antipsychotics 46 (79.3%) (deutetrabenazine: 46 [79.3%] versus placebo: 51 [86.4%]), anti-depressants (deutetrabenazine: 33 [56.9%] versus placebo 29 (49.2%), and antiepileptics (deutetrabenazine: 17 [29.3%] versus placebo: 15 [25.4%].

During the trial, the use of concomitant medication did not change substantively as the number of patients using various CNS medications remained stable and balanced between treatment groups compared with baseline. There were small increases in each group compared with baseline in the number of patients using opioids (deutetrabenazine, 16 patients [27.6%]; placebo, 12 patients [20.3%]). Per my review, there were no significant differences in the use of other classes of concomitant medications between treatment groups.

Table 11: Summary of CNS-Active and Other Common (>20% of Patients)

Concomitant Medications Used at Baseline (Safety Population; N=117)

Therapeutic pharmacological subgroup Preferred term	deutetrabenazine	Placebo (N=59) n (%)	Total (N=117) n (%)
Any concomitant medication	58 (100)	57 (96.6)	115 (98.3)
Antipsychotics	46 (79.3)	51 (86.4)	97 (82.9)
Antidepressants	33 (56.9)	29 (49.2)	62 (53.0)
Antiepileptics	17 (29.3)	15 (25.4)	32 (27.4)
Anxiolytics	12 (20.7)	12 (20.3)	24 (20.5)
Hypnotics and sedatives	11 (19.0)	11 (18.6)	22 (18.8)
Opioids	10 (17.2)	10 (16.9)	20 (17.1)

Source: Study C-18 CSR (Table 14.1.8); page 66

Rescue Medication
There was no planned use of "rescue medication" during the trial.

Efficacy Results – Primary Endpoint

As described in more detail in *Analysis of Primary Efficacy Endpoint* in Section 7.0, the primary efficacy endpoint was the study was the change in AIMS (items 1 through 7) as assessed by blinded central video rating from Baseline (defined for each subject as the value from the Day 0 visit) to Week 12 using the mITT analysis set and analyzed by MMRM methods. As shown in Table 12: AIMS Scale: Change in AIMS Score from Baseline to Week 12 (mITT, N=113; MMRM), deutetrabenazine was statistically superior to placebo on the primary efficacy endpoint.

Table 12: AIMS Scale: Change in AIMS Score from Baseline to Week 12 (mITT, N=113; MMRM)

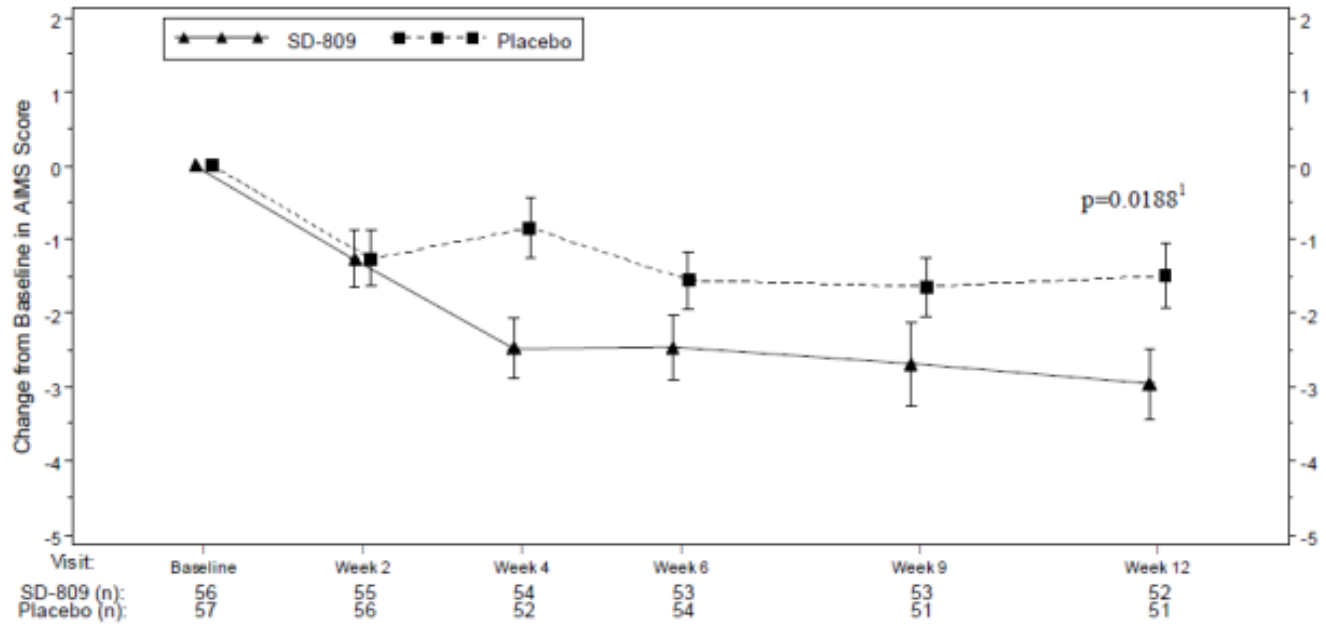
Visit	deutetrabenazine N=56	Placebo N=57	Difference in means (deutetrabenazine - placebo) and SE
N	56	57	--
Mean Baseline Score (SD*)	9.7 (4.14)	9.6 (3.78)	

AIMS total score change from baseline MMRM at Week 12, n	52	51	--
LS mean (SE)	-3.0 (0.45)	-1.6 (0.46)	-1.4 (0.60)
Minimum, Maximum	-16, 3	-9, 5	--
95% CI	-3.9, -2.1	-2.5, -0.7	-2.6, -0.2
p-value			**0.0188**

CI = confidence interval; LS mean = least-squares means; MMRM = mixed model repeated measures; SE = standard error; AIMS = Abnormal Involuntary Movement Scale; mITT=modified Intent-to-Treat; *Standard Deviation
Source: Statistical Review --CSR (Page 72)

Please refer to Figure 1 for a graph displaying the improvement in AIMS total dyskinesia score over time during the double-blind treatment period. Separation between the treatment groups was apparent at week 4 and maintained through week 12 (p=0.0188 at week 12).

Figure 1: Mean (SE) Change from Baseline in AIMS Score by Treatment and Study Visit (mITT Population; N=113)

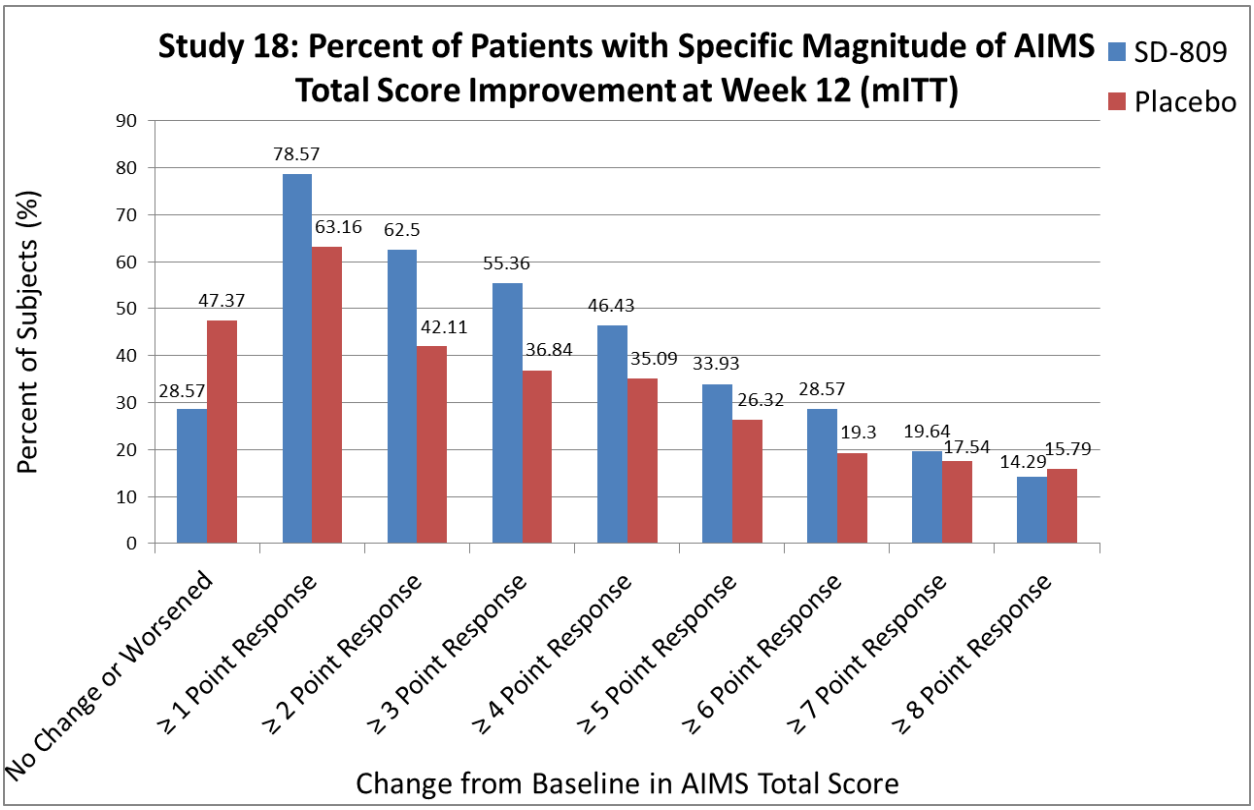


Source: CSR C-18, page 72

In order to better visualize the proportion of subjects who achieved various thresholds of AIMS score changes, Biometrics reviewer Dr. Semhar Ogbagaber prepared a response histogram Figure 2. Treatment with deutetrabenazine is associated with a consistently higher magnitude of AIMS Total Score Improvement at Week 12 (mITT) compared to placebo. Differences are

most apparent at point responses between 1 to 3 points.

Figure 2: Percent Response (AIMS Total Score) for Each Treatment Group at Week 12 by Response Threshold



Source: Statistical Review, page 23

The differential effects of deutetrabenazine compared to placebo in demographic subgroups and subpopulations were analyzed (Tables 13-16). However, it was difficult to derive any substantive conclusions based on the small sample size. Analysis by region did support the idea that US subjects were more responsive to treatment with deutetrabenazine compared to non-US subjects.

Table 13: Subgroup Analysis by Race: AIMS Total Score (mITT)

	Baseline	**LS◊ Mean Change from Baseline**	**LS◊ Mean Difference from**

						Placebo	
Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
White							
Placebo	42	9.40 (3.86)	38	-1.52	0.53	--	--
deutetrabenazine	37	10.24 (3.90)	35	-3.35	0.54	-1.83	0.73
Non-White							
Placebo	15	10.13 (3.64)	13	-2.37	1.31	--	--
deutetrabenazine	19	8.53 (4.44)	17	-2.94	1.16	-0.58	1.13

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Statistical Reviewer's Results

Table 14: Subgroup Analysis by Gender: AIMS Total Score (mITT)

	Baseline		**LS◊ Mean Change from Baseline**			**LS◊ Mean Difference from Placebo**	
Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
Men							
Placebo	26	8.04 (2.75)	22	-0.85	0.69	--	--
deutetrabenazine	28	8.68 (4.12)	25	-2.18	0.61	-1.33	0.73
Women							
Placebo	31	10.90 (4.07)	29	-2.19	0.66	--	--
deutetrabenazine	28	10.64 (3.98)	27	-3.74	0.67	-1.55	0.92

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Statistical Reviewer's Results

Table 15: Subgroup Analysis by Age: AIMS Total Score (mITT)

	Baseline		**LS◊ Mean Change from Baseline**			**LS◊ Mean Difference from Placebo**	
Treatment	N	Mean (SD*)	N	Mean	SE#	Mean	SE#

Group							
Age < 56							
Placebo	31	9.00 (4.06)	25	-1.01	0.61	--	--
deutetrabenazine	24	9.46 (4.01)	21	-2.56	0.60	-1.55	0.75
Age >= 56							
Placebo	32	10.31 (3.37)	26	-1.80	0.70	--	--
deutetrabenazine	26	9.81 (4.28)	31	-3.24	0.65	-1.44	0.92

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Statistical Reviewer's Results

Table 16: Subgroup Analysis by Region: AIMS Total Score (mITT)

	Baseline		**LS◊ Mean Change from Baseline**			**LS◊ Mean Difference from Placebo**	
Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
US							
Placebo	46	9.65 (3.89)	40	-1.71	0.53	--	--
deutetrabenazine	47	9.77 (4.28)	44	-3.25	0.49	-1.55	0.66
Non-US							
Placebo	11	9.36 (3.47)	11	-1.29	0.95	--	--
deutetrabenazine	9	9.11 (3.41)	8	-2.12	1.10	-0.82	1.39

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Reviewer's Results

Reviewer Comment: The differential effects of deutetrabenazine compared to placebo in demographic subgroups and subpopulations did not reveal any salient findings.

Data Quality and Integrity – Reviewers' Assessment

This reviewer did not have major concerns or questions about the quality and veracity of the data. OSI findings are summarized in Section 4.6.

Efficacy Results – Secondary and other relevant endpoints

Key Secondary Endpoints

The key secondary efficacy endpoint was the proportion of subjects who are a treatment success at Week 12 based on the CGIC. A treatment success was defined as Much or Very Much Improved on the CGIC at the Week 12 visit. The key secondary endpoints were tested hierarchically given the primary analysis was statistically significant ($p < 0.05$). However, SD809 failed to separate from placebo at the 5% level of significance on the first key secondary endpoint, CGIC ($p = 0.40$). All other key secondary endpoints were then considered only exploratory.

Exploratory endpoints:

A fair percentage of patients in each treatment group experienced treatment success according to the PGI-C. A higher percentage of patients experienced treatment success with deutetrabenazine (24 patients [42.9%]) than with placebo (17 patients [29.8%]), a difference that was not statistically significant ($p=0.149$).

Other secondary outcome analyses performed by the Applicant held less value due to the small sample size and because of statistical vulnerability due to the multiplicity of analyses performed.

6.2. C-23: Randomized, double-blind, placebo-controlled, fixed-dose study of deutetrabenazine for the treatment of tardive dyskinesia

6.2.1. Study Design

Trial Design

The overall treatment period was 12 weeks in duration (4 week titration period, 8 week maintenance period), followed by a 1-week washout period. Subjects were randomly assigned in a 1:1:1:1 ratio to receive one of three fixed-dose regimens of deutetrabenazine or placebo. The randomization was stratified by baseline use of dopamine receptor antagonists (currently taking versus not currently taking a dopamine receptor antagonist). Subjects underwent dose adjustment over the initial 4 weeks of treatment until the randomized dose was achieved. Investigators were allowed to determine whether a dose reduction (allowed once during maintenance) or suspension (allowed during dose escalation or maintenance) was necessary due to clinically significant AE's. All dose reductions during the study were managed in a blinded fashion through the IRT.

The trial was performed in the patient population intended for marketing deutetrabenazine. To participate, subjects had to have a clinical diagnosis of TD and had symptoms for at least 3 months prior to screening. The subjects TD symptoms must have been bothersome and/or cause functional impairment. The inclusion and exclusion criteria were appropriate given the objectives of the trial. Salient criteria are listed below.

Inclusion Criteria:

- Subject is between 18 and 80 years of age, inclusive.
- Subject has a history of using a dopamine receptor antagonist for at least 3 months (or 1 month in subjects 60 years of age and older). See Appendix 15.
- Subject has a clinical diagnosis of TD, and has had symptoms for at least 3 months prior to Screening.
- The subject's TD symptoms are bothersome to the subject or cause functional impairment.
- At the Screening and Baseline visits, the subject has: Moderate or severe abnormal movements as judged by the Investigator based on Item 8 of the AIMS AND
- A total motor AIMS score of ≥6 (based on Items 1 through 7) as assessed by the Principal Investigator. Note: A video recording of the AIMS assessment at Screening will be reviewed by a blinded central rater to confirm eligibility prior to randomization.
- For subjects with underlying psychiatric illness:
    - Subject is psychiatrically stable and has had no change in psychoactive medications (including, but not limited to neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for ≥30 days before Screening (45 days for antidepressants).
- Subjects on long-acting (depot) medications have been on stable therapy
    - (dose, frequency) for ≥3 months before Screening.
- Subject has a mental health provider who is aware of the subject's participation in the trial, and does not anticipate any changes to the subject's treatment regimen (drug, dose and frequency) over the next 3 months

Exclusion Criterion:

- Subject has received any of the following medications within 30 days of Screening or Baseline:
    - Tetrabenazine, reserpine, α-methyl-p-tyrosine (AMPT), botulinum toxin (within 3 months of Screening), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
    - Metoclopramide, promethazine, and prochlorperazine

    - Stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine,
    - lisdexamphetamine, etc.), or monoamine oxidase inhibitors (MAOIs)
    - Levodopa or dopamine agonists
- Subject has participated in any previous study of deutetrabenazine in which they received deutetrabenazine.
- Subject has a neurological condition other than TD that may interfere with assessing the severity of dyskinesias.
- Subject has a serious untreated or undertreated psychiatric illness at Screening or baseline.
- Subject has active suicidal ideation at Screening or Baseline.
- Subject has history of any of the following within 6 months of Screening:
    - Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on C-SSRS), irrespective of level of ambivalence at the time of suicidal thought
- A previous actual, interrupted or aborted suicide attempt
- Subject has a score ≥11 on the depression subscale of the Hospital Anxiety and
- Depression Scale (HADS) at Screening or Baseline.
- Subject is developmentally disabled or has evidence of dementia.
- Subject has an unstable or serious medical illness at Screening or Baseline.
- Subject has history (within 3 months) or presence of violent behavior.
- Subject has a QTcF value >450 ms (males) or >460 ms (females), or >480 ms (with right bundle branch block [RBBB]) on 12-lead ECG at Screening.
- Subject has a positive urine drug screen (for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, or opiates) at Screening or Baseline, except if subject is receiving a stable dose of a benzodiazepine.

As noted previously, the dose range of the investigational product, deutetrabenazine, was estimated using pK measurements of the reference listed product, Xenazine (tetrabenazine). Xenazine is labeled for an initial starting dose of 12.5 mg/d, increasing by 12.5 mg weekly based upon clinical response. The maximum recommended daily dose is 50 mg/d given in divided doses. The starting dose of 6 mg of deutetrabenazine provides an AUC of total (α+β)-HTBZ that is comparable to 12.5 mg of tetrabenazine (the approved starting dose for the treatment of chorea associated with HD), but with a lower peak concentration and reduced plasma fluctuation.

Deutetrabenazine and placebo tablets had been manufactured according to current Good Manufacturing Practices regulations. Deutetrabenazine tablets or placebo, were be supplied as 6, 9, 12, 15, and 18 mg tablets and were packaged in blister packs and labeled according to applicable regulatory guidelines. Placebo tablets for deutetrabenazine contained the same excipients as deutetrabenazine.

The study treatments dose levels for titration were as follows:

Table 17: Study C-23 Dose Titration Steps

	Treatment by Visit During Dose-Escalation Period			
Visit	Placebo	deutetrabenazine	deutetrabenazin	deutetrabenazine
Baseline	Placebo BID	6 mg BID	6 mg BID	6 mg BID
Week 1	Placebo BID	6 mg BID	9 mg BID	9 mg BID
Week 2	Placebo BID	6 mg BID	12 mg BID	12 mg BID
Week 3	Placebo BID	6 mg BID	12 mg BID	15 mg BID
Week 4	Placebo BID	6 mg BID	12 mg BID	18 mg BID

Assignment to treatment was based upon 1:1 randomization ratio through a web-based automated system. Patients were initially dosed at Visit 2 (Baseline).

During the treatment period the Applicant, investigators and their site personnel, and patients were blinded to treatment assignment. The active and placebo investigational product were identical in appearance and packaged in investigational product kits by an independent vendor according to the randomization code. The randomization was stratified by baseline use of dopamine receptor antagonists (currently taking versus not currently taking a dopamine receptor antagonist). As noted previously, randomization and stratification were performed through the Interactive Web Response System (IWRS).

Dose modifications were pre-specified for patients receiving a potent CYP2D6 inhibitor with a limit of 36 mg/d. The maximum dose was otherwise 48 mg/d. The goal of titration was to achieve an optimal level of dyskinesia control in which the patient is tolerating the treatment regimen or until the maximum permitted dose is reached. The dose of deutetrabenazine was increased on a weekly basis until there was adequate control of dyskinesia, the subject experienced a protocol defined clinically significant AE (defined as related to study drug and either a moderate or severe in intensity or meets the criteria for a SAE).

If a subject experiences a clinically significant AE, the Investigator used his or her judgment to determine if a dose reduction or suspension is necessary. Dose adjustments were made based on all available information including the subject's and caregiver's (if required) reports of AEs and dyskinesia control, the clinical assessment of safety and efficacy by the Investigator, and

information from rating scales. A dose reduction of 6 mg/day was allowed at a time. Discontinuations were reviewed by the study's medical monitor.

An Independent Data Monitoring Committee (IDMC) was established prior to study start, with an appropriate charter to direct decisions and communications, maintain a firewall to preserve the blinding and integrity of the study, and monitor the trial safety results at intervals throughout the study. The IDMC as comprised of at least two clinicians and a statistician not otherwise associated with the trial.

Table 18: Schedule of Assessments

	Screening		Dose Escalation				Maintenance				Follow Up		Uns
Week	Up to -4	[1]	1	2	3	4	5, 6,7	8	9, 10, 11	12/ ET[2]	13	[3]	
Visit window (days)			± 1	± 3							± 1	± 3	
Activity													
Clinic Visit[4]	X	X		X		X		X		X	X		X
Telephone Contact			X		X		X		X			X	
Informed Consent/Assent	X												
Inclusion/Exclusion Criteria	X	X											
Medical History/Demographics	X												
Vital Signs	X	X[5]		X		X[5]		X		X[5]	X		X
Weight	X	X								X			X[7]
Physical Examination	X	X[6]								X			X[6,7]
Complete Neurological Exam	X									X			X[7]
Height	X												
12-lead ECG	X	X		X		X		X		X			X[7]
Chemistry/Hematology/UA	X	X						X		X			X[7]
Urine drug screen	X	X											X[7]
Randomization via IRT[8]		X											
Blinded CYP2D6 Genotype		X											
Pregnancy Test/FSH[9]	S	U											X[7]
HBsAg/Prothrombin time (INR)	X												X[7]
Provide diary card for next visit						X		X					X[7]
Blood sampling for deutetrabenazine and								[10]		[10,1]			[13]
AIMS	X	X		X		X		X		X			X[7]
Video recording of AIMS[11]	X	X		X		X		X		X			X[7]
UPDRS – III (motor)	X	X		X		X		X		X	X		X[7]
BARS		X		X		X		X		X	X		X[7]
HADS	X	X		X		X		X		X	X		X
C-SSRS[12]	X	X		X		X		X		X	X		X
ESS		X		X		X		X		X	X		X[7]
CGIC				X		X		X		X			X[7]
PGIC						X		X		X			X[7]

MoCA		X						X		X			X[7]
Modified CDQ-24		X								X			X[7]
Dispense Study Drug		X		X		X		X					X[7]
Assess Study Drug Accountability/Compliance				X		X		X		X			X[7]
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; CGIC, Clinical Global Impression of Change; C-SSRS, Columbia Suicidality Severity Rating Scale; ECG, electrocardiogram; ESS Epworth Sleepiness Scale; FSH, follicle stimulating hormone; HADS, Hospital Anxiety and Depression Scale; HBsAg, hepatitis B surface antigen; INR, International Normalized Ratio; IRT, Interactive Response Technology; MoCA, Montreal Cognitive Assessment; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; SAE, serious adverse event; UA, urinalysis; UPDRS, Unified Parkinson's Disease Rating Scale.

Source: Study Protocol C-23, page 11

A population pharmacokinetic analysis was performed using data from all subjects to examine the pharmacokinetics of deutetrabenazine and to explore the potential effect of various covariates on the pharmacokinetics of deutetrabenazine and to provide information relating to subject compliance with drug and, if possible, explore the relationship between pharmacokinetics and change in AIMS score. Procedures were in place to evaluate drug accountability, dispensing and return. Treatment compliance was determined by pill count performed during the patient visit. A patient was considered compliant if they had taken over 80%-105% of the expected tablets of study drug.

Patients receiving strong CYP2D6 inhibitors (bupropion, fluoxetine, paroxetine, or quinidine) were limited to a maximum of 36 mg/d of deutetrabenazine. A list of prohibited drugs was provided in the protocol, as was a list of prohibited QTc prolonging drugs.

Subjects who fully completed the study participated in a screening period, a 12-week placebo-controlled treatment period, and a 1 week washout period before initiation of a 104-week open label extension period. Subjects not participating in the long-term safety study of deutetrabenazine will had a follow-up telephone contact three weeks after the Week 13 visit Subjects were free to discontinue participation at any time. Investigators were required to withdraw subjects if the type, frequency, or severity of any AE became unacceptable or intolerable or if a subject exhibited active suicidal ideation with at least some intent to act, or if the subject was lost to follow-up, confirmed to be pregnant, or was unable to tolerate the treatment dose after a one-time dose reduction. If subjects withdrew prematurely from the study, the reason for withdrawal was recorded and subjects underwent early termination assessments (see Procedures and Schedule above). It was considered crucial to obtain follow-up data for subjects withdrawn for safety-related reasons.

Study Endpoints

The primary efficacy assessment measure was the AIMS, which is described under Study Endpoints in Section 7.1. Similar to the previous study, the AIMS was digitally video-recorded using a standard protocol at Screening, Baseline, and Weeks 2, 4, 8, and 12. The videos from Screening, Baseline, and Weeks 2, 4, 8, and 12 were independently reviewed and rated by a blinded central rater(s) who is an expert in movement disorders. The Screening video was centrally reviewed and rated prior to randomization to ensure subject eligibility based on confirmation of a total motor AIMS score ≥6.

For evaluation of the primary endpoint, videos were recorded and submitted to the central rater in a blinded manner with respect to visit number and date of recording. A detailed video review manual was established to ensure appropriate and consistent review procedures by the central video raters.

Similar to study C-18, The CGI-C was specified as a secondary outcome measure and assessed by site investigators at the end of Week 2, Week 4, Week 8 and the Week 12/early termination visit. The protocol specified that, if possible, the same person should administer and rate the scale at all time points. As noted previously, this endpoint is more difficult to interpret, as the investigator rater was not blinded to the independent AIMS raters' authorization for and history of treatment dose increases, which could bias the assessment of global TD improvement.

Secondary analyses were conducted in a hierarchical order. The proportion of subjects who are a treatment success at Week 12, based on the CGIC, was first analyzed using a logistic regression model with treatment group and baseline use of dopamine receptor antagonists as factors. The comparison between 36 mg and placebo was not statistically significant such that subsequent comparisons were exploratory rather than confirmatory.

Additional exploratory efficacy assessments administered in this study were similar to study C-18. This included PGI-C, SDQ, modified CDQ-24, BARS, HADS, MoCA, UPDRS, ESS and C-SSRS.

Reviewer Comment: The statistical hierarchy was very stringent and limiting. The 24 mg and 12 mg a day cohorts would be vulnerable to not statistically separating in the event the 36 mg cohort failed to separate from placebo based on the pre-specified treatment success comparison. Also, no 48 mg/day cohort was tested in the C-23 study although the dosage is listed in labeling.

Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for this study was dated July 8, 2014. The SAP defined three analysis sets for this study**:**

1. Intent-to-Treat Population: The Intent-to-Treat (ITT) Population included all randomized subjects. In analyses and summaries based on the ITT Population, subjects were included in the treatment group to which they were randomized, regardless of the treatment that was actually received.

2. Modified Intent-to-Treat Population: The Modified Intent-to-Treat (mITT) Population included all subjects in the ITT Population who met the inclusion criterion of a baseline AIMS score ≥6 (as assessed by central video rating), were randomized to treatment, received study drug, and had at least one post-baseline AIMS assessment. The primary analysis of efficacy was completed in the mITT Population.

3. Per Protocol Population: The Per Protocol Population included subjects who had no major protocol deviations and had a non-missing AIMS total score at Week 8 or Week 12. For subjects treated with deutetrabenazine, corresponding measurable levels of active metabolites must be present at the same visit as the non-missing AIMS total score at Week 8 or Week 12 for the subject to be included in the Per Protocol Population.

4. Safety Population: The Safety Population included all subjects who were administered any study drug. Subjects who are assigned a subject number but withdrew prior to dosing were not included in the Safety Population.

Handling of Missing Data:

For endpoints analyzed using MMRM, all available data from the subject were used. For CGIC responder status, subjects whose status at Week 12 is not known, as well as subjects who were not Much or Very Much Improved at the Week 12 visit, were considered to be treatment failures.

For proportion endpoints based on CGIC and PGIC, patients with missing data at each visit were classified as a treatment failure for the analyses. For the proportion endpoint based on 50% or greater reduction in AIMS score, patients with missing data at each visit were classified as not having a reduction for the analysis. For the proportion endpoint based on responder definitions for the AIMS score, patients with missing data at each visit were classified as non-responders for the analysis.

With respect to AIMS assessed by the site rating, if a response to one question was missing, the missing response was replaced with the average of the remaining responses. If responses to two or more questions were missing, the missing responses were not replaced and the total score was set to missing.

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint for this study was the change in total motor AIMS score as assessed by blinded central video rating from baseline (defined for each patient as the value from the day 0 visit) to week 12. The primary analysis compared the change in total motor AIMS score from baseline to week 12 between the deutetrabenazine 36 mg/day group and the placebo group using a 2-sided test at the alpha=0.05 level of significance and was carried out using a linear MMRM with the change in the total motor AIMS score as the dependent variable. The model included fixed effects for treatment group, visit (four levels: weeks 2, 4, 8, and 12), the treatment group-by-visit interaction, baseline total motor AIMS score, and the baseline use of DRAs. The unstructured covariance model was used. The Satterthwaite method was used to calculate the denominator. There were multiple sensitivity analyses that are outlined in the Statistical Analysis Plan.

Analysis of the Key Secondary Endpoint:

Key secondary efficacy endpoints were tested according to the hierarchical method as follows:

1. The proportion of patients who were a treatment success based on the CGIC at week 12, defined as Much Improved or Very Much Improved, was analyzed using a comparison between deutetrabenazine 36 mg/day and placebo was tested.
2. The change in the total motor AIMS score from baseline to week 12 was tested for
3. Deutetrabenazine 24 mg/day compared with placebo using the same model as for the primary analysis.
4. The proportion of patients who were a treatment success based on the CGIC at week 12 was tested for deutetrabenazine 24 mg/day compared with placebo using the same type of model as for the first key secondary efficacy endpoint (CGIC).
5. The change in the total motor AIMS score from baseline to week 12 was tested for deutetrabenazine 12 mg/day compared with placebo using the same type of model as for the primary analysis.
6. The proportion of patients who were a treatment success based on the CGIC at week 12 was tested for deutetrabenazine 12 mg/day compared with placebo using the same type of model as for the CGIC.

For CGIC tests, the Mantel-Haenszel estimate of common odds ratio, 95% confidence interval (CI) for the common odds ratio, and CMH test p-value for the comparisons (12, 24, and 36 mg/day versus placebo) were presented at each visit. Ninety-five percent CIs around the proportion of treatment successes were calculated with the Wilson (score) confidence limits for the binomial proportion by treatment group. If any of the expected cell counts were less than 5, exact Clopper-Pearson confidence limits were used for the binomial proportion.

The proportion of patients who were a treatment success, based on the CGIC, at weeks 2, 4, 8, and 12 was summarized using descriptive statistics for all treatment groups. In addition, the

CGIC ratings at each visit was summarized as categorical data using descriptive statistics for all the treatment groups There were multiple sensitivity analyses that are outlined in the Statistical Analysis Plan.

Additional Secondary Analyses

The following additional secondary efficacy endpoints were analyzed:

- The change in the mCDQ-24 score from baseline to week 12.
- The proportion of patients who were a treatment success at week 12, based on the PGIC. A treatment success was defined as Much Improved or Very Much Improved on the PGIC at the week 12 visit.
- The proportion of patients who had a 50% or greater reduction in AIMS score from baseline to week 12.
- The percent change in AIMS score from baseline to week 12.
- The cumulative proportion of responders based on the change in AIMS score from baseline to week 12, ranging from a 10% improvement from baseline to a 90% improvement from baseline in steps of 10 percentage points.

No interim analysis of the trial was planned or performed. Please refer to the Biostatistics review for a detailed evaluation of the Applicant's statistical analyses.

Protocol Amendments

There were two protocol amendments all of which involved minor protocol clarifications. There were no substantive changes made to the original protocol.

Data Quality and Integrity: Applicant's Assurance

This reviewer did not have major concerns or questions about the quality and veracity of the data. OSI findings are summarized in Section 4.6.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant attests that this study was conducted in accordance with accepted practices for the protection of human subjects, use of institutional review boards and independent ethics committees, and adherence to Good Clinical Practice (GCP). All clinical studies were performed under the Applicant's IND.

Financial Disclosure

The financial disclosures by clinical investigators (Form 3454) were reviewed for all investigators in all covered clinical studies (C-18, C-20 and C-23). Five investigators (b) (6) participated in financial arrangements or held financial interests that were required to be disclosed. However, The Applicant placed into effect controls (i.e., randomized, double-blind study design) that appropriately mitigated any potential conflict of interest bias.

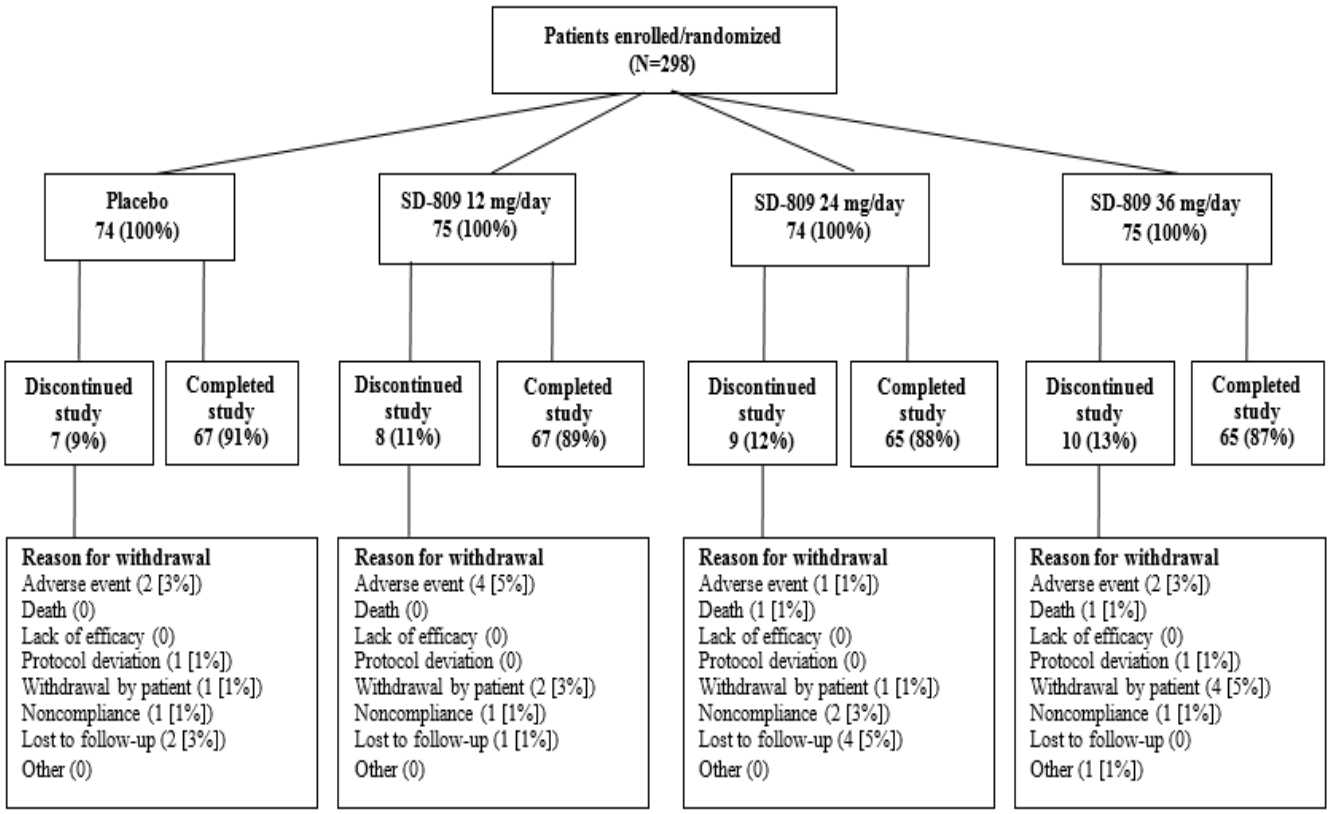
Patient Disposition

A total of 298 patients with TD were enrolled and randomly assigned to treatment with deutetrabenazine 12, 24, and 36 mg/day and placebo (75, 74, 75, and 74 patients, respectively) and were included in the ITT Population. Five of the 298 randomized patients were not treated because they withdrew prior to dosing. They included 3 patients in the deutetrabenazine group (1 [1%] patient in each of the 12, 24, and 36 mg/day groups) and two (3%) patients in the placebo group (see Figure 3).

The proportion of patients who completed the study (at least 12 weeks of double-blind treatment) was similar among treatment groups: 67 (89%), 65 (88%), and 65 (87%) patients in the deutetrabenazine 12, 24, and 36 mg/day groups, respectively, and 67 (91%) patients in the placebo group. Two patients died during the study, one (1%) patient in each of deutetrabenazine 24 and 36 mg/day groups.

A total of 222 patients were included in the pre-specified mITT Population: 60, 49, and 55 patients for the deutetrabenazine 12, 24, and 36 mg/day groups, respectively, and 58 patients in the placebo group. Please see Figure 3 for a summary of the Patient Disposition. For the mITT Population, 206 of 222 (93%) patients completed at least 12 weeks of double-blind treatment; this included 54 (90%), 45 (92%), and 52 (95%) patients in the deutetrabenazine 12, 24, and 36 mg/day groups, respectively, and 55 (95%) patients in the placebo group. A total of 16 (7%) patients discontinued from the study during the treatment period. Discontinuation rates ranged from 5% to 10% in the deutetrabenazine groups and were similar to the placebo group (5%). Overall, the most frequent reason for study discontinuation was withdrawal of consent by the patient (6 [3%] patients) followed by adverse events (5 [2%] patients).

Figure 3: Study C-23- Patient Disposition (ITT Population)



Source: CSR C-23, page 81

Protocol Violations/Deviations

Major protocol violations were specifically highlighted in the clinical study report. Overall, 18 (6%) patients were not adherent to treatment, and 7 (2%) patients took a prohibited concomitant medication. Of these 7 patients, 3 were in the deutetrabenazine 36 mg/day group, two were in the deutetrabenazine 24 mg/day group, and one was in the deutetrabenazine 12 mg/day group. Two patients treated with deutetrabenazine received prohibited concomitant medication treatment with dopamine agonists, which have the potential to blunt the treatment effect. However, post-hoc statistical analysis supported the idea that prohibited concomitant medications taken by other patients treated with deutetrabenazine or placebo were not anticipated to affect outcomes.

Ninety-five deviations from the inclusion/exclusion criteria were reported for 75 (25%) patients in the ITT Population, with the most common deviations being hepatic impairment (which also included missed prothrombin time/INR tests [24 deviations]), missing laboratory values (20 deviations, 10 of which were for missing FSH values at screening), and positive UDS (15 deviations). Overall, 71 (24%) patients missed or had an incorrect procedure or assessment and

107 (36%) missed or had an out-of-window visit. Study medication compliance deviations were reported by 91 (31%) patients. Seven (2%) patients received an incorrect study drug, 15 (5%) patients received prohibited concomitant medications or procedures, 6 (2%) patients did not provide appropriate written informed consent, and 34 (11%) patients deviated from the protocol for other reasons.

Reviewer Comment:

Protocol deviations were roughly balanced among the treatment groups. The amount of subjects with medication compliance deviations was sizeable but not unexpected given the duration of the trial. While a low percentage (2%) of subjects received incorrect study drug, it is surprising given use of the IVRS system. Collectively, these deviations likely did not impact the overall efficacy or safety findings.

Table of Demographic Characteristics

Please see Table 19 for a tabulation of demographic characteristics for the safety population sample. Both sexes were reasonably well represented in this larger study. The majority of subjects were under 65 years old and the mean age was around 56 years old overall. This is representative of the target population given middle aged to elderly patients frequently have a longer duration of total antipsychotic exposure as well as exposure to typical antipsychotics compared to younger patients. Patients of African-American and Caucasian races were well-represented in the study sample. However, there were no subjects of Asian ethnicity that participated in the study. The demographics in the mITT Population were very similar to those in the Safety Population: the mean age was 57.0 years, 52% of the patients were female, and 79% were white.

Table 19: Study C-23-Specific Baseline Characteristic (Safety Population; N=293)

Demographic variables	Placebo (N=72)	deutetrabenazine	deutetrabenazine	deutetrabenazine	Total (N=293)
Age, years					
n	72	74	73	74	293
Mean (SE)	54.6 (1.42)	57.0 (1.16)	55.6 (1.33)	58.3 (1.34)	56.4
Gender, n (%)					
Female	37 (51)	42 (57)	41 (56)	42 (57)	162 (55)
Male	35 (49)	32 (43)	32 (44)	32 (43)	131 (45)
Race, n (%)					
White	59 (82)	58 (78)	54 (74)	61 (82)	232 (79)

Black	12 (17)	15 (20)	19 (26)	10 (14)	56 (19)
Asian	0	0	0	0	0
American Indian or Alaskan Native	1 (1)	1 (1)	0	2 (3)	4 (1)
Native Hawaiian or Pacific Islander	0	0	0	0	0
Other	0	0	0	1 (<1)	1 (<1)
Ethnicity, n (%)					
Hispanic or Latino	7 (10)	6 (8)	3 (4)	7 (9)	23 (8)
Not Hispanic or Latino	64 (89)	64 (86)	69 (95)	65 (88)	262 (89)
Not reported	0	3 (4)	1 (1)	1 (1)	5 (2)
Unknown	1 (1)	1 (1)	0	1 (1)	3 (1)
Weight, kg					
n	72	74	73	74	293
Mean (SE)	82.8 (2.18)	80.8 (2.44)	86.8 (2.20)	78.5 (2.04)	82.2 (1.12)
Height, cm					
n	72	74	73	74	293
Mean (SE)	168.3 (1.09)	167.7 (1.24)	168.7 (1.10)	167.6 (1.23)	168.1 (0.58)
BMI, kg/m^2					
n	72	74	73	74	293
Mean(SE)	29.18 (0.722)	28.69 (0.792)	30.64 (0.822)	27.99 (0.718)	29.12 (0.385)
Education, n (%)					
≤12 years	40 (56)	44 (59)	44 (60)	39 (53)	167 (57)
>12 years	32 (44)	30 (41)	29 (40)	35 (47)	126 (43)

Source: CSR C-23 (page 86)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Please see Table 20 for a summary of subject baseline characteristic. The treatment groups were reasonably well balanced across the examined baseline parameters. One notable exception was the baseline total AIMS score for the deutetrabenazine 24 mg/day treatment group was slightly lower (7.7) compared baseline scores of the other treatment groups (~8.5). The number of years since initial TD diagnosis had a wide range but was comparable between treatment groups; this is important as the duration of TD may moderate the treatment effect. Background comorbid illnesses were overwhelmingly psychiatric disorders in both treatment groups. As a whole, the baseline characteristics of the study population were roughly congruent

with the expected US target population.

Table 20: Study-Specific Baseline Characteristic (Safety Population; N=293)

Demographic variables	Placebo (N=72)	deutetrabenazine	deutetrabenazine	deutetrabenazine	Total (N=293)
Time since TD diagnosis, years					
n	72	74	73	74	293
Mean (SE)	6.03 (0.631)	5.49 (0.631)	4.98 (0.706)	5.89 (0.621)	5.60 (0.323)
Baseline total motor AIMS score					
n	72	74	73	74	293
Mean (SE)	8.5 (0.39)	8.6 (0.36)	7.7 (0.41)	8.6 (0.45)	8.4 (0.20)
Baseline mCDQ-24 total score					
n	72	73	73	74	292
Mean (SE)	40.5 (2.34)	37.2 (2.36)	34.4 (2.29)	34.9 (2.13)	36.7 (1.14)
Baseline use of a DRA, n (%)					
Yes	56 (78)	56 (76)	57 (78)	53 (72)	222 (76)
No	16 (22)	18 (24)	16 (22)	21 (28)	71 (24)
Background comorbid illness, n (%)					
Schizophrenia	31 (43)	32 (43)	42 (58)	40 (54)	145 (49)
Schizoaffective disorder	11 (15)	8 (11)	7 (10)	4 (5)	30 (10)
Bipolar disorder	17 (24)	15 (20)	7 (10)	12 (16)	51 (17)
Depression	11 (15)	17 (23)	11 (15)	16 (22)	55 (19)
Other	2 (3)	2 (3)	6 (8)	2 (3)	12 (4)
Impaired CYP2D6 function, n (%)					
Yes	14 (19)	12 (16)	10 (14)	14 (19)	50 (17)
No	58 (81)	61 (82)	62 (85)	60 (81)	241 (82)
Missing	0	1 (1)	1 (1)	0	2 (<1)

Source: CSR C-23, page 88

Reviewer Comment: The baseline total AIMS score for the deutetrabenazine 24 mg/day group in the mITT population was 9.4 and comparable to other treatment groups (average of 9.6). Given

the primary efficacy analysis was based on the mITT population, it is unlikely the initial misbalance seen in the baseline safety population would impact efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At least one concomitant medication Table 21 was present at baseline in 288 (98%) patients: 218 (99%) patients in the overall deutetrabenazine group and 70 (97%) patients in the placebo group. Overall, 230 (78%) patients were receiving an antipsychotic medication, and use was comparable across the dose groups.

Table 21: Summary of CNS-Active Concomitant Medications Present at Baseline by Treatment Group (Safety Population; N=293)

Therapeutic class, n (%)	Placebo (N=72)	deutetrabenazine	deutetrabenazine	deutetrabenazine	Total (N=293)
Antipsychotics	57 (79)	57 (77)	61 (84)	55 (74)	230 (78)
Antidepressants	35 (49)	46 (62)	37 (51)	39 (53)	157 (54)
Antiepileptics	25 (35)	27 (36)	16 (22)	19 (26)	87 (30)
Anxiolytics	15 (21)	16 (22)	18 (25)	21 (28)	70 (24)

Source: CSR C-23 page 90

Initiation or change of antipsychotics treatment occurred most often in the placebo group (7%) compared to the deutetrabenazine groups (0% to 3%) and involved quetiapine, lurasidone, olanzapine, haloperidol, paliperidone, perphenazine, and ziprasidone. Interestingly, of nine patients experiencing changes in their antipsychotic medications (two in the deutetrabenazine 24 mg/day group, two in the 36 mg/day group, and five in the placebo group), most experienced an increase in the dose of antipsychotic medication and also a reduction in AIMS score from baseline to week 12. Table 21 provides a summary of CNS concomitant medications started or changed post-baseline.

Table 22: Summary of CNS-Active Concomitant Medications Started or Changed Post baseline by Treatment Group (Safety Population; N=293)

Therapeutic class, n (%)	Placebo (N=72)	deutetrabenazine	deutetrabenazine	deutetrabenazine	Total (N=293)

Antidepressants	2 (3)	2 (3)	4 (5)	3 (4)	11 (4)
Antiepileptics	1 (1)	1 (1)	0	0	2 (<1)
Antipsychotics	5 (7)	0	2 (3)	2 (3)	9 (3)
Anxiolytics	1 (1)	2 (3)	0	2 (3)	5 (2)

Source: CSR C-23 page 90

Reviewer Comment: Changes in CNS active medications were comparable among the study groups.

Treatment compliance

Treatment compliance with study medication was high, with 94% of all patients ≥80% to 105% compliant and a mean compliance rate of 97.60%. Table 23 summarizes drug compliance by treatment group. Rates of compliance were similar among all the groups with only a small percentage of subjects reporting < 80% drug compliance.

Table 23: Study Drug Compliance by Treatment Group (Safety Population; N=293)

Variable Statistic	Placebo (N=72)	12 mg/day (N=74)	24 mg/day (N=73)	36 mg/day (N=74)	All deutetrab	Total (N=293)
Categorical Study Drug Compliance, n (%)						
<80%	2 (3)	4 (5)	3 (4)	2 (3)	9 (4)	11 (4)
≥80% to 105%	68 (94)	70 (95)	67 (92)	70 (95)	207 (94)	275 (94)
>105%	2 (3)	0	3 (4)	2 (3)	5 (2)	7 (2)
Study Drug Compliance, %						
n	72	74	73	74	221	293
Mean (SE)	98.62 (0.748)	95.48 (1.757)	98.37 1.049)	97.96 (0.963)	97.26 (0.756)	97.60 (0.600)

Source: CSR C-23 page 92

Efficacy Results - Primary Endpoint

As described in more detail in *Analysis of Primary Efficacy Endpoint, t*he primary efficacy endpoint was the study was the change in AIMS (items 1 through 7) as assessed by blinded central video rating from Baseline (defined for each subject as the value from the Day 0 visit) to Week 12 using the mITT analysis set and analyzed by MMRM methods. The mITT Population (N=222) included all patients in the ITT Population with a baseline AIMS score ≥6 as assessed by

central video rating, were randomized to treatment, received study drug, and had at least one post baseline AIMS assessment.

The primary efficacy endpoint, the change in total motor AIMS score from baseline to week 12 with deutetrabenazine 36 mg, was analyzed for the mITT Population. At week 12, the primary endpoint was met with deutetrabenazine 36 mg/day resulting in a significantly greater reduction from baseline in LS mean (SE) total motor AIMS score than placebo (-3.3 [0.42] versus -1.4 [0.41], respectively; Table 18), yielding a treatment effect (95% CI) of -1.9 (-3.09, -0.79; p=0.001). At week 12, treatment with deutetrabenazine 24 mg/day resulted in a greater reduction from baseline in LS mean (SE) total motor AIMS score than placebo (-3.2 [0.45] versus -1.4 [0.41]), yielding a treatment effect (95% CI) of -1.8 (-3.00, -0.63; p=0.003). However, while deutetrabenazine 12 mg/day resulted in a greater reduction from baseline in LS mean (SE) total motor AIMS score than placebo (2.1 [0.42] versus 1.4 [0.41]), it was about 1 point less than the treatment effect seen at the higher doses. See Table 24 for complete results.

Due to the hierarchical statistical testing approach, the AIMS results at 12 mg and 24 mg were considered exploratory as the CGIC at week 12 for deutetrabenazine 36 mg/day was not statistically significant.

Table 24: Abnormal Involuntary Movement Scale: Change in Total Motor AIMS Score from Baseline to Week 12 (mITT Population; N=222)

Statistic	Placebo (N=58)	deutetrabenazine	deutetrabenazine	deutetrabenazine
N	56	53	45	52
LS mean (SE)	-1.4 (0.41)	-2.1 (0.42)	-3.2 (0.45)	-3.3 (0.42)
LS mean difference (deutetrabenazine –	--	-0.7	-1.8	-1.9
95% CI	--	-1.84, 0.42	-3.00, -0.63	-3.09, -0.79
p-value	--	0.217	0.003	0.001

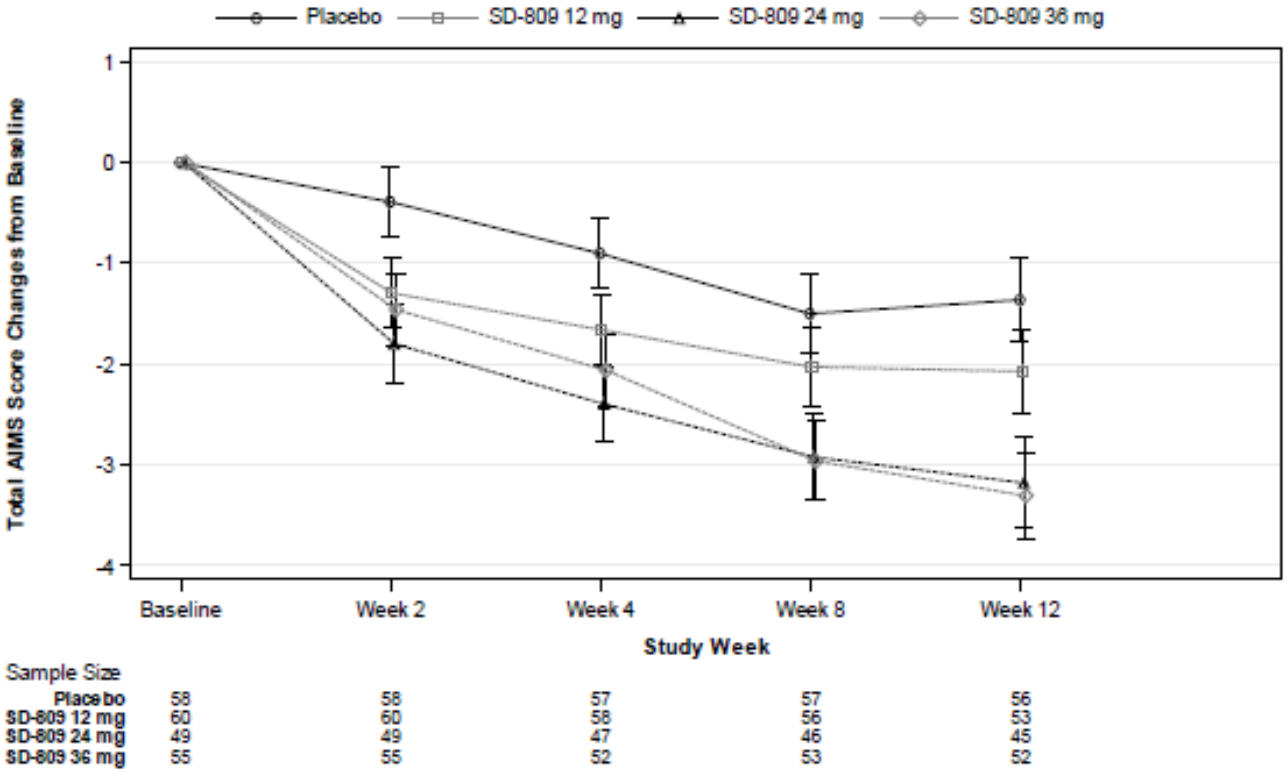
Source: CSR C-23 (Page 93)

Reviewer Comment:

While the use of a hierarchical testing approach led to the AIMS results at the 12 and 24mg/day doses to be considered exploratory findings, the differential treatment effect seen with the use of deutetrabenazine 24 mg/day appears robust when compared to placebo. Consequently, it appears that both 24 mg/day and 36 mg/day are doses that would lead to statistically significant reductions in total motor AIMS score compared to placebo.

Please refer to Figure 4 for a graph displaying the improvement in AIMS total dyskinesia score over time during the double-blind treatment period. Statistically significant differences among two treatment groups (24 mg/day and 36 mg/day) and placebo were apparent at week 2. This persisted throughout the duration of the study.

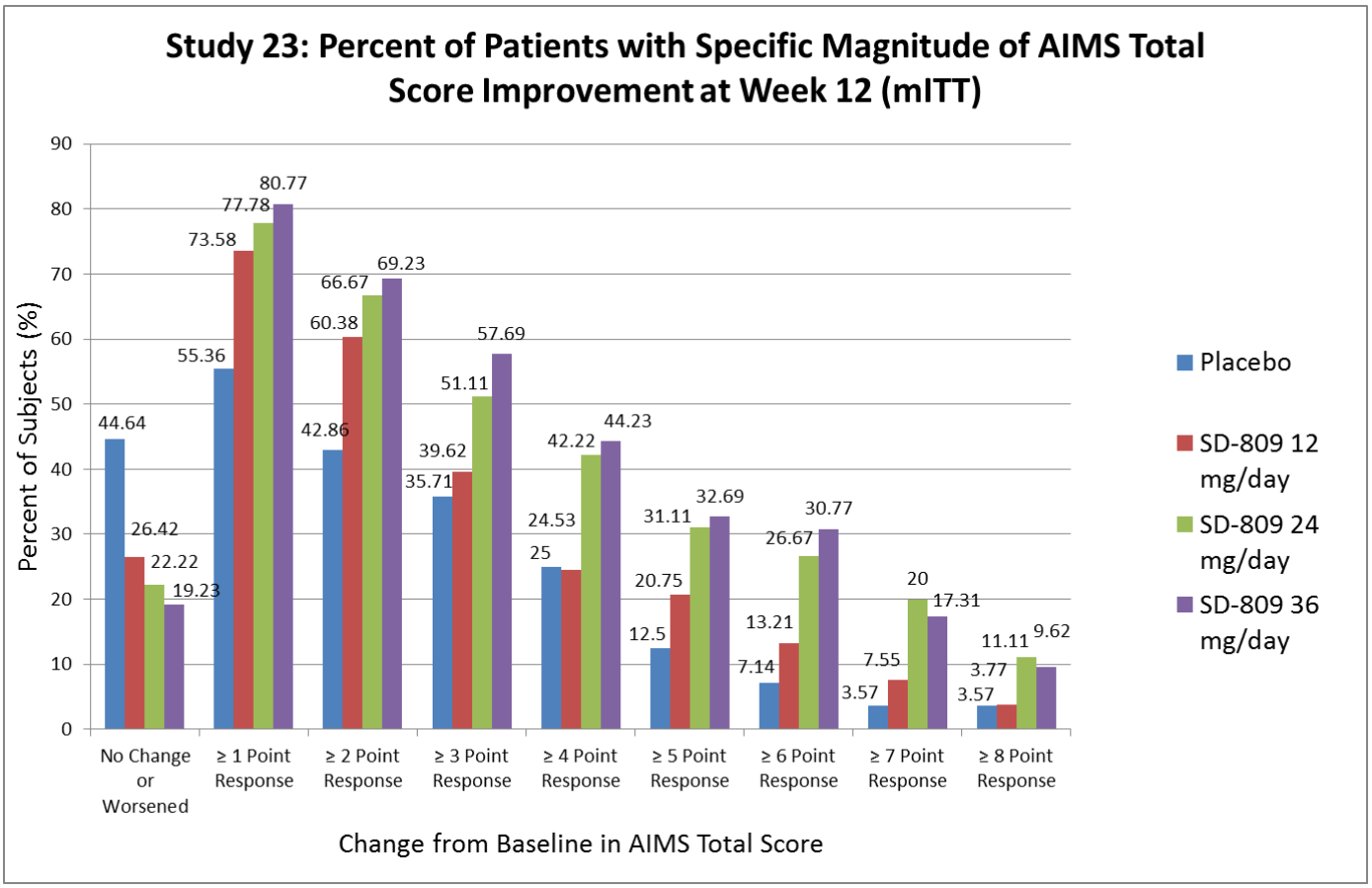
Figure 4: Least Squares Mean (SE) of Total Motor AIMS Score Changes from Baseline to Each Visit by Treatment Group (mITT Population; N=222)



Source: CSR C-23, page 95

In order to better visualize the proportion of subjects who achieved various thresholds of AIMS score changes, Biometrics reviewer Dr. Semhar Ogbagaber prepared a response histogram Figure 5. Treatment with deutetrabenazine is associated with a consistently higher magnitude of AIMS Total Score Improvement at Week 12 (mITT) compared to placebo. Differences between deutetrabenazine (24 and 36 mg/day) and placebo are most apparent at point responses between 1 to 3 points.

Figure 5: Percent Response (AIMS Total Score) for Each Treatment Group at Week 12 by Response Threshold



Source: Statistical Reviewer's Results page 18

Subgroup Analysis

The differential effects of deutetrabenazine compared to placebo in demographic subgroups and subpopulations were analyzed (Tables 25-28). However, it was difficult to derive any substantive conclusions based on the small sample size among various treatment groups. Analysis by race, gender and age did not reveal any specific findings (dose dependent or differential effects). Furthermore, results of a sensitivity analysis of treatment-by-region (US versus EU) interaction performed for the change in AIMS score at week 12 found no meaningful difference in treatment effect between the US and EU for any group.

Table 25: Subgroup Analysis by Race: AIMS Total Score (mITT)

	Baseline	LS◊ Mean Change from Baseline	LS◊ Mean Difference from Placebo

Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
White							
Placebo	49	9.49 (2.72)	47	-1.26	0.45	--	--
deutetrabenazine 12 mg/day	46	9.65 (2.53)	41	-1.99	04.6	-0.74	0.63
deutetrabenazine 24 mg/day	36	9.28 (2.91)	33	-3.29	0.52	-2.03	0.68
deutetrabenazine 36 mg/day	45	10.20 (3.33)	43	-3.40	0.46	2.14	0.63
Non-White							
Placebo	9	9.33 (2.78)	9	-1.85	1.10	--	--
deutetrabenazine 12 mg/day	14	9.50 (1.99)	12	-2.27	0.97	-0.42	1.38
deutetrabenazine 24 mg/day	13	9.62 (3.10)	12	-2.76	1.05	-0.90	1.41
deutetrabenazine 36 mg/day	10	9.40 (2.67)	9	-2.99	1.11	-1.14	1.48

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Statistical Reviewer's Results page 20

Table 26: Subgroup Analysis by Race: AIMS Total Score (mITT)

	Baseline		**LS◊ Mean Change from Baseline**			**LS◊ Mean Difference from Placebo**	
Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
Men							
Placebo	31	9.74 (2.54)	30	-1.80	0.61	--	--
deutetrabenazine 12 mg/day	28	9.21 (2.02)	24	-2.26	0.67	-0.46	0.87
deutetrabenazine 24 mg/day	24	9.71 (2.68)	21	-3.29	0.71	-1.49	0.90
deutetrabenazine 36 mg/day	23	10.00 (2.98)	20	-2.98	0.71	-1.19	0.92
Women							
Placebo	27	9.15 (2.90)	26	-0.89	0.58	--	--
deutetrabenazine 12 mg/day	32	9.97 (2.67)	29	-2.04	0.53	-1.07	0.77
deutetrabenazine 24 mg/day	25	9.04 (3.18)	24	-3.02	0.60	-2.13	0.81
deutetrabenazine 36 mg/day	32	10.09 (3.41)	32	-3.56	0.52	-2.66	0.77

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Statistical Reviewer's Results page 22

Table 27: Subgroup Analysis by Age: AIMS Total Score (mITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
Age < 58							
Placebo	31	9.61 (2.68)	29	-1.83	0.54	--	--
deutetrabenazine 12 mg/day	29	9.55 (2.16)	24	-1.77	0.57	0.066	0.73
deutetrabenazine 24 mg/day	23	8.78 (2.79)	20	-3.35	0.63	-1.52	0.78
deutetrabenazine 36 mg/day	23	10.65 (3.16)	22	-2.62	0.59	-0.78	0.77
Age > = 58							
Placebo	27	9.30 (2.78)	27	-0.36	0.60	--	--
deutetrabenazine 12 mg/day	31	9.68 (2.64)	29	-2.07	0.57	-1.71	0.82
deutetrabenazine 24 mg/day	26	9.88 (3.01)	25	-2.95	0.62	-2.59	0.86
deutetrabenazine 36 mg/day	32	9.62 (3.23)	30	-3.63	0.56	-3.27	0.82

*Standard Deviation, #Standard Error, ◊Least Squares
Source: Statistical Reviewer's Results page 23

Table 28: Subgroup Analysis by Age: AIMS Total Score (mITT)

	Baseline		LS◊ Mean Change from Baseline			LS◊ Mean Difference from Placebo	
Treatment Group	N	Mean (SD*)	N	Mean	SE#	Mean	SE#
US							
Placebo	30	9.57 (2.60)	28	-1.17	0.58	--	--
deutetrabenazine 12 mg/day	37	9.47 (2.32)	32	-2.12	0.55	-0.95	0.78
deutetrabenazine 24 mg/day	24	9.62 (2.90)	22	-3.58	0.67	-2.4	0.86
deutetrabenazine 36 mg/day	32	10.28 (3.13)	29	-3.29	0.57	-2.12	0.80
Non-US							
Placebo	28	9.36 (2.87)	28	-1.52	0.60	--	--
deutetrabenazine 12 mg/day	23	9.91 (2.56)	21	-1.91	0.66	-0.38	0.87
deutetrabenazine 24 mg/day	25	9.12 (3.00)	23	-2.68	0.63	-1.16	0.86
deutetrabenazine 36 mg/day	23	9.74 (3.36)	23	-3.29	0.64	-1.76	0.87

*Standard Deviation, #Standard Error, ◊Least Squares

Source: Statistical Reviewer's Results page 25

A pre-specified analysis of the change in AIMS score by baseline DRA use (currently taking versus not currently taking a DRA) assessed the treatment effect in the mITT Population. At all dose levels, the treatment effect was greater in patients not taking a DRA at baseline compared with patients taking a DRA at baseline. Patients not taking a DRA at baseline experienced a clinically meaningful treatment effect (-2.4 to -3.0) at all deutetrabenazine doses whereas those taking a DRA at baseline experienced a clinically meaningful treatment effect in the deutetrabenazine 24 and 36 mg/day groups (-1.5 and -1.7, respectively).

Data Quality and Integrity - Reviewers' Assessment

This reviewer did not have major concerns or questions about the quality and veracity of the data. OSI findings are summarized in Section 4.6.

Efficacy Results - Secondary and other relevant endpoints

The first key secondary efficacy endpoint was the proportion of patients who were a treatment success, defined as Much Improved or Very Much Improved, based on the CGIC at week 12 for deutetrabenazine 36 mg/day. As reflected in Table 29, a greater proportion of patients (44%) were considered a treatment success at week 12 after treatment with deutetrabenazine 36 mg/day than after treatment with placebo (26%); however, the result was not statistically significant (p=0.059). A greater proportion of patients (49%) were considered a treatment success at week 12 after treatment with deutetrabenazine 24 mg/day than treatment with placebo 24 mg/day than treatment with placebo (26%). However, because of the hierarchical testing approach taken and the lack of statistical significance on the CGIC for 36 mg/day, the CGIC results at the 12 and 24 mg/day doses were considered exploratory.

Table 29: Clinical Global Impression of Change: Proportion of Patients Considered a Treatment Success Based on the CGIC at Week 12 for deutetrabenazine Compared with Placebo (mITT Population; N=222)

Variable	Placebo (N=58)	deutetr abenazi ne	deutetr abenazi ne	deutetr abenazi ne
n	58 (100)	60	49	55 (100)
Treatment success, n (%)	15 (26)	17 (28)	24 (49)	24 (44)

Success 95% CI	16.3, 38.4	18.5, 40.8	35.6, 62.5	31.4, 56.7
Odds ratio (deutetrabenazine/p	--	1.15	2.71	2.11
OR 95% CI	--	0.509, 2.610	1.211, 6.052	0.960, 4.645
p-value	--	0.734	0.014	0.059

Source: CSR C-23 page 94

Exploratory endpoints:

A fair percentage of patients in each treatment group experienced treatment success according to the PGI-C. A higher percentage of patients experienced treatment success with deutetrabenazine 36 mg/day (40%) and deutetrabenazine 24 mg/day (45%) than with placebo (31%). However, these differences were not statistically significant Table 30.

Table 30: Patient Global Impression of Change: Proportion of Patients Who Were a Treatment Success at Week 12 as Determined by the PGIC (mITT Population; N=222)

Variable	Placebo (N=58)	deutetr abenazi ne	deutetr abenazi ne	deutetr abenazi ne
n	58	60	49	55
Treatment success, n (%)	18 (31)	14 (23)	22 (45)	22 (40)
Success 95% CI	20.6, 43.8	14.4, 35.4	31.9, 58.7	28.1, 53.2
Odds ratio	--	0.69	1.82	1.51
OR 95% CI	--	0.302, 1.563	0.826, 3.994	0.694, 3.285
p-value	--	0.372	0.134	0.296

Source: CSR C-23 page 118

The mCDQ-24 total scores improved from baseline to week 12 in all treatment groups. The 24 and 36 mg/day groups improved to a greater extent (-10.2 and -10.7, respectively) than the placebo group (-7.1). However, again, the results were not statistically significant.

6.3. deutetrabenazine-C-20: An Open-Label, Long-Term Safety Study of deutetrabenazine for the Treatment of Moderate to Severe Tardive Dyskinesia

Overview and Objective

The purpose of this trial was to evaluate the safety and tolerability of long-term maintenance therapy with deutetrabenazine. Furthermore, it was to provide data evaluating the efficacy of long-term maintenance therapy of deutetrabenazine to reduce the severity of abnormal involuntary movements of TD.

Trial Design

This is an open-label, single-arm study in which subjects with moderate to severe TD who had successfully completed a parent study (Study SD-809-C-18, Study SD-809-C-23, or any other controlled study of deutetrabenazine for the treatment of moderate to severe TD. Subjects who have successfully completed a parent study were eligible to enroll into this study after they completed a 1-week washout period and the final evaluation in the parent study.

The study was divided into a screening period, a titration period (up to 6 weeks), a long-term treatment period (up to 2 years), and a posttreatment safety follow-up period (4 weeks). Overall study participation is planned for up to 110 weeks. All patients, regardless of parent study treatment, were treated with deutetrabenazine in this study. The starting dose was deutetrabenazine 12 mg/day (6 mg twice daily) regardless of previous treatment in the parent studies. Patients underwent dose adjustment over the initial 6 weeks of treatment to identify a dose of deutetrabenazine that controlled dyskinesias and was well tolerated (i.e., an adequate dose). During the titration period, the dose of deutetrabenazine was increased on a weekly basis in increments of 6 mg of the total daily dose. The dose established during the titration period was continued during the long-term treatment period, but if there was a need to optimize dyskinesia control or minimize adverse events, further dose adjustments (no more than one dose adjustment per week) were permitted.

To reduce patient burden, after obtaining informed consent/assent, some data collected in the parent studies were used in the SD-809-C-20 study and provided some of the baseline data for SD-809-C-20. The titration period lasted up to 6 weeks. During this period of time, all patients (and caregivers, if required) interacted weekly with the clinical site through week 6 of the titration period to evaluate safety and establish a dose of deutetrabenazine that adequately controlled dyskinesias and was well tolerated. After the titration period was complete, patients received the maintenance dose established during the titration period until week 106 or the early termination visit (ET). During the remainder of the Long-Term Treatment Period, subjects returned to clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at Week 15 and ending at Week 106 (i.e., after 2 years of Long-Term Treatment Period). Following

discontinuation of deutetrabenazine at week 106, patients returned at week 107 for evaluation of safety, dyskinesia, and motor function. Patients had a follow-up telephone contact at week 110 to assess adverse events and concomitant medication use since week 107. It should be noted that CYP2D6 genotyping was performed in a blinded manner in the parent studies to allow evaluation of the effect of phenotype on safety parameters at the conclusion of the study.

Salient inclusion criteria included:

- Patient was at least 18 years of age at screening.
- Patient successfully completed Study SD-809-C-18 or Study SD-809-C-23
- Patient had a history of using a DRA for at least 3 months (or 1 month in patients 60 years of age and older). See Appendix 15 of the protocol (Appendix 16.1.1) for a list of DRAs.
- Patient had a clinical diagnosis of TD and had symptoms for at least 3 months prior to screening.
- For patients with underlying psychiatric illness:
  - Patient was psychiatrically stable and has had no change in psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) for at least 30 days before screening (45 days for antidepressants).
- Patients on long acting (depot) medications were on stable therapy (dose, frequency) for at least 3 months before screening.
- Patient had a health care provider who was aware of the patient's participation in the trial and did not anticipate any changes in the patient's treatment regimen (drug, dose, or frequency) in the next 3 months.

Salient exclusion criteria included:

- Patient received tetrabenazine within 7 days of baseline.
- Patient received any of the following medications within 30 days of baseline:
- Reserpine, α-methyl-p-tyrosine, botulinum toxin (within 3 months of baseline), and medications with strong anticholinergic activity (trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden)
  - Metoclopramide, promethazine, and prochlorperazine
  - Stimulants (e.g., methylphenidate, amphetamine/dextroamphetamine, and lisdexamphetamine) or monoamine oxidase inhibitors
- Patient had a neurological condition other than TD that might have interfered with assessing the severity of dyskinesias.
- Patient had a serious untreated or undertreated psychiatric illness at baseline.
- Patient had active suicidal ideation at baseline.

- Patient had a score ≥11 on the Hospital Anxiety and Depression Scale – Depression Subscale (HADS-D) at baseline.
- Patient had a Fridericia's corrected QT interval (QTcF) value >450 ms (males), >460 ms (females), or >480 ms (with right bundle branch block) on 12-lead ECG at baseline.

Five dosage strengths of deutetrabenazine were available for use: 6, 9, 12, 15, and 18 mg tablets. For all patients, deutetrabenazine was dosed as follows:

- All treatment regimens were administered twice daily with meals, approximately 10 hours apart during the day.
- The starting dose was deutetrabenazine 12 mg/day (6 mg twice daily) regardless of previous treatment in the parent study. Prior treatment assignment from the parent study remained blinded.
- The maximum total daily dose of deutetrabenazine was 48 mg/day (24 mg twice daily) unless the subject was on a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, or bupropion), in which case the maximum daily dose was 36 mg.
- Daily doses up to 36 mg/day were given as a single tablet twice daily, whereas daily doses of 42 mg/day and 48 mg/day were given as two tablets twice daily.

Dosing during the titration period was managed using the following guidelines. The starting dose was deutetrabenazine 12 mg/day. The dose of deutetrabenazine was adjusted (upward or downward) by 6 mg not more than once per week until there was adequate control of dyskinesia (as determined by the investigator in consultation with the patient, and caregiver if appropriate), the patient experienced a protocol-defined clinically significant adverse event (defined as related to deutetrabenazine and either moderate or severe in intensity or meeting the criteria for a serious adverse event), or the maximal allowable dose was reached. Once adequate control of dyskinesia had been achieved, the dose of deutetrabenazine was not to be increased further.

Dosing during the maintenance period was managed using the following guidelines. Patients returned to the clinic for evaluation of safety and dyskinesia once every 13 weeks, starting at week 15 and ending at week 106 (i.e., after 2 years of long-term treatment). When needed, dose adjustments were made based on all available information, including the patient's and caregiver's reports of adverse events and dyskinesia control, information from rating scales, and all safety evaluations. If a patient experienced a clinically significant adverse event that was attributed to deutetrabenazine, the investigator used his or her judgment to determine if a dose reduction or suspension was necessary. Dose adjustments were made based on all available information including the patient's and caregiver's reports of adverse events and dyskinesia control, the clinical assessment of safety and efficacy by the investigator, and information from rating scales.

Dose reductions generally occurred in increments of 6 mg/day, except when a strong CYP2D6 inhibitor (i.e., paroxetine, fluoxetine, or bupropion) was added, in which case a greater dose reduction may have been required. Dose reductions in this context were reviewed with the medical monitor. Suspension for more than 7 days was reviewed by the medical monitor. If the subject restarted deutetrabenazine within 7 days of suspension, the full dose of deutetrabenazine was resumed without titration. If the patient restarted deutetrabenazine greater than 7 days following a suspension, re-titration was required.

An Independent Data Monitoring Committee (IDMC) was not utilized for this study. The Applicant (or designee) was responsible for assuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the eCRFs. Arrangements were made to allow for investigators to have emergency access to the study medical monitor.

Procedures were in place to evaluate drug accountability, dispensing and return. Treatment compliance was determined by pill count performed during the patient visit. A patient was considered compliant if they had taken over 80%-105% of the expected tablets of study drug.

Patients receiving strong CYP2D6 inhibitors (bupropion, fluoxetine, paroxetine, or quinidine) were limited to a maximum of 36 mg/d of deutetrabenazine. A list of prohibited drugs was provided in the protocol, as was a list of prohibited QTc prolonging drugs. Specific concomitant psychiatric medications were permissible. Subjects that received psychoactive medications (including, but not limited to, neuroleptics, benzodiazepines, anticonvulsants, and mood stabilizers) must have been on a stable dose for ≥30 days (oral medication) before Screening and in the opinion of the treating psychiatrist, no changes in drug or dose were expected over the next 3 months.

Subjects were free to discontinue participation at any time. Investigators were required to withdraw subjects if the type, frequency, or severity of any AE became unacceptable or intolerable or if a subject exhibited active suicidal ideation with at least some intent to act, or if the subject was lost to follow-up, confirmed to be pregnant, or was unable to tolerate the treatment dose. If subjects withdrew prematurely from the study, the reason for withdrawal was recorded and subjects underwent early termination assessments (see Procedures and Schedule above). It was considered crucial to obtain follow-up data for subjects withdrawn for safety-related reasons.

Study Endpoints

The efficacy endpoints were as follows:

- The change in total motor AIMS score from Baseline of this study at each visit that this is measured, as assessed by the site rating.
- The proportion of patients who are a treatment success, based on the CGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the CGIC from Baseline of this study.
- The change in mCDQ-24 from Baseline of this study at each visit that this is measured.
- The proportion of patients who are a treatment success, based on the PGIC at each visit that this is measured. A treatment success is defined as Much or Very Much Improved on the PGIC from Baseline of this study.

The secondary assessment measures (PGIC, CGIC, etc.) were identical to those used in study C-18 and C-23.

The following safety endpoints were assessed:

- Incidence of AEs, SAEs, severe AEs, drug-related AEs, AEs leading to withdrawal during the following periods:
- Observed values and changes from baseline in clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Observed values and changes from baseline in vital signs
- Observed values in ECG parameters and abnormal findings
- Number of subjects with on-treatment QTcF values >450 ms, >480 ms, >500 ms.
- Observed values and changes in UPDRS Part III (motor examination), BARS, HADS,C-SSRS, ESS, and MoCA
- Duration of time to achieve stable doing of deutetrabenazine

The safety endpoints will be discussed in greater detail as part of Section 8 (Review of Safety).

Reviewer Comment:

Reviewer comment: This study has many endpoints for efficacy, safety, and pharmacokinetics using the Safety Population. There are no primary or secondary outcomes per se and no hierarchy for analysis is proposed. It should be noted that the AIMS score was locally read and centrally raters were not utilized.

Statistical Analysis Plan

The Statistical Analysis Plan (SAP) for this study was dated August 18, 2016. The SAP defined two analysis sets for this study:

The Intent-to-Treat (ITT) population included all patients who were enrolled in the study, regardless of whether or not a patient received a dose of study drug. The Safety population will include all patients who were administered any study drug. Patients who were enrolled but withdrew prior to dosing will not be included in the safety population

Handling of Missing Data:

The SAP indicated that procedures for handling missing data would depend on the type of endpoint. For AIMS assessed by the site rating, if a response to one question is missing, the missing response will be replaced with the average of the remaining responses. If responses to two or more questions are missing, the missing responses will not be replaced and the total score will be set to missing. The methods for handling withdrawals and missing in the context of analyzing secondary efficacy outcomes are outlined in Section 4.4 of the SAP.

Analysis of Efficacy/Safety Endpoints

All continuous efficacy endpoints were summarized for actual values and changes from baseline of this study to each visit using descriptive statistics. All categorical efficacy endpoints were summarized at each visit using descriptive statistics. In addition, the CGIC and PGIC ratings at each visit will be summarized using descriptive statistics.

Serum chemistry and hematology results and changes from Baseline are to be summarized at each visit using descriptive statistics. In addition, all serum chemistry and hematology results are to be categorized into the following categories using the laboratory reference ranges: below lower limit of normal, normal, above upper limit of normal. Shift tables summarizing changes in status from screening/baseline to each post-baseline visit were planned.

An Interim Analysis was conducted based on patient data accrued as of June 30, 2016.The CSR. This was conducted in support for the purpose of preparing the NDA.

Protocol Amendments

There were three amendments to the protocol for this study; salient aspects of these amendments are highlighted below.

Amendment 1 (dated May 28th, 2014) to the protocol was issued before any patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol:

- Additions to the list of prohibited medications, including tetrabenazine (within 7 days of baseline); α-methyl-p-tyrosine, anticholinergics, and any investigational medication (within 30 days of baseline); and botulinum toxin (within 3 months of screening)
- Clarification that after 3 months changes in psychoactive medications were allowed if approved by the investigator, and any changes in concomitant medications were documented in the eCRF

Amendment 2 (dated July 08, 2014) to the protocol was issued before any patients were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol:

- Promethazine and prochlorperazine were added to the exclusion criteria, (b) (4) were removed.
- Additional guidance was provided on specific anticholinergics (i.e., trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden) and stimulants (i.e., methylphenidate, amphetamine/dextroamphetamine, lisdexamphetamine, etc.) considered exclusionary.
- Exclusion criteria were modified such that suicidal behavior or intent to act on suicidal ideation was exclusionary within 6 months of baseline, (b) (4)

Amendment 3 (dated October 14, 2015) to the protocol was issued after 181 patients were enrolled into the study. Changes to the protocol were considered to have no negative impact on the safety of patients already enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol:

- Patients who previously participated in another study of deutetrabenazine for the treatment of moderate to severe TD, including Study SD-809-C-23, were allowed to participate in Study SD-809-C-20.
- The long-term treatment period was extended from 1 year to 2 years, and clinic visits were added at weeks 67, 80, 93, and 106/ET. The follow-up clinic visit was changed to week 107, and telephone contact was changed to week 110.
- Hepatic or renal impairment at screening of the parent study was considered exclusionary.

In addition to the protocol amendments described previously, there were three country specific (Germany, Czech Republic, and Hungary) amendments that did not involve major procedural changes.

6.3.1. **Study Results**

Compliance with Good Clinical Practices

The Applicant attests that this study was conducted in accordance with accepted practices for the protection of human subjects, use of institutional review boards and independent ethics committees, and adherence to Good Clinical Practice (GCP). All clinical studies were performed under the Applicant's IND.

Financial Disclosure

The financial disclosures by clinical investigators (Form 3454) were reviewed for all investigators in all covered clinical studies (C-18, C-20 and C-23). Five investigators (b) (6) participated in financial arrangements or held financial interests that were required to be disclosed. However, The Applicant placed into effect controls (i.e., randomized, double-blind study design) that appropriately mitigated any potential conflict of interest bias.

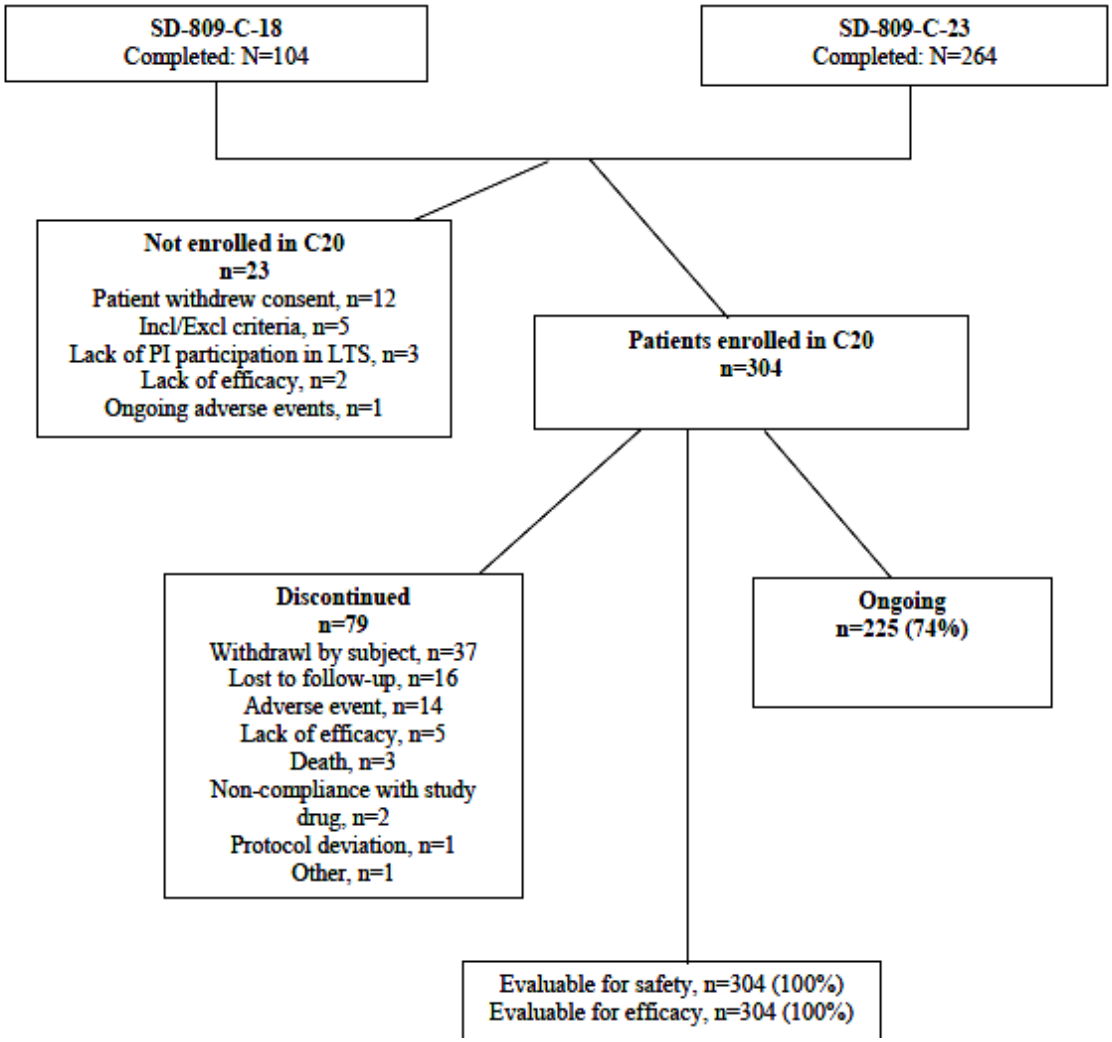
Patient Disposition

Of the 368 patients with TD who had successfully completed a qualifying parent study (i.e., Study SD-809-C-18 or Study SD-809-C-23) at the time of the data cutoff, 304 patients at 76 centers met entry criteria and were enrolled into this study.

As of the data cutoff (June 30, 2016), of the 23 patients who were not enrolled, 12 patients withdrew consent, five patients were excluded on the basis of inclusion/exclusion criteria, three patients were excluded due to lack of Principal Investigator participation in the long-term study, two patients experienced lack of efficacy, and one patient experienced ongoing adverse events before the baseline visit.

As of the data cutoff date, a total of 79 patients had discontinued the study. The highest overall rate of study discontinuation was observed in patients who received placebo in the parent studies. The most frequent reason for study discontinuation was withdrawal by subject, which occurred for 37 patients during the overall treatment period. Furthermore, 65 patients (35%) discontinued study in the US compared to 14 patients (12%) outside of the US.

Figure 6: Patient Disposition



Source: CSR C-20, page 64

By the time of the 120 Day Safety Update, the number of patients in the safety population increased by 39 subjects. 343 patients received deutetrabenazine in this study including 232 patients who had received deutetrabenazine parent study treatment and 111 patients who had received placebo in the parent study. A total of 238 patients (69%) were ongoing in the study as of the January 3, 2017, data cutoff date for the 120-Day Safety Update. Thirty-nine patients rolled over into the study after the NDA data cutoff and were included in the 120-Day Safety Update; all had successfully completed the parent study (C-23).

Protocol Violations/Deviations

Based on the sNDA cutoff date, a total of 193 patients (63%) had one or more protocol deviations (see Table 31). There were five waivers granted by the medical monitor for 26 patients (9%) with 28 inclusion/exclusion criteria. deviations reported. The most common exclusion criteria deviations were for hepatic impairment (8 of 28 deviations [29%]), HADS score ≥11 (7 of 28 deviations [25%]), and creatinine clearance <50 mL/min (5 of 28 deviations [18%]). Most of the patients with HADS-D score ≥11 had normal/stable HADS-D scores during Study SD-809-C-20.

Table 31: Protocol Deviations (ITT Population; N=304)

CRF Category, n (%)	**deutetra benazin**
Patients with at least one deviation	193 (63)
Inclusion/exclusion criteria	28 (9)
Missed or incorrect procedure/assessment	77 (25)
Missed or out of window visit	103 (34)
Prohibited concomitant medication/procedure	22 (7)
Study drug compliance	57 (19)
Received incorrect study treatment	18 (6)
Subject did not provide appropriate informed consent	17 (6)
Other	8 (3)

While the deviation rate was relatively high, many of the events were related to out of window visits and issues related to drug compliance. Based on my review of the deviation report, there were no distinct trends or overly concerning events that would grossly impact the safety conclusions. Similarly, review of the 120 DSUR did not reveal any new trends or concerning patterns.

Reviewer Comment:

Five of the eight patients who had deviations for hepatic impairment and were missing values at baseline; the deviation was related to an omission of data rather than laboratory abnormalities.

Table of Demographic Characteristics

Patient demographics by parent study treatment (prior deutetrabenazine and prior placebo) were similar in regard to age (mean 57.1 and 54.3 years, respectively), sex (44% and 46% men, respectively), race (77% and 78% white, respectively), and weight (mean 83.0 and 83.8 kg, respectively) in the ITT population (**Table 32**).

Table 32: Demographic Characteristics by Parent Study Treatment (ITT Population; N=304)

Demographic variable Statistic	Prior deutetrabe	Prior placebo (N=102)	Total (N=304)
Age, years			
N	202	102	304
Mean (SE)	57.1 (0.70)	54.3 (1.14)	56.2 (0.61)
Min, max	21, 81	24, 76	21, 81
Gender, n (%)			
Female	114 (56)	55 (54)	169 (56)
Male	88 (44)	47 (46)	135 (44)
Race, n (%)			
American Indian or Alaskan Native	0	1 (<1)	1 (<1)
Asian	1 (<1)	1 (<1)	2 (<1)
Black	44 (22)	20 (20)	64 (21)
White	156 (77)	80 (78)	236 (78)
Other	1 (<1)	0	1 (<1)
Ethnicity, n (%)			
Hispanic or Latino	14 (7)	11 (11)	25 (8)
Not Hispanic or Latino	180 (89)	89 (87)	269 (88)
Not reported	6 (3)	1 (<1)	7 (2)
Unknown	2 (<1)	1 (<1)	3 (<1)
Weight, kg			
Mean (SE)	83.0 (1.48)	83.8 (1.95)	83.2 (1.18)
Min, max	47, 182	45, 167	45, 182
Height, cm			
Mean (SE)	168.4 (0.74)	168.1 (0.97)	168.3 (0.59)
Min, max	148, 198	150, 191	148, 198
BMI, kg/m^2			
Mean (SE)	29.28 (0.508)	29.61 (0.658)	29.39 (0.403)
Min, max	16.2, 66.8	18.1, 59.3	16.2, 66.8

Source: CSR C-20, page 67

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

In the overall ITT Population, the mean duration of TD was 5.69 years and the mean baseline total motor AIMS score was 8.9. At baseline, 75% of the ITT Population were using a DRA, and 13% were using a strong CYP2D6 inhibitor. Disease duration, baseline use of DRAs, and CYP2D6 inhibitors were comparable between the two groups (Table 33).

Almost all patients had comorbid psychiatric illness (149 patients [49%] with schizophrenia, 35 patients [12%] with schizoaffective disorder, 58 patients [19%] who were bipolar, 51 patients [17%] wit6h depression, 10 patients [3%] with other comorbid illnesses, and one patient [<1%] with a missing comorbid illness). Similarly, the percentage of subjects who used strong CYP2D6 inhibitors, were CYP2D6 poor metabolizers, or who had impaired CYP2D6 function were comparable.

Table 33: Study-Specific Baseline Characteristics by Parent Study Treatment (ITT Population; N=304)

Variable Response	Prior deutetrabenazine (N=202)	Prior placebo (N=102)	Total (N=304)
Time since TD diagnosis, years			
Mean (SE)	5.59 (0.410)	5.87 (0.552)	5.69 (0.329)
Min, max	0.3, 37.8	0.3, 36.3	0.3, 37.8
Baseline total motor AIMS score (site)			
Mean (SE)	8.9 (0.26)	8.9 (0.37)	8.9 (0.21)
Min, max	0, 20	1, 19	0, 20
Baseline use of DRA, n (%)			
Yes	147 (73)	80 (78)	227 (75)
No	55 (27)	22 (22)	77 (25)
Background comorbid illness, n (%)			
Schizophrenia	101 (50)	48 (47)	149 (49)
Schizoaffective disorder	21 (10)	14 (14)	35 (12)
Bipolar	33 (16)	25 (25)	58 (19)
Depression	40 (20)	11 (11)	51 (17)
Other	7 (3)	3 (3)	10 (3)

Missing	0	1 (<1)	1 (<1)
Baseline mCDQ-24 total score			
Mean (SE)	37.0 (1.36)	43.2 (1.79)	39.1 (1.10)
Min, max	1, 97	4, 83	1, 97
Use of strong CYP2D6 inhibitor, n (%)[a]			
Yes	29 (14)	12 (12)	41 (13)
No	173 (86)	90 (88)	263 (87)
Poor CYP2D6 metabolizer, n (%)			
Yes	12 (6)	3 (3)	15 (5)
No	188 (93)	99 (97)	287 (94)
Missing	2 (<1)	0	2 (<1)
Impaired CYP2D6 function, n (%)[b]			
Yes	41 (20)	15 (15)	56 (18)
No	159 (79)	87 (85)	246 (81)
Missing	2 (<1)	0	2 (<1)

Source: CSR C-20, page 68

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Mean overall treatment compliance was relatively high (86.7%). Approximately 72% of patients had a compliance rate of ≥80% to 105%. The Applicant believes that true compliance is underestimated due to the fact that a number of patients did not return blister cards/bottles during the study. In cases where patients did not return their blister cards/bottles, compliance was calculated as zero.

Concomitant Medications

Antipsychotics and antidepressants were the most frequently used types of concomitant medications during the study. The most frequently used antipsychotic at baseline was quetiapine (71 patients [23%]), and the most frequently used antidepressant used at baseline was trazodone (48 patients [16%]). Use of CNS-active concomitant medications was similar between patients who received deutetrabenazine in the parent studies and patients who received placebo in the parent studies (Table 34).

Table 34: Summary of CNS-Active and Other Frequently Used Concomitant

Medications (>20% of Total Patients) (Safety Population; N=304)

Therapeutic class	Deutetrabenazine (N=304) n (%)
Patients receiving concomitant medications	299 (98)
Antipsychotics	237 (78)
Antidepressants	167 (55)
Lipid modifying agents, plain	86 (28)
Anxiolytics	83 (27)
Antiepileptics	82 (27)
Other analgesics and antipyretics	74 (24)
Drugs for peptide ulcers and GERD	65 (21)

Source: CSR C-20, page 70

Efficacy Results - Primary Endpoint

There was a mean decrease in AIMS score of –3.6 (0.25) from baseline to week 6 as the dose of deutetrabenazine was titrated to an average of 35.5 mg/day. There was gradual improvement thereafter, from week 6 to week 54, where the mean (SE) change in the total motor AIMS score was –5.1 (0.52). The mean dose at week 54 was 38.1 mg. **Table 35** displays change in AIMS score per particular time point.

Table 35: Abnormal Involuntary Movement Scale: Change in Total Motor AIMS Score from Baseline (Site Rating) of this Study to Each Visit through Week 67 (ITT Population; N=304)

Time point Statistic	Deutetrabenazine (N=304)
Baseline, n	304
Mean (SE)	10.8 (0.27)
Min, max	0, 25
Week 2 change, n	296
Mean (SE)	-1.7 (0.18)
Min, max	-16, 9
Week 4 change, n	286

Mean (SE)	-3.2 (0.23)
Min, max	-18, 6
Week 6 change, n	266
Mean (SE)	-3.6 (0.25)
Min, max	-19, 8
Week 15 change, n	233
Mean (SE)	-4.1 (0.29)
Min, max	-18, 11
Week 28 change, n	179
Mean (SE)	-4.1 (0.33)
Min, max	-17, 8
Week 41 change, n	126
Mean (SE)	-4.7 (0.41)
Min, max	-16, 8
Week 54 change, n	78
Mean (SE)	-5.1 (0.52)
Min, max	-17, 6
Week 67 change, n	27
Mean (SE)	-5.9 (0.95)
Min, max	-16, 5

Source: CSR C-20, page 72

Data Quality and Integrity - Reviewers' Assessment

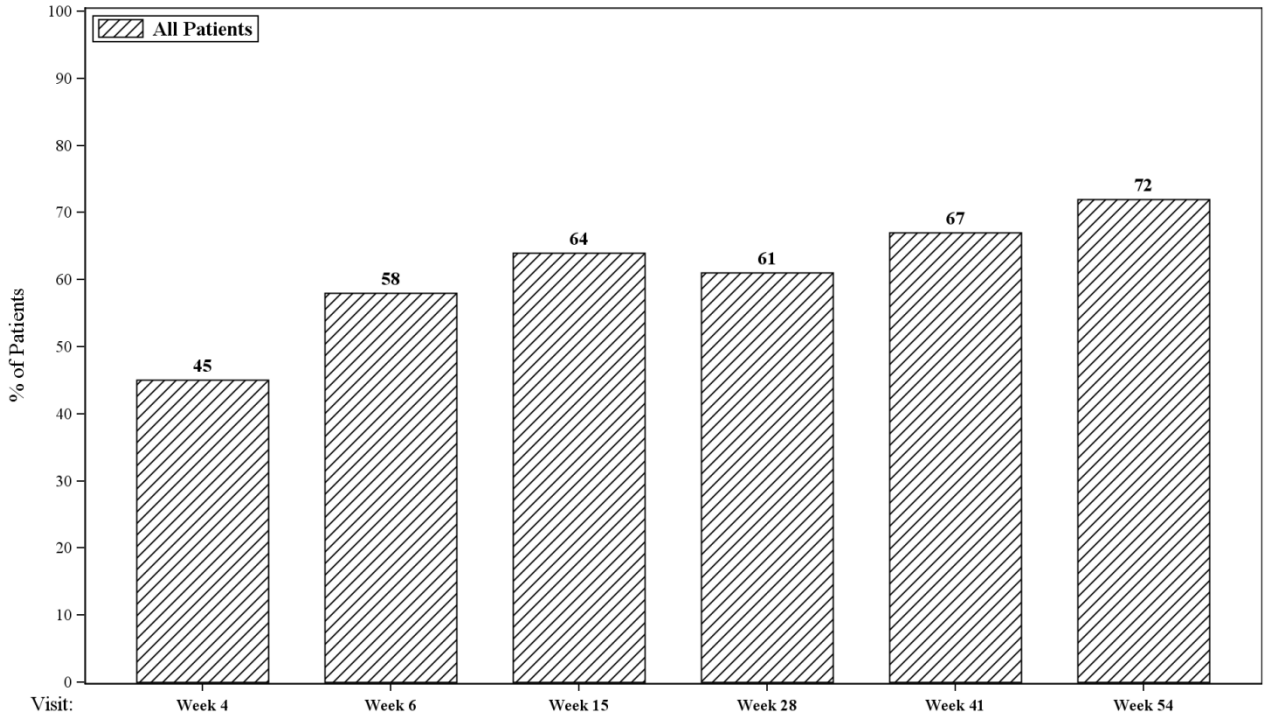
This reviewer had no concerns over the quality and integrity of the data

Efficacy Results - Secondary and other relevant endpoints

Because this was an open trial with a single treatment arm, secondary efficacy analysis will only be briefly discussed. The percentage of patients in the ITT Population with investigator-reported treatment success (defined as Much Improved or Very Much Improved) at each visit based on the CGIC is summarized in Figure 7. The proportion of patients considered a treatment success based on CGIC at weeks 15, 28, and 54 was 64% (148 of 233 patients), 61% (109 of 179 patients), and 72% (56 of 78 patients), respectively. Ninety-four percent of patients

had improvement at week 54. At week 15, 22% were very much improved, and this was maintained through week 54 (27%).

Figure 7: Proportion of Patients Who Were a Treatment Success Based on the CGIC at Each Visit for All Patients through Week 54 (ITT Population; N=304)



Source: CSR C-20, page 84

No additional analyses for efficacy were presented given the limitations of interpreting results in the context of an open label study design.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. **Primary Endpoints**

The Applicant indicated in the submission that Studies C-18 and C-23 are considered pivotal and Study C-20 is considered supportive for evaluating the efficacy of deutetrabenazine for the treatment of TD. The general primary efficacy endpoint measure was the change in total motor AIMS score (sum of Items 1 through 7) from baseline to each visit that total motor AIMS score was measured, as assessed by the blinded central video rating. The change from baseline to week 12 in total motor AIMS score was the primary efficacy endpoint in Studies C-18 and C-23.

The subject populations were relatively similar between studies with respect to demographics, medical history and concomitant medications. The mean total motor AIMS score at baseline was similar across treatment groups within each study and ranged from 10.5 to 10.7 for Study C-18 and 9.4 to 10.1 for Study C-23.

The major important difference between the two studies that affect the interpretation of the primary efficacy measure was differences in dosing regimens. In C-18, doses were titrated to an optimal dose over 6 weeks, based on dyskinesia control and tolerability. In C-23 patients were assigned to placebo, 12 mg/day, 24 mg/day, or 36 mg/day and escalated to target dose over a period of up to 4 weeks before receiving 8 weeks of treatment.

The question regarding whether the primary efficacy endpoint associated with deutetrabenazine is clinically meaningful was addressed by the Applicant in the submitted NDA Integrated Summary of Efficacy. In study C-18, deutetrabenazine significantly reduced the severity of dyskinesia in patients with TD as indicated by the change in AIMS score (blinded, centrally read video rating) from baseline to week 12 (treatment effect of -1.4; p=0.0188). Treatment success on the CGIC and PGIC was observed in a greater proportion of deutetrabenazine-treated patients than placebo-treated patients, although the differences were not statistically significant. In Study C-23, deutetrabenazine significantly reduced the severity of dyskinesia as indicated by the change in AIMS score (blinded, centrally read video rating) from baseline to week 12. Treatment with deutetrabenazine doses of 24 and 36 mg/day led to treatment effects of -1.8 (p=0.003) and -1.9 (p=0.001), respectively, compared with placebo. There were similar findings related to treatment success and other secondary endpoints for the 24 mg and 36 mg treatment groups as compared to Study C-18. However, these results were not statistically significant due to the testing hierarchy.

In spite of the limitations related to interpretation of the secondary endpoints, it is reasonable to infer that a decrease of approximately 1-2 points in AIMS total dyskinesia would represent clinically meaningful change in TD symptoms. Such a reduction may represent a 10-30% improvement in score for many patients. More importantly, it may reflect a reduction from moderate to mild symptoms for a particular body area (i.e., muscles of facial expression, lips). As noted previously, TD symptoms can be quite disabling and have a detrimental impact on one's quality of life. The totality of the data supports the idea that an average reduction of approximately 2 points may considerably improve abnormal involuntary movements resulting

in tangible improvement in how TD patients function and feel.

7.1.2. Secondary and Other Endpoints

Of the two pivotal studies submitted by the Applicant, no secondary endpoints had adequate multiplicity adjustment specified in the SAP. This has been previously discussed in the Study Results sections of the individual studies. The Applicant proposed the inclusion of CGI data for in the product label, but this is not appropriate because the finding was not replicated in a statistically-rigorous manner by pre-specification and control for multiple testing.

7.1.3. Subpopulations

Please refer to Sections 6.1.2 and 6.2.2 for subgroup analyses of the individual pivotal efficacy. Given the small size of Study C-18 and the flexible dosage range used, it is not possible to make useful conclusions about sub-population analysis and dose response relationships in the context of this trial. Furthermore, while Study C-23 was larger, the limited number of subjects in each subgroup and similarly precluded one from making firm conclusions. The statistical reviewer had concerns about pooling data due differences in study design and dosage. He did conduct individual study analyses by race, gender and age which did not reveal any specific findings (dose dependent or differential effects). There was one sub-group comparative analysis in Study C-23 (DRA versus non DRA) that was statistically significant. At all dose levels, the treatment effect was found to be greater in patients not taking a DRA at baseline compared with patients taking a DRA at baseline. Patients not taking a DRA at baseline experienced a clinically meaningful treatment effect (-2.4 to -3.0) at all deutetrabenazine doses whereas those taking a DRA at baseline experienced a clinically meaningful treatment effect in the SD- 809 24 and 36 mg/day groups (-1.5 and -1.7, respectively).

7.1.4. Dose and Dose-Response

Please refer to Section 4.5 for a summary of Clinical Pharmacology information and the OCP team review for additional details related to dose/blood level/response and subpopulation differences.

While Study C-18 employed flexible dosing, it is evident that most patients ended up taking relatively larger doses of deutetrabenazine during the maintenance period. The median total daily dose was 36 mg with a range from 18 mg to 48 mg. The study design was appropriate for a Phase 2/3 dose finding study to help establish the overall efficacy of deutetrabenazine, but it did not provide nuanced data to help determine the lowest effective dose of deutetrabenazine.

Furthermore, this is the only short term efficacy study that studied the treatment effect of doses above 36 mg.

On the other hand, Study C-23 was able to provide information on the treatment effect of different deutetrabenazine dosing fixed dosing regimens compared to placebo. Due to pre-specified sequential testing order, the Applicant tested the proportion of patients with treatment success with deutetrabenazine 36 mg/day as the first key secondary endpoint followed by change from baseline in AIMS total score deutetrabenazine 24 mg/day. The 24 mg/day dose was only nominally statistically significant based on the Applicant's pre-specified statistical analysis plan. Despite the statistical limitations, it appears that 36 mg and 24 mg doses have a comparable treatment effect with no dose dependent treatment effects evident above 24 mg. Altogether, these findings support the following dosing recommendations outlined in the label (12 mg/day to 48 mg/day).

The OCP team review was in agreement with these dosing recommendations. Additional dose-related conclusions from the OCP review, based on relevant PK studies, the established exposure-response relationships, and the understanding of the mechanism of drug elimination, were:

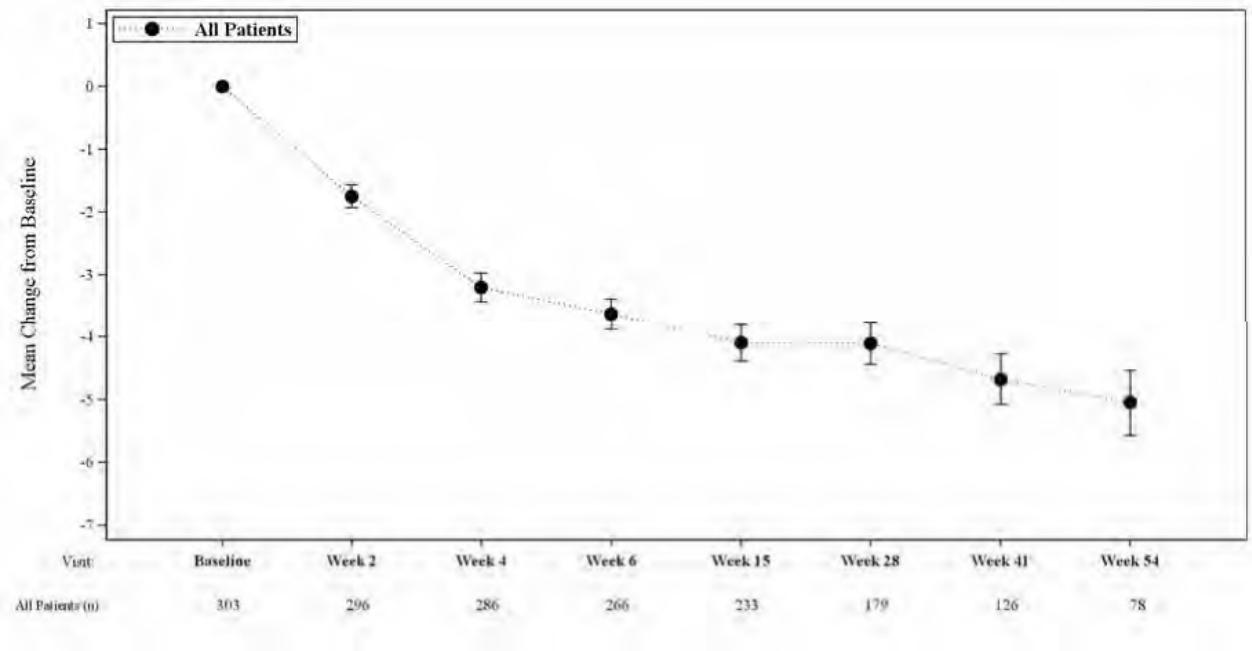
- No dosage adjustment is necessary based on body weight, age, gender, race, and BMI.
- Deutetrabenazine should be administered with food.
- Dose reductions to a maximum of 36 mg/day should occur, when co-administered with a strong CYP2D6 inhibitor or for a known CYP2D6 poor metabolizer.
- Deutetrabenazine use in patients with hepatic impairment is contraindicated
- Medications that can prolong the QT (change language)

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The time to onset of treatment effect and the persistence of clinical efficacy with continuous treatment was established in the deutetrabenazine clinical development program. As shown in Figure 4, there was a numerical separation of the mean AIMS between placebo and two treatment groups (36 mg, 24 mg) after as early as two weeks of treatment. This effect persisted through week 12. Results were similar in Study C-18.

As of 30 June 2016, the majority of patients in Study C-20 had received treatment with deutetrabenazine for more than 28 weeks. As shown in Figure 8, results for AIMS scores through week 54 show that there was no evidence for loss of efficacy (5-point decrease versus baseline) as measured by AIMS in these patients.

Figure 8: Mean (±SE) of Total Motor AIMS Score Changes from Baseline to Each Visit through Week 54 in Study C-20 (Site Rating; ITT Population; N=304)



Source: Study SD-809-C-20 CSR, Figure 2

Lastly, persistence of clinical benefit after the treatment has been stopped could not be assessed with the current data. The AIMS was not conducted at follow-up visits in after cessation of study medication in the placebo controlled studies. Furthermore, many patients were transitioned to the open label study.

7.2. Integrated Assessment of Effectiveness

Evidentiary Standard

The Federal Food, Drug, and Cosmetic Act (the Act) requires that a drug's effectiveness is established by substantial evidence, as defined by Section 505(d) as "evidence consisting of adequate and well-controlled investigations … on the basis of which it could fairly and responsibly be concluded … that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling…" As described in the FDA *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998), the usual requirement is for more than one adequate and well-controlled investigation.

In the current sNDA, both Study C-18 and C-23 sufficiently provide this evidence (Section 6.1 and Section 6.2). The choice and methodology involving in assessing the primary efficacy

measure (i.e., central video raters who were blind to visit number, subject identification, and treatment), reduced inter-rater variability and expectancy bias associated with on-site raters. In both studies, deutetrabenazine was statistically superior to placebo on the primary efficacy endpoint of the AIMS total dyskinesia score change from baseline at the end of Week 12. Study C-20 which re-randomized of subjects initially treated with placebo to receive deutetrabenazine, provided additional evidence of continued drug effect.

However, there are some limitations in the evidence that warrant discussion. Study C-18 did not provide much support identifying a range of potentially therapeutic doses. Most subjects were on daily doses of 36 mg and higher limiting the generalizability of the deutetrabenazine separation versus placebo. Similarly, while higher doses were found to be in effective in Study C-18, a 48 mg cohort was not investigated as part of Study C-23. While the proposed label suggests dosing up to 48 mg a day, there was limited data to support this from Study C-18. Nonetheless, based on C-20, it appears that dosing up to 48 mg has been reasonably well tolerated and effective.

Further deficiencies involved the structure of the statistical analysis hierarchy of Study C-23. The Applicant tested the proportion of patients with treatment success with deutetrabenazine 36 mg/day as the first key secondary endpoint followed by change from baseline in AIMS total score deutetrabenazine 24 mg/day. The 24 mg/day dose was only nominally statistically significant (p=0.003) because of this. The Biometrics Reviewer was confident that moving 24 mg/day change from baseline in AIMS total score up on the statistical hierarchy would obviated this issue.

Clinical Meaningfulness

The primary efficacy endpoint was the change from baseline on the AIMS total dyskinesia score. Furthermore, as established in earlier sections, the AIMS is widely used and accepted in clinical and research settings for assessing the presence and severity of TD. While there were no primary efficacy endpoints characterizing functional consequences of dyskinetic movements (which might directly answer the question of clinical meaningfulness) it is readily apparent that TD can be socially stigmatizing and have adverse effects on one's affect to function in a variety of domains. As a result, a reduction in dyskinetic movements would be expected to reduce the adverse consequences frequently associated with TD.

Due to the limitations of the statistical hierarchy in both pivotal studies, all of the secondary endpoints were essentially interpreted as exploratory endpoints. Nonetheless, the collective evidence does support the notion that deutetrabenazine treated patients at doses greater than 24 mg/day was associated with a higher proportion of treatment success assessed via the CGI-C versus placebo. For example, the odds ratio associated with treatment success for the 36 mg/day group versus placebo in Study C-23 was 2.11. Evidence from the extension phase

suggests that the maximal effect of treatment is not yet reached at the time of the primary efficacy endpoint, and symptoms may continue to improve in subsequent months. Consequently, it is expected that patients affected by TD, caregivers, and clinicians will prioritize use of this drug over off-label treatments that have largely been utilized without a strong evidence base.

Presentation of Effectiveness in Labeling

As discussed in Section 10.1, evidence supporting the effectiveness of deutetrabenazine should be presented by describing the methods and results of Studies C-18 and C-22. The trial designs (duration, randomized treatments, eligibility criteria, endpoint description, etc.) should be communicated to contextualize the results. The study population should be described, including demographic variables and baseline characteristics such as the continued use of antipsychotic medication(s). The change in AIMS total dyskinesia score from Baseline to the end of Week 12 should be presented (including placebo-subtracted differences), as should a histogram indicating the proportion of patients achieving different magnitudes of AIMS changes from baseline (to display the range of results in individuals). A graphical depiction of the open label results would also be useful for communicating the effectiveness of treatment beyond the initial 12 weeks.

8 Review of Safety

8.1. Safety Review Approach

The overall approach to the safety review of the sNDA application consisted of an initial comprehensive review of the Applicant's approach and results. Much of this data was highlighted in the integrated summary of safety including the separate safety datasets.
As the safety database for this sNDA application was relatively small, attention was focused on the characterization and classification of all adverse events in C-18 (flexible dose), C-23 (fixed dose), and C-20 (open label long term safety study). Given the salient differences in study design and population, pooling of certain safety data was not possible.

The TD developmental program was also inspected for unexpected reactions, deaths, and serious and severe adverse events. In cases of their occurrence, the individual narrative summaries were reviewed for relevant details. As the safety database for this HD application was relatively small, I was able to review similar data for that indication. I also spoke Ken

Bergmann M.D. (Medical Officer-Division of Neurologic Products) about his NDA review and any salient safety concerns he thought were applicable to my review.

Given the RLD was Xenazine (tetrabenazine tablets, NDA 21894), particular attention was focused on adverse events from the tetrabenazine program included Parkinsonism, anxiety, agitation, akathisia, somnolence, bradykinesia, and dysphagia. Comparisons to the AE profile of deutetrabenazine to the RLD are made in Section 8.11 Integrated Assessment of Safety.

Particular attention was also given to determining rates/severity of suicidality and depression. There is a significant background incidence of both in the Huntington's disease population and consequently the box warning regarding suicidality and depression was included in the initial Austedo label. The applicability of this warning to the TD population was unclear and warranted investigation. Similarly, the effect on QTc, a major safety concern in the circumstances of elevated serum levels of the RLD, was also investigated.

MedDRA version 16.1 was used by the Applicant to code adverse events in C-18., C-20, and C-23. The quality, accuracy, and consistency of coding were reviewed with special attention to correctness of coding from the verbatim description of the event and potential splitting of related events using different Preferred Terms. While the Applicant's documentation of drug safety was reviewed (reports for the confirmatory trials, Summary of Clinical Safety, ISS, and supporting information),the analyses and tables in this section were created by using the Applicant's SDTM and ADaM standardized datasets and JMP 12.1, JMP Clinical 12.1 and MedDRA Adverse Event Diagnosis Service (MAED) software. When used in this review, the source of Applicant's tables is indicated in the caption.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The most recent 120-Day Safety Update (data cutoff date of 03 January 2017) was used to establish the extent of the safety population. The Safety Population across the TD development program included 390 subjects who received at least one dose of medication. However, it should be noted that the integrated safety analyses presented in the original NDA (data cutoff date of June 30, 2016) was used for the primary review of safety.

The Phase 1 program was comprised of 178 healthy adult volunteers who received deutetrabenazine. The majority were single dose exposures while 24 volunteers received multiple doses. In the Phase 3 program, Study C-18, C-23 and C-20 contained 58 patients, 221 patients and 343 patients respectively, who received at least one dose of drug. All studies in

the clinical development program for TD are complete with the exception of C-20, the open label safety study.

The Applicant's table (see Table 36: Deutetrabenazine Development program safety population) summarizes this program population at the time of 120 Day Safety Update:

Table 36: Deutetrabenazine Development program safety population

Study	Any SD-809 exposure	≥6 weeks	≥15 weeks	≥28 weeks	≥54 weeks	≥80 weeks	≥93 weeks	≥106 weeks
Phase 3 in patients with Tardive dyskinesia								
SD-809-C-18	58	53	--	--	--	--	--	
SD-809-C-23	221	197	1	--	--	--	--	
SD-809-C-20	343	332	310	259	161	69	27	13
Total TD patient exposure to deutetrabenazine (parent study + open-	390	361	329	291	185	93	48	18

Source: 120 Day Safety Report, page 20

The duration of exposure table below omits the Phase 1 volunteers and the participants of the HD trials. The deutetrabenazine titration group reflects treated patients in Study C-18 up through and Including week 12 plus data from C-20 up through and including week 15 for patients who were previously in the placebo treatment group in either Study C-18 or Study C-23. The majority of patients in the integrated safety dataset received deutetrabenazine for >9 weeks to ≤15 weeks. At this time point, the deutetrabenazine titration group had a mean total daily dose of 38.3 mg and a median daily dose was 36.0 mg (see Table 37).

Table 37: Study Drug Exposure at Each Visit by Patient Group (ISS Safety Population)

Variable Statistic	Placebo (N=131)	deutetrabenazine 12 mg (N=74)	deutetrabenazine 24 mg (N=73)	deutetrabenazine 36 mg (N=74)	deutetrabenazine titration 12-48 mg
Weeks treated, n (%)					
>9 to ≤15 weeks	120 (92)	66 (89)	64 (88)	64 (86)	140 (88)

Duration of treatment (days)					
N	131	74	73	74	160
Mean (SD)	79.4 (17.54)	79.0 (18.99)	77 5 19.91)	75.8 (22.13)	88.1 (24.28)
Median	84.0	84.0	84.0	84.0	105.0
Min, max	3, 102	2, 110	2, 90	5, 87	8, 105

Source: Integrated Safety Summary, page 37,
Applicant results verified

8.2.2. **Relevant characteristics of the safety population:**

The TD developmental program appears to be sufficiently diverse and reflective of the broad population that would be receiving the treatment. The relevant demographic characteristics of the study populations are discussed in the review of individual studies. Overall, the safety population's demography is typical of the clinical TD population. Furthermore, the severity and duration of illness as reflected in time since TD diagnosis and baseline AIMS score, were concordant with patients with moderate to severe TD.

Patients with significant hepatic or renal dysfunction were excluded from studies such that dosing adjustments related to these conditions were not investigated. CYP2D6 phenotype status was investigated as special group. However, there were only 9 poor metabolizers in deutetrabenazine titration group, making comparative analyses regarding the importance of this phenotype to the safety of the drug challenging. Concomitant medication restrictions were mostly observed. In spite of this, there were several deviations that occurred that will be discussed in later sections.

Table 38: Baseline Characteristics by Patient Group (Safety Population)

Variable **Response, n (%)**	**Placebo (N=131)**	**deutetrabenazine 12 mg (N=74)**	**deutetrabenazine 24 mg (N=73)**	**deutetrabenazine 36 mg (N=74)**	**deutetrabenazine titration 12-48 mg**

Time since TD diagnosis (years)					
Mean (SD)	6.20 (6.045)	5.49 (5.426)	4.98 (6.034)	5.89 (5.342)	5.94 (6.026)
Baseline AIMS score[a]					
Mean (SD)	9.0 (3.53)	8.6 (3.13)	7.7 (3.51)	8.6 (3.84)	9.2 (3.84)
Min, max	1, 19	0, 16	2, 16	2, 20	1, 20

Source: ISS, page 42

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This sNDA submission was complete and well organized. The organization and content of written reports followed prescribed formats, with particular attention to those described in ICH E3. The datasets containing information collected in Study C-18, C-20 and C-23 that provide the major supporting evidence of safety and effectiveness of deutetrabenazine were adherent to CDISC standards for SDTM and ADaM domains and variables. The Applicant was responsive to requests to modify an ISS dataset to facilitate analyses. Furthermore, an aggregate review of the safety data demonstrated consistency among case report forms and narratives of individual subjects. Consequently, there were no major concerns about data quality and integrity.

The clinical studies in this program were relatively small and the population fairly homogeneous with regard to demographic features. This made sub-group analyses challenging and their external validity questionable.

8.3.2. Categorization of Adverse Events

Per review of the protocols, the Applicant provided accurate definitions of AEs and serious SAEs. An adverse event or suspected adverse reaction was considered unexpected if it was not listed in the IB or was not listed at the specificity or severity that has been observed. Treatment-emergent AEs were defined as AEs that either began following initiation of treatment with study drug and were not present at Baseline, or if present at Baseline, worsened in severity following initiation of treatment with study drug in the current study. The incidence of TEAEs was also summarized by maximum severity and strongest relationship to study treatment by the Applicant. It is important to note that if an AE was not considered to be plausibly related to the study drug by the Applicant, it was not considered a TEAE.

The adverse events were collected and characterized in accordance with accepted ICH and FDA guidelines. Adverse events were coded using MedDRA version 16.1 in C-18, C-20, and C-23 but other versions of MedDRA in the Phase 1 studies. Review of the adverse events and tables derived from Applicant submitted datasets for the placebo controlled studies (C-18 and C-23) was performed to look for discrepancies in reporting. There was a wide range of adverse events occurring by site, even when the number of patients randomized by site (i.e.: Safety Population) was accounted for. Sites reporting no adverse events only had one or two patients enrolled. On the other hand there were sites with one or two enrollees that reported several AEs. The nature of the AEs reported at these sites was not different from other sites and there is no obvious reason for the differences. This wide range of reporting is not uncommon likely represents the different individual clinical threshold for reporting AEs by the site investigator and his or her staff. AE counts for the active versus placebo arms were comparable. Severity of AEs was investigated and AEs were followed to resolution. Lastly, verbatim terms appear to be fairly represented by Preferred Terms and only a few instances of splitting of terms appears to take place (related to worsening psychiatric illness).

8.4. Safety Results

8.4.1. Deaths

Two patients died due to adverse events in Study C-23.

Patient (b) (6) was a 67-year-old female who was randomized to deutetrabenazine 36 mg/day in Study C-23. She had a history of obesity, diabetes mellitus, hypercholesterolemia, and hypertension. She was taking atorvastatin for hypercholesterolemia, acetylsalicylic acid as cardiac prophylaxis, metoprolol for hypertension, and insulin for diabetes mellitus. At a clinic visit on day 25 the patient had a left olecranon fossa contusion and right knee abrasion as a result of falling forward 4 hours prior to her clinic visit. There was no head trauma or loss of consciousness. The events had no suspected cardiopulmonary etiology. On day 29 during a follow-up phone call the patient reported no new adverse events, medical call outs, or symptoms. On day 38 the patient died due to cardio-respiratory arrest as assessed by the coroner, who concluded that the multiple risk factors of hypertension, diabetes mellitus, and obesity were sufficient to explain the acute cardiopulmonary arrest. The Investigator considered the event of cardio-respiratory arrest as unlikely to be related to study drug.

Patient (b) (6) was a 77-year-old male who was randomized to deutetrabenazine 24 mg/day in Study C-23. He had a history of arterial hypertension and hypercholesterolemia. At baseline, relevant concomitant medications included haloperidol, olanzapine, valsartan, amlodipine, HCTZ, and atorvastatin. His first dose of deutetrabenazine 12 mg/day on day 1 and was on 12 mg/day at the time of the event onset. On day -1, ECG was normal. On day 7, the patient was found dead in bed. The patient had shown no signs of health deterioration the day before and no adverse events were noted. The cause of death was defined as sudden cardiac arrest death due to unspecified cardiac causes. The Investigator considered the event of sudden cardiac death as unlikely to be related to study drug.

Reviewer Comment: Patient was taking antipsychotic drugs that are known to cause QTc prolongation: haloperidol is a QT prolonging drug and a CYP2D6 inhibitor. Therefore, a relationship between study drug and death cannot be excluded. However, this seems unlikely based on the study dosage and patient's medical history.

In the long-term safety study (SD-809-C-20), four patients died after the ISS week 12/15 cutoff.

Patient (b) (6) was a 66-year-old male who had received placebo in the parent study. He was taking meloxicam for hip pain. The patient experienced decreased appetite, decreased weight, and abdominal discomfort and decided to discontinue deutetrabenazine (the daily dose was 24 mg/day) on day 48. On day 105, 56 days after the last dose of study drug and 25 days after the patient was withdrawn from the study, the patient presented to the emergency department with profound hypotension. The following day, the patient became unresponsive, subsequently, he died during follow-up. An autopsy revealed the cause of death to be

perforated gastric ulcer with acute peritonitis. Gastric perforation was considered by the Investigator to be unrelated to study drug.

Patient (b) (6) was a 64-year-old female who had received deutetrabenazine 24 mg/day in the parent study. She had a history of osteoarthritis, back pain, gastritis, esophagitis, and peptic ulcer disease, and she was taking acetaminophen (paracetamol) for pain and acetylsalicylic acid for cardiac prophylaxis. On day 29, the patient was hospitalized with gastric ulcer perforation and study drug dosing (36 mg/day) was interrupted. On day 31, the patient underwent a surgical resection, which confirmed the presence of a perforated gastric ulcer with peritonitis. The patient died on the same day as a result of septic shock. The Investigator considered all events to be unrelated to study drug

Patient (b) (6) was a 72-year-old male who had received deutetrabenazine 36 mg/day in the parent study. He had a history of coronary artery disease with stent placement, atrial fibrillation/flutter, type 2 diabetes mellitus, and dyslipidemia. The patient had a baseline QTcF of 440 msec in Study C-20. QTcF values were below 450 msec at weeks 2 and 4 and lengthened after placement of a dual chamber pacemaker on day 28 for atrial fibrillation with high-grade atrioventricular block. The placement of the pacemaker was associated with a predictable artificial conduction delay, with QTcF values ranging from 463 to 489 msec through day 253. The patient's cardiologist prescribed the prohibited beta-blocker sotalol 80 mg twice a day on day 272, without the knowledge of the principal investigator, and an ECG collected on day 287 revealed a QTcF of 511 msec. Based on the QTcF changes, the medical monitor directed the principal investigator, who then directed the subject, to suspend study drug on day 293. Five days later, on day 298, the patient died while in bed. The sotalol dose had been increased by the patient's cardiologist on day 289 to 120 mg twice a day. This event was assessed as unlikely related to study drug.

Patient (b) (6) was a 57-year-old female who participated in Study C-20 and had received deutetrabenazine 24 mg/day in the parent study. She had a history of chronic heart failure, migraines, and non-convulsive seizures and she was taking metoprolol succinate and acetylsalicylic acid for chronic diastolic congestive heart failure and lacosamide for non-convulsive seizures. On day 215, the patient was hospitalized due to generalized non-convulsive epilepsy, which was considered resolved on day 219. The patient discontinued study treatment on day 241 and was withdrawn from the study on day 245. On day 253, 13 days after the last dose of study drug, the patient was hospitalized with sepsis and pneumonitis. On day 259 or day 260, the patient was found unresponsive and hypotensive. Brain computed tomography scan findings and clinical examination were consistent with brain stem infarction. The patient died on day 260. The Investigator considered the events of sepsis, pneumonitis, and brain stem infarction to be unrelated to study drug.

Reviewer Comment: For each of the four deaths occurring in Study C-20 as part of the NDA submission, the Investigator considered the event to be unlikely or unrelated to study drug. Patients tended to have significant comorbid medical conditions that could solely explain the etiology of the event. I agree with the Investigators' assessments in all but one case.

The baseline use of deutetrabenazine combined with sotalol may have been a contributing factor to the death of Patient (b) (6) *Sotalol has pro-arrhythmic properties that could be exacerbated by medications that prolong the QT interval. The Investigator was not aware of the prohibited medication until 15 days after initial administration. The actual cause of death was not clear but arrhythmia would be high on the list of potential etiologies.*

Three fatal cases occurred in Study C-20 after the original NDA submission. Further information regarding these cases is being provided continuously.

Patient (b) (6) was a 71-year-old woman with a history of schizoaffective disorder, remote history of TIA or stroke, hypothyroidism, and morbid obesity with previous gastric bypass surgery. Concomitant medications of relevance included: fludrocortisone, vilazodone, thioridazine, citalopram, and donepezil. The patient was found deceased at home, sitting on the toilet on day 243. The patient was taking deutetrabenazine 12 mg/day at the time of onset of the event.

Between study days 13 and 132, QTcF ranged between 436 to 470 msec with sinus bradycardia and heart rates <50 beats/minute. At day 196, QTcF was 454 msec and serum potassium and magnesium were normal. The ECGs during (b) (6) unti (b) (6) show sinus bradycardia with rates <50 beats/minute. Other ECGs in (b) (6) have rates in the low 60s. BP and pulse were normal during study, except for an episode of hypotension on day 109 (BP 84/60) for which the patient was started on Florinef on day 224 by the patient's primary care physician. The conduction intervals were generally normal.

Reviewer Comment: Both citalopram and thioridazine are QT prolonging drugs known to cause TdP. The patient experienced QTc prolongation > 450 ms and arrhythmia could be a contributing factor. However, the death appears more consistent with a cardiovascular etiology, with other contributing clinical disorders including the history of possible cerebrovascular disease and hypokalemia. The Investigator's assessment was pending.

Patient (b) (6) was a 75-year-old female with schizoaffective disorder, hypertension, diet controlled type 2 DM, hyperlipidemia, and prior stroke from uncontrolled hypertension. Relevant concomitant medications included losartan, haloperidol, risperidone, and alprazolam. The patient was hospitalized on day 47 for generalized weakness and found to be dyspneic and hypertensive (180/100 mmHg).

An ECG revealed no acute changes, left axis deviation, and normal repolarization (QTc not provided). The patient was treated with IV urapidil (alpha blocker) and IV furosemide on the day of admission. Serum potassium was normal (4.7 mmol/L) the day after admission; however, potassium and ECG were not repeated during the hospitalization. Following treatment for hypertension and heart failure, the patient was discharged on day 55. Subsequently, the patient worsened again (fatigue, weakness) and eventually was found deceased on day 85. No autopsy was performed. In the parent study (C-23), the patient received 18 mg BID with no cardiovascular adverse events. In Study C-23, QTcF was 395 msec at baseline and ranged from 399 to 417 msec during treatment.

Patient (b) (6) was a 70-year-old female with a history of hypertension, type 2 diabetes mellitus, and depression. Relevant concomitant medications at study entry included bisoprolol, furosemide, glimepiride, simvastatin, and sertraline. As noted in the NDA, this patient had post-baseline ECGs classified as abnormal, potentially clinically significant at weeks 2 and 6 (possible inferior MI, anteroseptal MI); however, review of the tracings indicated poor R-wave progression in the anteroseptal leads that do not meet the criteria for anterior wall MI. QTcF values ranged between 422 and 450 msec. Subsequent ECGs were normal and no adverse events were recorded at the time. The patient was hospitalized on Day 399 for multiple fractures of the left humerus (serious adverse event) and was discharged after 3 days on enoxaparin for thromboembolic disease prevention. Patient received deutetrabenazine 42 mg/daily without interruption during this event. Approximately 2 months after the upper limb fracture (b) (6) the patient was admitted with hypoglycaemia (unknown value) and advanced heart failure was reported at that time as well. During the hospitalization, there was a sudden deterioration in the patient's general condition with respiratory distress. Two days later (b) (6) the patient expired. The fatal adverse event was initially called pulmonary embolism but later changed to heart failure, without explanation by the site investigator

Reviewer Comment: The precise cause of this death cannot yet be determined. There are multiple medical conditions that should be considered in the differential diagnosis. There were no changes from baseline in the ECGs. More information is required to help adjudicate causality.

8.4.2. Serious Adverse Events

In the development program for deutetrabenazine (safety population), there were a similar proportion of serious adverse events between patients in the deutetrabenazine treatment groups versus placebo-treated patients (Table 33). Furthermore, there were only a few of SAE's (see Table 39) in fixed dose groups with two (2.7%), six (8.2%), and four (5.4%) patients who received deutetrabenazine 12, 24, and 36 mg, respectively. As noted in Table 33, the events

were of diverse etiology and did not reflect any particular pattern. Several subjects experienced more than one SAE related to exacerbations in their medical condition.

With respect to the safety population, there was only one SAE that was considered by the Investigator to be possibly related to study drug. Patient (b) (6) was a 43-year-old female with TD who was randomized to deutetrabenazine 24 mg/day in Study SD-809 C-23. She had a history of two prior suicide attempts. On day 2 of the study, the patient had a serious adverse event reported as suicidal intention (preferred term: suicidal ideation). After taking the morning dose on day 2, the patient reported severe depressed mood accompanied with suicidal thoughts. The study drug was permanently discontinued beginning with the evening dose on the same day as a result of these events. Her mood appeared to resolve immediately after cessation of treatment. However, on Day 10 at the ET visit, she did endorse suicidal ideation (wish to be dead," "non-specific suicidal thought). Investigator considered the events of suicidal ideation and depression as possibly related to study drug.

Reviewer Comment: Given the patient's past psychiatric history, it is difficult to determine whether deutetrabenazine was a contributing factor to her affective instability. The time course and reoccurrence of symptoms after study drug cessation supports the idea that study drug did not contribute to the suicidal ideation and depression.

Table 39: Serious Adverse Events in the Overall Treatment Period by Preferred Term and Patient Group (Safety Population)

MedDRA preferred term, n (%)	Placebo (N=131)	Deutetra-benazine 12 mg (N=74)	Deutetra-benazine 24 mg (N=73)	Deutetra-benazine 36 mg (N=74)	Deutetra-benazine Titration 12-48 mg (N=160)
Patients with at least one serious AE	9 (6.9)	2 (2.7)	6 (8.2)	4 (5.4)	8 (5.0)
Abdominal pain	1 (0.8)[c]	0	0	0	0
Abscess jaw	1 (0.8)	0	0	0	0
Alcohol interaction	0	0	0	1 (1.4)	0
Appendicitis	0	0	1 (1.4)	0	0
Bipolar disorder	1 (0.8)	0	0	0	0
Cardio-respiratory arrest	0	0	0	1 (1.4)	0
Cellulitis	0	0	1 (1.4)	0	0
Depression	0	0	1 (1.4)	0	0

Epilepsy	0	0	0	0	1 (0.6)[a]
Face injury	0	1 (1.4)[b]	0	0	0
Failure to thrive	0	0	0	0	1 (0.6)[c]
Head injury	1 (0.8)	0	0	0	0
Jaw fracture	1 (0.8)	0	0	0	0
Laryngeal hypertrophy	1 (0.8)[f]	0	0	0	0
Mania	0	0	0	0	1 (0.6)
Mental status changes	0	0	0	0	1 (0.6)[d]
Neuroendocrine carcinoma metastatic	1 (0.8)[e]	0	0	0	0
Osteoarthritis	0	0	0	0	1 (0.6)
Overdose	1 (0.8)	0	0	0	0
Pancreatic duct stenosis	0	0	0	0	1 (0.6)
Pancreatic mass	1 (0.8)	0	0	0	0
Pneumonia	1 (0.8)	0	1 (1.4)	1 (1.4)	1 (0.6)
Pulmonary tuberculosis	0	0	0	0	1 (0.6)[f]
Procedural pain	0	0	0	0	1 (0.6)[c]
Psychomotor hyperactivity	0	0	0	1 (1.4)	0
Psychotic disorder	0	1 (1.4)	0	0	0
Renal failure acute	0	0	0	0	1 (0.6)[d]
Schizophrenia	0	0	0	0	1 (0.6)
Skeletal injury	0	1 (1.4)[b]	0	0	0
Sudden cardiac death	0	0	1 (1.4)	0	0
Suicidal ideation	0	0	1 (1.4)	0	0
Transient ischemic attack	0	0	0	0	1 (0.6)[a]

[a] Patient (b) (6) experienced two serious adverse events (epilepsy and transient ischemic attack).
[b] Patient (b) (6) experienced two serious adverse events (face injury and skeletal injury).
[c] Patient (b) (6) experienced 3 serious adverse events (abdominal pain, procedural pain, and failure to thrive).
[d] Patient (b) (6) experienced two serious adverse events (mental status changes and acute renal failure).
[e] Patient (b) (6) experienced two serious adverse events (metastatic neuroendocrine carcinoma and pancreatic mass).
[f] Patient (b) (6) experienced two serious adverse events (laryngeal hypertrophy and pulmonary tuberculosis).

Source: Adapted from Summary Clinical Safety, page 56

In the long-term safety study (C-20), the most common serious adverse events experienced during the overall treatment period were chronic obstructive pulmonary disease and schizophrenia (see Table 40). Three serious adverse events were considered by the Investigator possibly related to deutetrabenazine (stress urinary incontinence in Patient (b) (6) and intentional overdose and suicide attempt in Patient (b) (6); all other serious adverse events were considered unrelated or unlikely related to deutetrabenazine.

Reviewer Comment: Review of the narratives confirms that most of the SAE's did not appear to have a relationship to study drug. Patient (b) (6) was hospitalized for intentional overdose and suicide attempt on Day 134. Reportedly, the patient argued with her spouse over a minor issue and went into the bathroom, locked the door, and took an overdose of lorazepam. Given patient was on study medication for almost 5 months and there was a triggering incident prior to the overdose, I do not feel this event was related to study drug.

Table 40: Serious Adverse Events Occurring in ≥2 Patients in the Overall Treatment Period (Safety Population; N=304)

MedDRA System Organ Class MedDRA PT	Deutetrabenazine (N=304) n (%)
Number of patients with at least one serious adverse event	**29 (9.5)**
Infections and infestations	
Pneumonia	2 (0.7)
Urinary tract infection	2 (0.7)
Injury, poisoning, and procedural complications	
Fall	2 (0.7)
Psychiatric disorders	
Mental status changes	2 (0.7)
Schizophrenia	3 (1.0)
Suicidal ideation	2 (0.7)
Respiratory, thoracic, and mediastinal disorders	
Chronic obstructive pulmonary disease	3 (1.0)

Source: CSR 20 (page 94)

It should be noted that all case narratives and some CRF's were reviewed in the analysis of individual cases.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to withdrawal from the study occurred with similar frequency in placebo-treated patients and patients in the deutetrabenazine titration group (four patients [3.1%] vs four patients [2.5%]). No adverse events that led to withdrawal were reported for more than one patient, and almost all of the events were considered by the Investigator possibly related to study drug. In the long-term safety study (C-20), the most common reasons for patient discontinuation in the overall treatment period were diarrhea, depression, and anxiety (two patients each).

Many patients had a significant past psychiatric history such that an intermittent worsening of condition might be expected to occur as part of the natural progression of illness. As a result, determining the etiology of the some of the events below is challenging in light of this. However, as a whole, there were a relatively low number of discontinuations for both deutetrabenazine and placebo (see Table 41).

Table 41: Adverse Events Leading to Withdrawal in the Overall Treatment Period by Preferred Term and Patient Group (Safety Population)

Patient ID	Study	Treatment	Study Day	Reason
(b) (6)	C-18	Placebo	31	Heroin overdose
	C-23	Placebo	2	Diarrhea
	C-23	Placebo	1	Vomiting
	C-18	Placebo	14	Chest pain
	C-18	deutetra	18	Confusion
	C-23	12 mg	17	Prolonged QT
	C-23	12 mg	5	Vesicular Rash
	C-23	12 mg	10	Psychotic Disorder
	C-23	12 mg	32	Worsening schizophrenia
	C-23	24 mg	2	Suicidal ideation
	C-23	24 mg	7	Sudden cardiac death
	C-23	36 mg	3	Insomnia
	C-23	36 mg	38	Cardiorespiratory arrest
	C-23	36 mg	5	Psychomotor hyperactivity

ted

8.4.4. Scope of Adverse Events

Of the 1230 individual occurrences adverse events in the Safety Population, the majority were considered mild. Please review Section 8.3.2, Categorization of Adverse Events for further information regarding adjudication of events. During the overall treatment period, severe adverse events were reported for the same proportion of patients in the placebo and deutetrabenazine titration group (5 patients each, 3.8% and 3.1%, respectively). In the fixed-dose groups, one, three, and zero patients experienced severe adverse events in the deutetrabenazine 12, 24, and 36 mg groups, respectively. The vast majority of severe adverse events were in the context of serious adverse events (see section 8.4.2.)

Table 42: Classification of Adverse Events (Safety Population)

Classification of AE's in Safety Population		
Severity	Event Count	Event Count %
Severe	77	6 %
Moderate	385	31%
Mild	768	63 %

Reviewer Created

In the fixed-dose groups, 1, 3, and 0 patients experienced severe adverse events in the deutetrabenazine 12, 24, and 36 mg groups, respectively. Depression was the only severe adverse event reported in more than one patient (one placebo-treated patient and one patient receiving deutetrabenazine 24 mg).

In the long-term safety study (C-20), severe adverse events occurring in more than one patient were urinary tract infection (four patients), mental status changes (three patients), dehydration (two patients), fall (two patients), and sepsis (two patients).

Reviewer Comment: There was an overall low incidence of severe adverse events that occurred in the Safety Population. As noted previously, few of the severe events appear to be likely/probably related to study drug due to onset and duration of the event. Furthermore, many patients had comorbid medical conditions which made them vulnerable to serious medical events. Based on the aggregate data, there is not strong evidence that deutetrabenazine is associated with increased severity of adverse events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-related adverse events (independent of causality) were reported in similar frequencies in the placebo and deutetrabenazine titration groups (44 patients [52.6%] vs 61 patients [38.1%]. In the individual fixed dose groups, the frequencies of treatment-related

adverse events were all comparable, with 37 (49.3%), 32 (43.2%), and 38 (50.6%) patients in the deutetrabenazine 12, 24, and 36 mg groups, respectively experiencing an event.

Review of the AE listings revealed minimal splitting of terms. Examples of such Preferred Terms include somatic terms (*abdominal pain*, abdominal pain, gastritis) and psychiatric terms (*anxiety, depression, agitation,* and *restlessness*) were investigated to see if they represented different patients. A granular review did not reveal any obvious dilution of terms. I agreed with the groupings of TEAEs using preferred terms from MedDRA for both all three studies.

The adverse events (head count, removing unrelated ones such as infections) that occurred more than once with deutetrabenazine are as follows:

Table 43: Treatment-Related Adverse Events That Occurred in ≥2 Patients in the Overall Treatment Period by System Organ Class, Preferred Term, and Patient Group (Safety Population)

System Organ Class MedDRA preferred term, n (%)	Placebo	deutetrabenazine 12 mg	deutetrabenazine 24 mg	deutetrabenazine 36 mg	deutetrabenazine Titration
	N=133	N=75	N=74	N=75	N=160
Patients with at least 1 treatment-related AE	40(30.5%)	15 (20.0%)	12 (16.2%)	19 (25.3%)	58 (36.3%)
Gastrointestinal disorders					
Diarrhea	5 (3.8)	0	2 (2.7)	0	2 (1.3)
Dry mouth	5 (3.8)	4 (5.3)	1 (1.3)	1 (1.4)	1 (0.6))
Nausea	6 (4.5)	1(1.3)	0	0	3(1.9)
General disorders and administration site conditions					

System Organ Class MedDRA preferred term, n (%)	Placebo	deutetrabenazine 12 mg	deutetrabenazine 24 mg	deutetrabenazine 36 mg	deutetrabenazine Titration
	N=133	N=75	N=74	N=75	N=160
Fatigue	4 (3.0)	1(1.4)	1(1.4)	1(1.4)	5 (3.1)
Investigations	11 (8.2)	1 (0.8)			1 (0.6)
Weight increased	2(1.5)	0	1 (1.4)	0	2(1.3)
Nervous system disorders					
Dizziness	2 (1.5)	0	0	0	2 (1.3)
Headache	7 (5.3)	3 (4.0)	0	3 (4.0)	5 (3.1)
Somnolence	9(6.9)	0	1 (1.4)	2 (2.7)	17 (10.6)
Akathisia	0	0	1 (1.4)	0	2 (1.3)
Psychiatric disorders					
Anxiety	2 (1.5)	1 (1.4)	0	2 (2.7)	3 (1.9)
Depression	1 (0.8)	1 (1.4)	1 (1.4)	1 (1.4)	2 (1.3)
Insomnia	1 (0.8)	2 (2.7)	2 (2.7)	1 (1.4)	4 (2.5)

As noted in Table 43 **,** somnolence was the most frequent treatment-related adverse event reported in nine placebo-treated patients (6.9%), and 17 patients (10.6%) in the deutetrabenazine titration group. In the fixed dose groups, the frequency of patients who experienced somnolence was much lower, with zero, one (1.4%), and two (2.7%) patients in the deutetrabenazine 12, 24, and 36 mg groups, respectively.

Furthermore, treatment-related psychiatric disorders and nervous system disorders were more common in the deutetrabenazine titration group than in the placebo group. However, the differences appear minor (2 % versus 1%) given the magnitude of the study. Gastrointestinal disorders occurred more frequently in placebo treated cohort when compared than those in the deutetrabenazine titration group

Similar treatment-related adverse events were observed during long-term treatment (see Table 44).

Table 44: Treatment-Related Adverse Events with At Least Overall 2% Occurrence (Study C-20)

	Description of Actual Arm	
	deutetrabenazine	Total
	Count (%)	Count (%)
Total	N=304	N=304
Gastrointestinal disorders	47(15.5%)	47(15.5%)
Diarrhea	19 (6.3)	19 (6.3)
Dry mouth	11 (3.6)	11 (3.6)
Nausea	13 (4.3)	13 (4.3)
Salivary hypersecretion	6 (2)	6 (2)
Vomiting	9 (3)	9 (3)
General disorders and administration site conditions	16(5.3%)	16(5.3%)
Fatigue	16 (5.3)	16 (5.3)
Infections and infestations	36(11.8%)	36(11.8%)
Nasopharyngitis	17 (5.6)	17 (5.6)
Upper respiratory tract infection	8 (2.6)	8 (2.6)
Urinary tract infection	13 (4.3)	13 (4.3)
Injury, poisoning and procedural complications	6(2%)	6(2%)
Fall	6 (2)	6 (2)
Investigations	24(7.9%)	24(7.9%)
Weight decreased	7 (2.3)	7 (2.3)
Weight increased	17 (5.6)	17 (5.6)
Metabolism and nutrition disorders	7(2.3%)	7(2.3%)
Decreased appetite	7 (2.3)	7 (2.3)
Musculoskeletal and connective tissue disorders	18(5.9%)	18(5.9%)
Arthralgia	8 (2.6)	8 (2.6)
Muscle spasms	6 (2)	6 (2)

	Description of Actual Arm	
	deutetrabenazine	Total
	Count (%)	Count (%)
Musculoskeletal stiffness	6 (2)	6 (2)
Nervous system disorders	67(22%)	67(22%)
Akathisia	6 (2)	6 (2)
Dizziness	9 (3)	9 (3)
Dyskinesia	9 (3)	9 (3)
Headache	23 (7.6)	23 (7.6)
Somnolence	27 (8.9)	27 (8.9)
Tremor	7 (2.3)	7 (2.3)
Psychiatric disorders	54(17.8%)	54(17.8%)
Anxiety	30 (9.9)	30 (9.9)
Depressed mood	6 (2)	6 (2)
Depression	25 (8.2)	25 (8.2)
Insomnia	12 (3.9)	12 (3.9)
Respiratory, thoracic and mediastinal disorders	11(3.6%)	11(3.6%)
Cough	11 (3.6)	11 (3.6)
Vascular disorders	13(4.3%)	13(4.3%)
Hypertension	13 (4.3)	13 (4.3)

8.4.6. **Laboratory Findings**

Review of the tetrabenazine NDA and HD safety data did not suggest that deutetrabenazine would affect clinical laboratory findings in a significant manner. The Applicant's analysis was reviewed and shift tables created in JMP Clinical from the SDTM dataset. Clinical laboratory evaluations did not reveal any clinically important differences in mean test values between the patients in the deutetrabenazine and placebo groups in the placebo controlled studies.

Chemistry
There were no clinically meaningful changes from mean chemistry parameter values at baseline and no clinically meaningful shifts from normal to abnormal mean chemistry parameter values

were observed. However, there were increased liver function test values (including ALT and AST) were recorded for 5 patients in Study C-23 and 4 patients in Study C-20. In one patient (b) (6) Study C-23, 36 mg/day) shifts from normal to high values in ALT and AST led to a temporary interruption in study treatment. No action was taken with the study drug in any of the other patients and they were able to continue the study without issue. Liver enzyme laboratory results were analyzed in aggregate and reflected similar percentages of elevations among the patient treatment groups (see Table 45).

Table 45: Serum Liver Enzyme Results (Safety Population)

ALT Elevations

	Patient Treatment Group									
	Placebo		deutetrabenazine 12 mg		deutetrabenazine 24 mg		deutetrabenazine 36 mg		deutetrabenazine Titration	
ALT Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x Baseline	116	87.2%	65	86.7%	63	85.1%	68	90.7%	136	85.0%
Between 2x and 5x Baseline	15	11.3%	7	9.3%	9	12.2%	6	8.0%	19	11.9%
Between 5x and 10x Baseline	2	1.5%	3	4.0%	2	2.7%	1	1.3%	4	2.5%
Between 10x and 20x Baseline	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.6%
All	133	100.0%	75	100.0%	74	100.0%	75	100.0%	160	100.0%

AST Elevations

	Patient Treatment Group									
	Placebo		deutetrabenazine 12 mg		deutetrabenazine 24 mg		deutetrabenazine 36 mg		deutetrabenazine Titration	
AST Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x Baseline	127	95.5%	65	86.7%	66	89.2%	70	93.3%	149	93.1%
Between 2x and 5x Baseline	5	3.8%	9	12.0%	8	10.8%	5	6.7%	9	5.6%
Between 5x and 10x Baseline	1	0.8%	1	1.3%	0	0.0%	0	0.0%	2	1.3%
All	133	100.0%	75	100.0%	74	100.0%	75	100.0%	160	100.0%

Bilirubin Elevations

	Patient Treatment Group

	Placebo		deutetrabenazine 12 mg		deutetrabenazine 24 mg		deutetrabenazine 36 mg		deutetrabenazine Titration	
BILI Elevations	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x Baseline	105	78.9%	63	84.0%	67	90.5%	62	82.7%	124	77.5%
Between 2x and 5x Baseline	28	21.1%	12	16.0%	7	9.5%	13	17.3%	35	21.9%
Between 5x and 10x Baseline	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.6%
All	133	100.0%	75	100.0%	74	100.0%	75	100.0%	160	100.0%

Reviewer Created

Reviewer Comment: Individual narratives for the aforementioned cases were reviewed. Many of the patients had medical conditions (i.e., Hepatitis C) and concomitant medications which could have made them predisposed to liver enzyme elevations. There were no cases of Hy's Law in any of the trials.

With respect to hematology parameters, there were no clinically meaningful changes from mean hematology parameter values at baseline and no clinically meaningful shifts from normal to abnormal mean hematology parameters were observed. There were no notable changes in mean hematology parameter values over time in either placebo- or deutetrabenazine-treated patients. Nonetheless, there were a handful of adverse events related to hematologic abnormalities (anemia, white blood cell count increased) that occurred at similar frequencies in placebo-treated and deutetrabenazine treated patients. My review of the individual narratives did not support deutetrabenazine as a clear cause for any of these abnormalities.

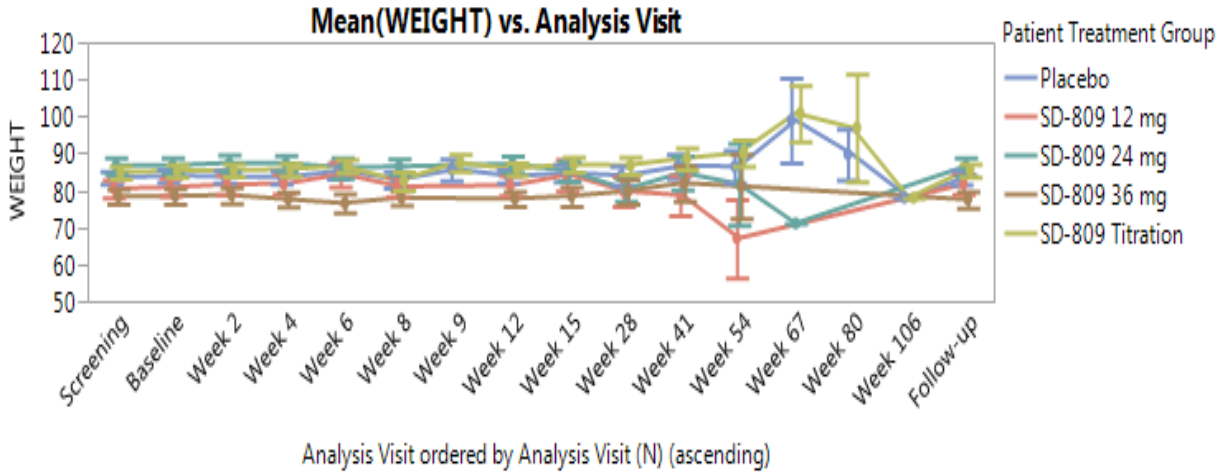
Lastly, there were no clinically meaningful changes in mean urinalysis parameter values (pH, specific gravity) from baseline and no clinically meaningful shifts from normal to abnormal mean urinalysis parameters were observed.

8.4.7. **Vital Signs**

There were no clinically significant effects of deutetrabenazine on vital signs, blood pressure, or pulse, in patients with TD. Changes from baseline in all blood pressure and heart rate measurements were minimal and comparable among the treatment groups at week 12/15. During the open label study, no clinically meaningful trends or changes from baseline were seen.

Similarly, there were marginal changes in body weight during the course of the study (Figure 8). Placebo-treated patients and patients in the deutetrabenazine titration group had increases in body weight of +0.2 kg and +0.4 kg, respectively. In the fixed dose groups, weight increase was approximately +1.0 kg. Lastly, in the open label safety study, the change in body weight was about + 0.1 kg at week 54 (see Figure 9).

Figure 9: Weight (kg) by Study Visit (All Subjects)



8.4.8. Electrocardiograms (ECGs)

During the drug developmental program, ECGs were performed as follows:

- **Study C-18**, a 12-lead ECG was conducted at screening, baseline, and weeks 2 and 12 or the last post-baseline observation. For patients on drugs that prolong the QT interval, a 12-lead ECG was also performed at weeks 4, 6, and 9.
- **Study C-23**, a 12-lead ECG was conducted at screening, baseline, and all clinic visits
- **Study C-20**, a 12-lead ECG was conducted at baseline and weeks 2, 4, 6, 28, 41, 54, and 106/early termination or the last post baseline observation. As noted previously, DPP requested changes in ongoing studies and in all future studies conducted under IND 120631 due to potential ECG-related concerns, which resulted in an amendment to Study C-20.

For all studies, a qualified physician at a central diagnostic center was responsible for assessing the ECG intervals (PR, QRS, QT, and QTcF) and for providing clinical interpretation of the ECG. Any ECG finding that was judged by the Investigator as a clinically meaningful change (worsening) compared with a baseline value was considered an adverse event, recorded on the CRF, and monitored. All ECGs were to be performed after at least 5 minutes of rest in a supine or semi-supine position.

In Study C-18, there were no investigator identified clinically significant ECG abnormalities during the study. In Study C-23, none of the patients had clinically significant abnormal ECG results reported during the study. Furthermore, none of the CV-related adverse events were temporally associated with QTcF prolongation. Consequently, there were no major safety signals seen upon review of the ECG parameters in the double blind studies.

However, at varying time points, there were modest increases in QTcF from baseline on deutetrabenazine relative to placebo. No specific pattern or dose dependent effect was observed.

Table 46: Mean Change (msec) from Baseline in QTcF (Safety Population)

Mean change QTcF from BL msec (SD)	C-18 Placebo (N=59)	C-18 Deutetra-benazine 12-48 mg (N=58)	C-23 Placebo (N=72)	C-23 Deutetra-benazine 12 mg (N=74)	C-23 Deutetra-benazine 24 mg (N=73)	C-23 Deutetra-benazine 36 mg (N=74)
Week 2	0.7 (16.58)	-1.9 (13.93)	0.3 (13.74)	1.8 (17.12)	3.9 (14.66)	0.1 (14.90)
Week 4	-0.7 (18.31)	3.4 (11.19)	-1.1 (17.05)	4.0 (17.81)	-1.2 (15.77)	2.2 (16.59)
Week 6	0.8 (22.40)	2.3 (20.03)	NA	NA[a]	NA	NA
Week 8	-0.2 (22.22)[b]	5.0 16.85)b	-0.4 (15.14)	-3.0 (14.94)	0.2 (15.03)	3.0 (15.91)
Week 12	-1.5 (18.47)	1.4 (14.55)	-4.7 (20.69)	6.5 (15.31)	2.7 (17.75)	3.4 (16.69)

Source, Cardiac Safety White Paper, page 31

This was further evidenced by reviewing the open label study data (see Table 47). A sizeable percentage (14%) of subjects had changes in baseline QTcF > 30 msec. While there are confounding factors (i.e.: medications, changes in medical condition, etc.) that could explain the increases in this interval, the data suggests that concurrent use of deutetrabenazine with other agents could lead to clinically significant increases in QTcF in a small percentage of the population. This will be furthered discussed in Section 8.4.9.

Table 47: Change in QTcF at Any Visit in Study C-20

	Number of patients (N=343)	Number of ECGs (N=1650)
Absolute QTcF >450 msec, n (%)	29 (8)	64 (4)
Absolute QTcF >480 msec, n (%)	6 (2)	15 (<1)
Absolute QTcF >500 msec, n (%)	3 (<1)	4 (<1)
Change from BL in QTcF >30 msec, n (%)	42 (14)	NA
Change from BL in QTcF >60 msec, n (%)	5 (2)	NA

8.4.9. **QT**

The Applicant conducted a Thorough QT study that was previously discussed by Dr Bergmann in his clinical review of NDA 208082 (Bergmann). Some of the salient findings from this study included that a single-dose administration of deutetrabenazine 12 mg and 24 mg led to maximum, time-matched, placebo-adjusted, average increases from baseline QTcF interval of 2.8 ms and 4.5 ms, respectively.

Further modeling was conducted to assess the potential for QT prolongation at supratherapeutic exposure to peak concentrations of major active deutetrabenazine metabolites, total (α+β)-HTBZ, using a population PK model for patients with HD with maximal exposure potential, i.e., patients with impaired CYP2D6 function who were receiving deutetrabenazine 48 mg per day.

The Applicant's conclusion was that *"these conditions yielded a mean Cmax for total (α+β)-HTBZ of 179 ng/mL. When this peak concentration was included in the regression equation that defines the relationship between plasma concentrations of total (α+β)-HTBZ and change in QTcF, the predicted placebo-adjusted, time-matched increase in the QTcF interval was 9.8 ms…"* The Applicant's interpretation was that this had no clinical impact

Initial review by the IRT led to the conclusion that "*no significant QTc prolongation effect of deutetrabenazine (deutetrabenazine) (12 and 24 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between deutetrabenazine (12 and 24 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. A marginal QT effect of tetrabenazine 50 mg was confirmed which is consistent with the increase*."

However, the IRT noted a major limitation in methodology in that *"the plasma α and β-HTBZ concentrations achieved with the single dose of 24 mg SD- 809 did not cover the expected steady state exposure (Cmax) following the highest therapeutic dose of 24 mg twice daily and the worst case clinical scenario (CYP2D6 poor metabolizer or administered a strong CYP2D6*

inhibitor). Clinically relevant QT prolongation might be expected in some patients at the highest therapeutic dose of 24 mg twice daily, especially in CYP2D6 poor metabolizer or patients co-administered a strong CYP2D6 inhibitor."

In the HD trials, Dr Bergmann noted that "*the mean (SD) QTc interval was slightly higher in the deutetrabenazine group compared with the placebo group at both screening (deutetrabenazine: 415.1 [18.0] ms versus placebo: 411.6 [18.7] ms) and Week 12(deutetrabenazine: 417.4 [17.6] ms versus placebo: 410.7 [20.9] ms). One patient in the deutetrabenazine group and three patients in the placebo group had a QTc >450 ms at Week 12. No participants in either group had a QTcF >480 ms."* (Bergmann).

The Applicant initially proposed to (b) (4) The IRT and Clinical Reviewer disagreed with this proposal due to previously discussed limitations of the TQT study and modeling. As part of discussions with the Applicant, the warning was removed with the following language added to section (b) (4) of the label (Label, 2017).

A clinically relevant QT prolongation may occur in some patients treated with AUSTEDO who are CYP2D6 poor metabolizers or are co-administered a strong CYP2D6 inhibitor [see Clinical Pharmacology (12.2, 12.3)].

(b) (4)

Reviewer Comment: My review of the HD data did not generate any concerns about clinically relevant prolongations in QT. However, these studies were both relatively small and prohibited use of antipsychotic medications. Approximately 80% of patients in the TD trials were on antipsychotic medications as well as other medications that have the potential to prolong the QT interval (i.e. antidepressants, antihistamines, etc.). Collectively, this leads to concern about the concurrent use of deutetrabenazine with medications that can prolong the QT interval.

As part of the 120 DSR, the Applicant provided additional cardiac safety data (SDN 9; 5/1/17) to strengthen support for the assertion that deutetrabenazine has no clinically significant cardiac liability. Additional data derived from modeling as well as a report by an external cardiovascular endpoint expert were provided for this purpose.

As part of a consult, the IRT reviewed these materials along with the current Austedo label. The team's conclusions are noted below (QT Interdisciplinary Review):

We disagree that deutetrabenazine has no significant cardiac liability.

- *In the thorough QT study only single doses of 12 and 24 mg were evaluated and the study did therefore not cover therapeutic (up to 24 mg BID) or supratherapeutic (CYP2D6 poor metabolizers or concomitant use with a CYP2D6 inhibitor) concentrations. Moreover, concentration-dependent QTc prolongation was observed in the study.*
- *The concentration-QTc model developed based on the thorough QT study data is based on the sum of α-HTBZ and β-HTBZ. An important assumption of this model is that the inhibition of hERG by α-HTBZ and β-HTBZ is similar and no data have been submitted to justify this assumption. The importance of this assumption is further strengthened by the observation that the ratio of α-HTBZ and β-HTBZ is changed in the presence of a CYP2D6 inhibitor.*
- *Deutetrabenazine when administered alone may not pose a significant cardiac liability; however, the risk of excessive QTc prolongation could occur when it is administered with a concomitant QT prolonging medication, with a CYP2D6 inhibitor or to patients who are CYP2D6 poor metabolizers. Administration of multiple drugs that prolong the QT interval to patients with underlying risk factors for torsade is of a concern with the use of deutetrabenazine.*
    - *In studies C-23 and C-20, there were 3 patients with QTc >500 ms and 6 patients with QTc >480 ms. No patient taking placebo had excessive QTc prolongation in study C-23. Patients with QTc prolongation were taking concomitant medications that are known to prolong the QTc interval. Furthermore, 4 patients were also taking CYP2D6 inhibitors that increase exposure to (α+β)-HTBZ. The percentage of patients with categorical QTc outliers may be under-reported because the timing of the ECGs relative to dosing was not controlled in the phase 3 trials.*
    - *No patients experienced torsade de pointes, but there were 6 patients in TD trials who died of cardiac events (1 each of sudden death and ventricular tachycardia).*

The IRT suggests that the label should theoretically have similar warnings for QT prolongation as those described in the package insert for tetrabenazine. However, this is not practical in the TD population given the high percentage of patients that will be on medications that can prolong the QTc interval.

Reviewer Comment: This issue is challenging given the background medications of the TD population. Avoiding use of deutetrabenazine in combination with medications that prolong the QT is highly impractical for that reason. I suggest labeling be modified to direct prescribers to obtain a baseline EKG prior to initiation of treatment and assess the QT interval before increasing the dosage in those subjects at increased risk of a prolonged QT interval.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Depression and Suicidality

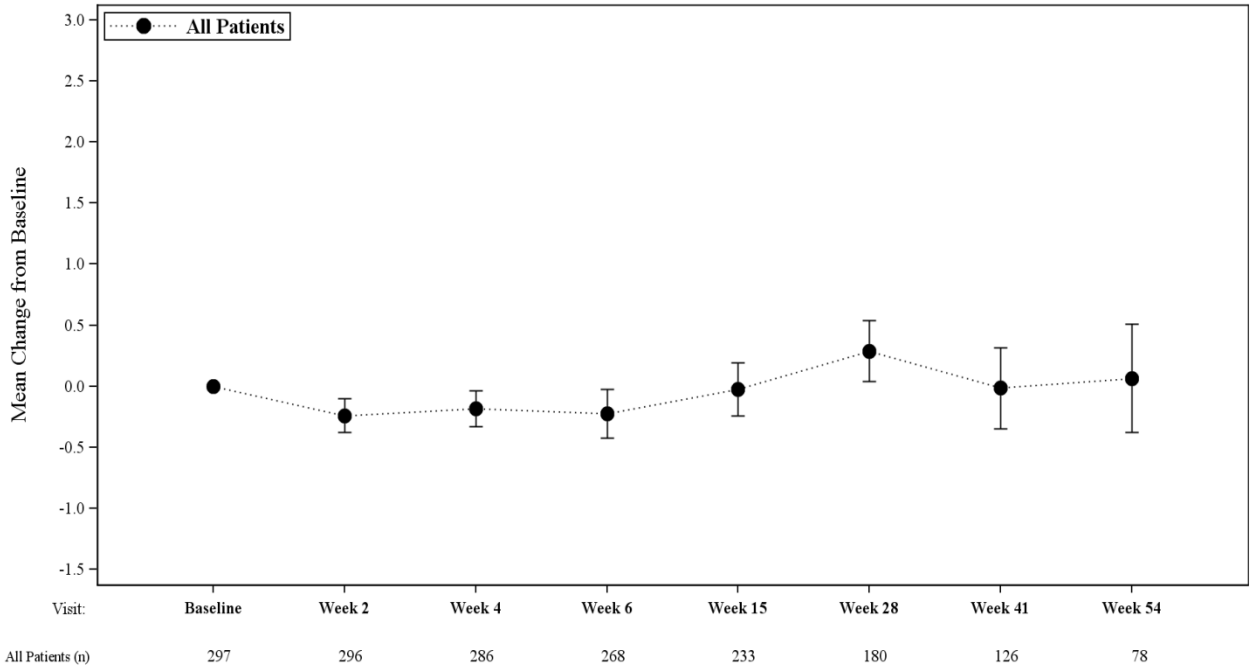
As noted in Section 8.1, there is a significant background incidence of both in the Huntington's disease population. Rates of depression were more than twice that found in the general population. One-half reported that they had sought treatment for depression, and more than 10% reported having at least one suicide attempt. In his review, Dr Bergmann noted the small sample size of the HD studies precluded an adequate determination of whether there was a clear increased risk of suicidality associated with treatment of deutetrabenazine. Furthermore, he commented that given background rates of depression in the *HD population, "the size of the population to see added risk due to treatment would be impossibly large"* (Bergmann). As a result, he deferred to the boxed warning in the RLD label to address this concern. Consequently the box warning regarding suicidality and depression was included in the initial Austedo label. However, the applicability of this warning to the TD population was unclear and warranted investigation.

The occurrence of depression and suicidality as a concomitant medical condition and as an Adverse Event were considered. Individual Medical History terms related to mood and various subtypes of depression and suicidality were grouped together for an initial analysis. Suicidality was analyzed independently as a secondary analysis.

Depression was evaluated through monitoring of adverse events and the HADS-D. Most depression events were mild or moderate. Severe depression was reported for one patient (Patient (b) (6) Study C-18; placebo), which was considered by the Investigator probably related to study drug. In this instance, study drug dose was suspended for 6 days. No further treatment was administered and the event resolve. There were no other "depression" adverse events that led to study discontinuation in the Safety Population.

The open-label data demonstrated that patients (7.2%) had a depression adverse event. Approximately, 50% of the study population was on background antidepressant medications. However, it does not appear any of these events lead to modification of dosage or discontinuation. The HADS-D change from baseline trajectories did not reveal any consistent increase in depressive symptoms (Figure 10).

Figure 10: HADS Summary Score Changes From Baseline of this Study to Each Visit for All Patients (Safety Population)



Source: CSR-20, page 389

Reviewer Comment: One of the limitations of the Applicant's analyses involves designation of treatment emergent AE's as having some type of relationship to study drug (i.e., suggestion of a relationship). I agree with this designation, but acknowledge it could dilute the frequency of events. However, when compared to placebo, there is not a consistent pattern that suggests deutetrabenazine differentially worsens depressive symptoms. This was further solidified by review of the individual case narratives that demonstrated other external factors and/or perhaps organic worsening depressive symptoms as the likely etiology of events.

Suicidality

Suicidality was monitored through the course of the clinical studies through the serial use of the C-SSRS and tracking of adverse events. At screening, a sizeable proportion of the study population (25% for suicidal ideation, 17% for suicidal behaviors) had positive C-SSRS scores at

screening (lifetime history). This reflects the severity of the population and possible predisposition to suicidal ideation/behaviors. However, review of the aggregate data did not reveal any safety signal with respect to deutetrabenazine having a differential effect on causing or worsening suicidality compared to placebo.

C-SSRS results (post-baseline) revealed a total of 14 patients in the safety population endorsed suicidal ideation. This included five placebo treated patients and nine deutetrabenazine treated patients (one (12mg), four (24 mg), two (36 mg), and two (deutetrabenazine titration)). There were only two patients that endorsed suicidal behaviors (one in the placebo group, one in the deutetrabenazine 24 mg group). There were no complete suicides. In the long-term safety study (C-20), nine patients had suicidal ideation, one patient had suicidal behavior, and no patient had completed suicide at any post baseline time point.

For one patient (Patient (b) (6), Study C-23, 24 mg), the suicidal ideation was a serious adverse event that started on Study Day 2. The event was considered moderate and possibly related to study drug and led to withdrawal from the study. However, as noted in Section 8.4.2, given the patient's past psychiatric history, it is difficult to determine whether deutetrabenazine was a contributing factor to her affective instability. The time course and reoccurrence of symptoms after study drug cessation supports the idea that study drug did not contribute to the suicidal ideation and depression.

In the long-term safety study, there were five patients (1.6%) with suicidality adverse events, three of which were designated as serious. These are highlighted below:

Patient (b) (6) was a 40-year-old female who participated in Study C-20 and had received deutetrabenazine in Study C-23. She had a history of schizophrenia, bipolar disorder, alcohol abuse (1 bottle of tequila per day), anxiety, depression, and suicidal ideation, and was taking hydroxyzine for anxiety secondary to schizophrenia and quetiapine fumarate for schizophrenia. The patient received the last dose of study drug on day 103 while on a dose of 36 mg/day. On day 215, the patient presented to the emergency department stating she was experiencing auditory hallucinations and "felt suicidal. Urinalysis was positive for amphetamine. The investigator considered the event of suicidal ideation as unrelated to deutetrabenazine.

Patient (b) (6) was a 79-year-old male who participated in Study C-20 and had received deutetrabenazine in Study C-23. He had a history of depression, schizoaffective disorder, and suicidal ideation. The patient had been receiving duloxetine hydrochloride for depression for several years as well as gabapentin for diabetic neuropathy. The patient's antidepressant therapy was changed from sertraline to duloxetine hydrochloride 12 days prior to the start of study treatment. He was on a 30 mg/day dose of deutetrabenazine at the time of the events. On day 45, the patient experienced a severe adverse event of worsening of depression associated with a severe family stressor. On day 55, the patient presented to the emergency

department with complaints of depression and suicidal ideation. Investigator considered the event of depression as unlikely related to study drug and the event of suicidal ideation.

Patient (b) (6) was described in Section 8.4.4. The investigator considered the events of intentional overdose and suicide attempt as possibly related to the study drug. However, the patient was on study drug for 134 days prior to the event and an external stressor (strife with husband); these were likely contributing factors.

In summary, the rates and severity of suicidal ideation/behaviors in the TD studies were relatively low. This data mitigates concerns about an increased risk of suicidality in the TD population and bolsters support for modifying the label to reflect this.

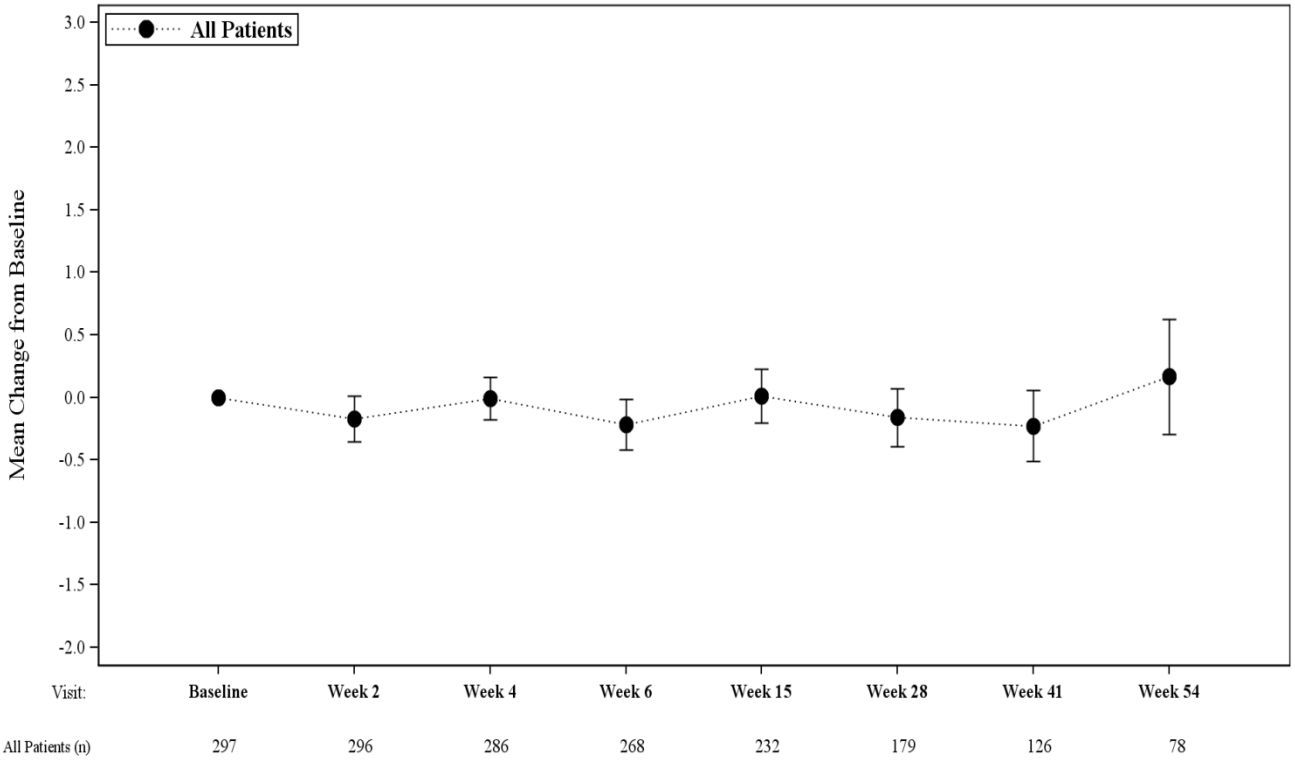
Reviewer Comment: The current label contains the warning "Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease." Consequently, the Applicant has already anticipated this warning does not apply to the TD population. It is important the prescribers understand the differentiation and it is well demarcated in the label.

8.5.2. Sedation and Somnolence

Somnolence and sedation were evaluated through monitoring of adverse events and the ESS. The TEAE (i.e., implying some causality) were reported for fewer patients in the placebo group than in the deutetrabenazine titration group (nine patients [6.9%] vs 18 patients [11.3%]). In the fixed dose groups, zero, one, and four patients in the deutetrabenazine 12, 24, and 36 mg groups, respectively, experienced somnolence or sedation. Most events were considered mild or moderate; however four events led to a dose reduction.

In the long-term safety study (C-20), 24 patients (7.9%) had an adverse event of somnolence or sedation. It should be noted that the somnolence rates were highest during the titration period. All events of somnolence or sedation reported in Study C-20 were mild or moderate in intensity; one event of moderate somnolence led to discontinuation from the study. ESS results did not demonstrate any significant patterns or trends. ESS scores were largely stable throughout the course of the open-label study (see Figure 11.

Figure 11: ESS-Total Score Changes From Baseline of this Study to Each Visit for All Patients Safety Population



Source C-20 CSR page 391

8.5.3. **Parkinsonism**

Parkinsonism was evaluated through monitoring of adverse events and the motor assessment score of the UPDRS. Adverse events of parkinsonism and related events were reported for 3 patients in the deutetrabenazine titration group and one placebo-treated patient. One patient in the fixed dose groups experienced an adverse event of parkinsonism (receiving deutetrabenazine 36 mg). All of the parkinsonism adverse events were considered mild or moderate in severity, and none were serious or led to discontinuation from the study. One patient had a dose reduction due to abnormalities in gait. In the long-term safety study (C-20), 12 patients (3.8%) had an adverse event related to parkinsonism. Again, all were mild to moderate, and none led to discontinuation from the study.

In all patient groups, UPDRS results revealed small decreases in score over time. Consequently, there was no evidence of increased motor impairment over time.

8.5.4. **Akathisia**

Akathisia and restlessness were evaluated through monitoring of adverse events, including all preferred terms that could map to akathisia (akathisia, hyperkinesia, psychomotor hyperactivity, and restlessness), and BARS summary assessment scores. Akathisia adverse events were reported for four patients (2.5%) in the deutetrabenazine titration group and one placebo-treated patient. Additionally, one patient in each of the deutetrabenazine 12, 24, and 36 mg dose groups experienced adverse events that could map to akathisia and restlessness.

The low prevalence of akathisia was further reflected in data from Study C-20. Five patients (1.3%) had an adverse event of akathisia. None of these events led to dose reductions or discontinuations. Small decreases in the BARS summary scores were observed for all patient groups up to week 12/15. However, there was not a consistent pattern or trend noted

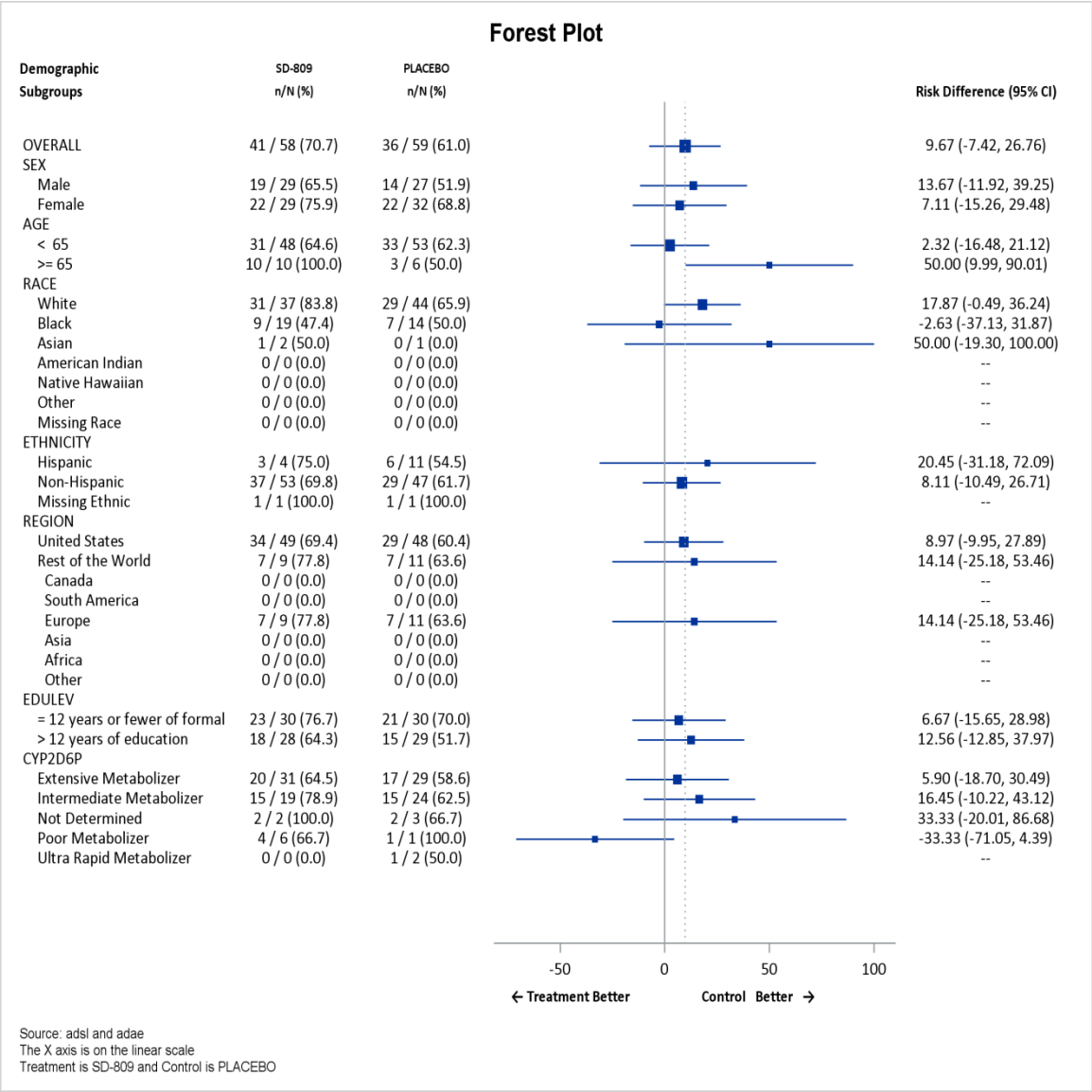
Reviewer Comment: Given the results of the parkinsonism and akathisia AE analysis, it appears that these symptoms are less prominent in the TD population (versus HD). This appears to have been a problematic issue in the HD population based on my review of the RLD. The Applicant may consider removing the warning (Akathisia, agitation, restlessness, and parkinsonism: reduce dose or discontinue if this occurs) from the warnings and precautions portion of the label applicable to the TD population.

8.6. **Safety Analyses by Demographic Subgroups**

Safety analyses by demographic sub-groups were conducted for each individual placebo controlled trial to explore the effect of possible interactions on safety signals/events. Pooled analyses were not utilized due to variations in study design and subsequent dosing regimens. Across measurements (e.g. vital signs, diagnostic labs, etc.) there were no specific demographic sub-groups that consistently had a significantly different safety profile as compared to the safety population.

The Office of Computational Science-Demographic Service assisted with intrinsic factor analysis (i.e.: gender, age, BMI, and CYP2D6 status, region) of the overall incidence of adverse events. Applicant provided ADSL & ADAE datasets were used generate the subgroup analyses.
In general, no factor including total motor AIMS score and impaired CYP2D6 function had a notable effect on the overall incidence of adverse events when comparing the deutetrabenazine titration group with the placebo-treated patients. Concomitant use of a strong CYP2D6 inhibitor at baseline also had no notable effect on adverse event frequency. An example of such analysis is shown in Figure 12 for Study C-18.

Figure 12: Study C-18 Forest Plot of Hazard Ratios by Patient Subgroups



Source: Reviewer Created via Office of Computation Science Output Table Program. ADSL dataset Study C-18.

Reviewer Comment: Subgroup analyses were hampered by the small patient population for certain demographic subgroups. For example, in Study C-18, there was only one CYP2D6 PM in the placebo treatment group. As a result, this made comparative analyses challenging and difficult to extrapolate to a larger population.

8.7. Additional Safety Explorations

8.7.1. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

A formal CSS review has not yet been completed. However, the reviewer (Alicja Lerner M.D.) had the following concerns:

- The current data on dependence, withdrawal and rebound was provided based on a small number of patients and from assessments collected for too short time period, thus precluding informed conclusions as to presence or absence of withdrawal and/or rebound

(b) (4)

As a result, she recommended the following

- Although no cases of abuse or misuse were reported in clinical trials we recommend continuing post marketing assessment of AEs suggestive of abuse-potential. These assessments should be included in the standard Periodic Adverse Event Reports (PADERS).
- Applicant should submit all data related to dependence, withdrawal, and rebound that are collected from the still on-going study # SD-809-C-20, including all adverse events and vital signs, and available scores of the efficacy and safety scales administered during the withdrawal period.
- Also, when assessing rebound it should be considered that during the first week of abrupt drug withdrawal the measures of disease symptoms frequently return to the baseline, and only in the next 2-3 weeks these measures may show rebound. Therefore all scales should be used for at least 3 weeks (at the end of each week) during the discontinuation period.

Reviewer Comment: The recommendations are reasonable in light of the limited data acquired after cessation of study medication. Having withdrawal and rebound data will be of great utility to clinicians in helping describe risks of stopping study medication.

8.8. Integrated Assessment of Safety

An overall review of the safety results from the clinical developmental program for TD supports the idea that deutetrabenazine is well tolerated over the range of designated therapeutic doses (12 mg to 48 mg). However, there are a few notable safety issues that warrant discussion as they impact the benefit/risk assessment of the compound.

Depression and suicidality

As mentioned previously, depression and suicide are much more common in the HD than the general population. Depression and suicidal ideation were observed in the premarket developmental program related to HD and TD. In his clinical review, Dr Bergmann noted only a handful of subjects in the HD placebo controlled trial had worsening depression or SI as an AE. None of the events were severe; however the applicability to the general HD was limited due to the small sample. With respect to TD, there were no consistent patterns or signals that emerged in the context of treatment with deutetrabenazine versus placebo. The rates of suicidal ideation were comparable to the background rate for the patient population. The ideation events that did occur were likely secondary to external stressors rather than precipitated by study medication. While the program was not powered to detect tangible differences in suicidal behaviors, the lack of such behaviors in the Safety Population was grossly reassuring.

This is in comparison to the RLD's 12-week, double-blind placebo-controlled study, 10 of 54 patients (19%) treated with Xenazine were reported to have an adverse event of depression or worsening depression compared to none of the 30 placebo-treated patients. In two open-label studies, the rate of depression/worsening depression was 35%. In all of the HD chorea studies of Xenazine (n=187), one patient committed suicide, one attempted suicide, and six had suicidal ideation.

As the risk of worsening depression and suicidality in the TD population appears differentially less compared to the Xenazine HD population, the boxed warning in the Austedo label regarding depression and suicidality is seemingly not applicable and should be omitted for this indication.

QT Prolongation

Based on inadequacies described in Section 8.4.9., I disagree with the notion that deutetrabenazine is associated with minimal cardiac liability. Clinical data from the registration studies support the idea that the compound will be dosed towards the higher part of the therapeutic range (i.e.: doses 36 mg and greater) implying a high percentage of subjects will be at risk for potential increases in QT. While the proposed label restricts dosing to 36 mg for those subjects using a CYP2D6 inhibitor, there are still significant concerns about using this dosage given exposures of B-HTBZ can increase 6.5x fold when using such medications. The Applicant did not provide data to further characterize the effect of each metabolite on QT interval. The clinical data also was concerning given numerous deaths that occurred during the

trials. While none of the deaths were clearly linked to prolongation of QT interval, the severity, chronicity of medical illness, and concomitant medication use surpass that seen in most psychiatric disease indications. Consequently, this leads to patients more vulnerable to QT prolongation and the possibility of torsades de pointes. The totality of the evidence supports the idea that deutetrabenazine may prolong the QT interval and warnings should be instituted to those patients that are CYP2D6 PM, take CYP2D6 inhibitors, or are co-administered that can prolong the QT interval.

Sedation and Somnolence

Somnolence and sedation were evaluated through monitoring of adverse events and the ESS. The TEAE (i.e., implying some causality) were reported for fewer patients in the placebo group than in the deutetrabenazine titration group (9 patients [6.9%] vs 18 patients [11.3%]). In the fixed dose groups, zero, one, and four patients in the deutetrabenazine 12, 24, and 36 mg groups, respectively, experienced somnolence or sedation. Most events were considered mild or moderate; however, four events led to a dose reduction. In the HD program, in Study C-15, somnolence as an AE occurred in 5 (11%) patients taking deutetrabenazine and only two patients in the placebo arm (4.4%).

In the Xenazine clinical program, sedation/somnolence occurred in 17 of 54 (31%) in the Xenazine arm and in one (3%) placebo patient. Sedation was the reason up- titration of Xenazine was stopped and/or the dose of Xenazine was decreased in 15/54 (28%) patients.

While the rates of sedation appear lower in the TD population, it does seem likely that deutetrabenazine has the potential to cause or exacerbate sedation. As the warning (sedation/somnolence: may impair the patient's ability to drive or operate complex machinery) appears in the Austedo label, it has generalized applicability to the TD population and should be unchanged.

Summary

In summary, a risk assessment of deutetrabenazine generates several specific safety issues that can be mitigated by modifying Austedo labeling and medication guides. PMR and/or REMS are not necessary as the safety issues identified are not novel. Furthermore, this product's safety profile is informed by prior experience with Xenazine. Comparative analyses of the safety databases leads to the conclusion that deutetrabenazine has a more advantageous safety profile.

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Labeling Recommendations

10.1. Prescribing Information

- **2.0 Dosing and Administration**:
  - 2.1 Dosing information was modified to reflect starting dosage to both TD and HD.
  - 2.3/2.4: Dosage adjustments for Strong CYP2D6 Inhibitors and Poor CYP2D6 Metabolizers were specified
- **4 Contraindications**:
  - Contraindications were carried forward from the XENAZINE label. The suicidality contraindication was only applicable to HD patients who are suicidal or have inadequately treated depression.

- **5.3 QT Prolongation**: Revisions are being proposed to more clearly describe the relationship between deutetrabenazine and prolongation of the QT interval. Specifically, language was added noting that in patients taking a strong CYP2D6 inhibitor who are poor metabolizers may have higher drug levels higher resulting in clinically significant QT prolongation. A dose reduction may be necessary in these individuals or those taking other drugs known to prolong the QT interval. In order to mitigate this risk, language instructing clinicians to assess the QT interval prior to increasing the deutetrabenazine dose was added.

- **6.0 Adverse reactions:** This section was separated by disease indication

- **7.0**
  - **7.2 Drug Interactions**: Drugs that cause QT prolongation are highlighted. Revised language includes the following statement:
    (b) (4) *assess the QT interval prior to initiation of treatment and before increasing the dosage of AUSTEDO when used in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications."*

- **12.0**

- **12.2 Pharmacodynamics**: The language was updated to state higher exposures to AUSTEDO or its metabolites have not been evaluated. (b) (4) .

- **14.0 Clinical Studies:** The following revisions are being proposed:
  - Language (b) (4) was removed (b) (4)
  - AIMS score was clarified as being the Total AIMS Score (across body regions) versus a score that implies differences related to a specific region of the body
  - (b) (4)

10.2. Patient Labeling

The Applicant submitted a Medication Guide. The guide was modified to describe common adverse reactions and to further clarify technical terms {i.e.; QTc prolongation as irregular heartbeat). OPDP's modifications were agreed to by the review team.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None.

12 Postmarketing Requirements and Commitments

The following post-marketing commitments will be proposed to the Applicant based on findings from this clinical review.

1. To better assess the persistence of deutetrabenazine treatment for TD, perform a study in which subjects who have demonstrated an adequate response to deutetrabenazine are randomized to receive placebo or continue their current dose. (b) (4) (b) (4)
2. (b) (4)

13. Appendices

13.1. References

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/s/

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