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APPLICATION NUMBER:

208082Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

2ND REVIEW CYCLE – COMPLETE RESPONSE

Application Type	NDA 505(b)(2)
Application Number	208082
Priority or Standard	Class 2 Resubmission
Submit Date	2016 October 03
Received Date	2016 October 03
PDUFA Goal Date	2017 April 03
Division / Office	DNP / ODE1 / OND
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	2017 February 27
Established Name	Deutetrabenazine (SD-809)
(Proposed) Trade Name	Austedo
Therapeutic Class	VMAT2 inhibitor
Applicant	Teva Pharmaceuticals, Inc.
Formulation	Oral tablets: 6, 9, and12 mg
Dosing Regimen	Up to 24 mg BID
Indication	Treatment of chorea in
Intended Population	Huntington's Disease

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

SD-809 or deutetrabenazine is the deuterated form of tetrabenazine, an orphan status designated drug approved for the treatment of chorea due to Huntington's disease (HD). While SD-809 has been designated a new molecular entity (NME), it is also a 505(b)(2) application using tetrabenazine (Xenazine, NDA 21894) as the Reference Listed Drug (RLD).

This is the second review cycle for this drug. The NDA submission was issued a Complete Response Letter (CRL) because the clinical pharmacology studies were not adequate to determine whether all major human metabolites of SD-809 had been identified. That information was needed to assess whether the bridge to the RLD was scientifically justified.

The clinical trials submitted in support of approval were fully reviewed in the first review cycle. The results of a single positive pivotal study (First-HD) were judged by the reviewer to be of sufficient quality to support a claim of effectiveness for the treatment of chorea in HD. In the clinical development program no new, novel, previously undescribed, or more frequent events occurred in the SD-809 safety population when compared to that of the RLD. While approvable on the basis of clinical efficacy and safety, the full risk of SD-809 could not be assessed because of the unanswered questions related to drug metabolites. Review of the safety update from an on-going open label safety study in HD provided in this Class 2 resubmission does not change the initial assessment of clinical risk and the risk-to-benefit balance for this drug remains favorable.

With resolution of the clinical pharmacology questions regarding metabolites and the bridge to the RLD, my clinical assessment of the safety and efficacy of SD-809 is in support of its **approval.**

The first cycle clinical review, relevant parts of which are summarized in the clinical sections below, is available in DARRTS:

http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af803e9849

1.2 Risk Benefit Assessment

SD-809 represents an additional oral therapeutic option for treating the chorea of HD patients. The clinical safety profile of SD-809 is acceptable given the severity of this disorder and the demonstrated benefit. The identified clinical safety concerns, shared by

the reference listed drug (RLD) for this 505(b)(2) application, can be adequately addressed through appropriate product labeling (including a boxed warning about depression and suicidality) and the Medication Guide.

As demonstrated by clinical trials performed in support of this application, SD-809 appears to provide benefits similar to the other available therapy for chorea, tetrabenazine, and represents a worthy additional oral treatment option for persons with Huntington's disease.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

SD-809 (deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Under the proposed proprietary name Austedo, approval is being sought for the treatment of chorea associated with Huntington's disease (HD).

The drug product is a tablet with 6, 9, or 12 mg of deutetrabenazine. The maximum proposed dose is 48 mg /d given orally in two divided doses with food. In persons who are poor metabolizers of CYP 2D6 or persons receiving concomitant medication that strongly inhibits CYP 2D6, the maximum proposed dose is 36 mg/d in two divided doses.

2.5 Presubmission Regulatory Activity Related to Class 2 Resubmission

Type A Post-Action Meeting - September 20, 2016
Following issuance of the Complete Response Letter on May 27, 2016, the sponsor requested further discussion on the development of SD-809. The discussion centered upon new data from bioanalytical characterization of M1 and M4 that purportedly demonstrated that M1 and M4 are minor metabolites, and to reach agreement with FDA that the bioanalytical results presented for M1 and M4 identifying them as minor complete the characterization of the metabolites of SD-809 in humans.

The sponsor discussed their plan and the Agency reiterated that this will be a review issue and recommended that the sponsor submit all supporting information/justification in the NDA resubmission.

The sponsor also had questions regarding the re-submission requests from the Controlled Substance Staff (CSS). The Complete Response Letter contained the following:

> "The data provided in the application suggest a possible rebound effect following withdrawal of deutetrabenazine. You need to conduct a systematic evaluation of clinical dependence. We recommend that you evaluate clinical dependence in patients as they complete Study ARC-HD (SD-809-C-16). We suggest you evaluate patients for signs and symptoms of clinical dependence for two weeks after discontinuing deutetrabenazine. In patients who chose to discontinue treatment with deutetrabenazine early, you should extend the follow up period after discontinuing deutetrabenazine to 3 weeks.
>
> You should administer the following scales to evaluate patients for signs of rebound:
> - Hospital Anxiety and Depression Scale (HADS)
> - Columbia Suicide Severity Rating Scale (C-SSRS)
> - Epworth Sleepiness Scale (ESS)
> - Montreal Cognitive Assessment (MoCA)
> - Total Maximal Chorea Score (TMC)
> - Unified Huntington Disease Rating Scale, including behavioral and cognitive scores
> - Unified Parkinson's Disease Rating Scale Speech/Dysarthria
> - Barnes Akathisia Rating Scale (BARS)
> - Berg Balance Test Score (BBT)
>
> We recommend you submit for FDA review your planned analyses for abuse potential and rebound."

CSS was not present at the meeting and responded in writing on November 2, 2016. In the meeting, the sponsor responded to the CRL that the comments from CSS relating to the assessment of possible rebound effect and clinical dependence were not an approvability issue. The sponsor indicated that because this assessment relies on completion of Study SD-809-C-16, which continues through marketing authorization in the US, it cannot be addressed as part of this complete response submission. The sponsor also reiterated that there was nothing in the side effect profile of the drug to suggest withdrawal or drug-seeking behavior.

CSS noted that "CSS agrees with the Sponsor that the drug is indeed not likely to have increased abuse potential" however, CSS on review of SD-809-C-15 (First HD) thought that the drug "appeared to produce rebound in ~20% of patients during the first week of withdrawal and tolerance that started week 9 during the treatment." Because this had not been evaluated in the development program in a systematic fashion with "appropriate tools and timing for the assessment of withdrawal symptoms …CSS repeats the request for the

evaluation of dependence, withdrawal and rebound and that you provide approximate dates of the final analysis of the study. The Sponsor should provide the requested data as soon as the study # ARC-HD (SD-809-C-16) is finished and analyzed; at this point it will be considered a Post-Marketing Commitment (PMC)."

Reviewer's comment: This is further discussed below in the review of safety, Section 7.6.4.

3 Ethics and Good Clinical Practices

Submission quality and integrity, compliance with Good Clinical Practices and financial disclosures were previously reviewed and deemed acceptable. No new studies in this indication or investigators were added in the interim.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.4 Clinical Pharmacology

The major reason of non-approval was due to residual review questions about the metabolites of deuterated tetrabenazine. In the CR letter, FDA indicated that the original analyses of the human [14C]-ADME and mass-balance study SD-809-C-12 was not adequate to determine whether SD-809 metabolites M1 and M4 were major or minor.

The sponsor validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) bioanalytical methods for M1 and M4 metabolites and analyzed the retained clinical plasma samples from the mass-balance study SD-809-C-12 for these metabolites.

Based on the reanalysis, M4 was determined to be a minor metabolite (about 6% of total drug related material (TDRM). The mean ratio of M1 as a percentage of TDRM was about 10%. Therefore, M1 is not a major human metabolite as defined by ICH M3(R2) as it does not circulate at levels greater than 10% of the total drug-related exposure.

This information reviewed during this resubmission was deemed adequate by the Clinical Pharmacology reviewer to support the approval of NDA 208082.

As a result no additional nonclinical pharmacological toxicology studies are needed.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 Clinical Studies (source: Complete Response Safety Update, page 16)

Study number	Design	Subject population	Subject characteristics	Treatment	Number of subjects exposed to SD-809	Study status
Phase 3 Study – randomized, double-blind, placebo-controlled, efficacy, and safety (SD-809 tablets)						
SD-809-C-15 (First-HD)	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of SD-809 in subjects with chorea associated HD	Adult subjects with manifest HD and chorea	Age range 23-74 years 55.6% male	SD-809 or placebo 6 to 48 mg/day, administered BID, titrated based on chorea control and tolerability	45 subjects	Complete
Phase 3 study – open-label, long-term safety (SD-809 tablets)						
SD-809-C-16 (ARC-HD), ARC-Rollover	Open-label, single-arm, long-term safety study of SD-809	Adult subjects with HD and chorea who completed First-HD	Age range 23-75 years 57.3% male	SD-809 6 to 72 mg/day, administered BID, titrated based on chorea control and tolerability	82 subjects[a]	Ongoing
SD-809-C-16 (ARC-HD), ARC-Switch	Open-label, single-arm, long-term safety study of SD-809	Adult subjects with HD and chorea currently receiving Xenazine[b]	Age range 32-75 years 59.5% male	SD-809 starting regimen based on algorithm for achieving AUC of total (α+β)-HTBZ comparable to that of Xenazine; titrated after 1 week based on chorea control and tolerability to maximum of 72 mg/day	37 subjects	Ongoing

5.2 Review Strategy

The designs of the cited trials are described in the first cycle review.

This clinical review looks at updated safety information on SD-809 for the period beginning on the closing date for the first review cycle 120 day Safety Update (March 31, 2015) and extending until the cut-off date for this complete response (March 31, 2016) . Because the First-HD trial had been completed, only open label data from the extension trial C-16 is new for this second cycle.

The sponsor reports that an additional 379 patients have been treated in development programs for indications of tardive dyskinesia and Tourette's syndrome. While these are populations very different from the HD population, some safety data from these programs is also reviewed.

6 Review of Efficacy

Efficacy Summary

No new efficacy data is submitted in this Complete Response.

The efficacy of SD-809 was demonstrated in the First-HD study (n=90), a randomized trial in which SD-809 was compared to placebo. Over an 8 week period, HD patients were given increasing doses of medication based upon control of their involuntary movement, up to a maximum of 48 mg/d given in two split doses. They were then observed on this stable dose for 4 weeks. Throughout this period, the severity of the movement disorder was blindly rated using the Total Maximal Chorea Score, a part of a standardized rating scale for HD. In addition, participants and their physicians were independently asked to rate how they felt they were doing overall. Over half the patients reached 48 mg/d. At the end of the study, the SD-809 group had reduced their chorea on average 2.5 points more than the placebo treated group, a statistically significant difference. In addition, 51% of the SD-809 group felt they were either "Much Improved" or "Very Much Improved" compared with only 20% of the placebo group. The patients' investigators thought 42 % of SD-809 patients and 13% of the placebo patients were so improved. These results were also statistically significant.

The study was judged by this reviewer to be of sufficient robustness and quality to support a claim of effectiveness for the treatment of chorea in HD.

7 Review of Safety

Safety Summary

First Cycle Safety Summary (from the primary clinical review, DARRTS 5/24/2016)

At the time of the 120 day Safety update, the safety population across the development program for SD-809 encompassed 229 persons who received at least one dose of medication.

There were no deaths reported in HD studies. Two deaths had occurred in the tardive dyskinesia development program; neither appeared to be drug related.

There were 624 instances of AEs. Of these, 19 were labelled as SAEs occurring in 13 patients. In the randomized and blinded Study C-15, 221 TEAEs occurred in 57 of 90 randomized patients: 111 events in 27 SD-809 patients and 108 events in 30 Placebo patients. Three patients with depression and suicidality were plausibly drug related serious adverse events. The rest appeared unrelated and common to neurologically ill patients. The most common adverse events occurring in SD-809 patients at a rate greater than placebo include: somnolence (11%), dry mouth (9%), fatigue (9%), insomnia (7%), anxiety (4%), back pain and constipation.

Events that were related to drop out in Phase 3 trials in addition to the SAEs noted above include 5 patients with depression, with or without suicidal ideation, and akathisia.

Dose reductions occurred in 17 patients in Phase 3 trials for somnolence (9), dizziness or imbalance (3), worsening depression (3) and akathisia (2).
Adverse events of special interest including suicidality and depression, akathisia, Parkinsonism, dysphagia, sedation and somnolence, and abuse potential including withdrawal and rebound were addressed at length in the first cycle review.

Second Cycle Safety Summary

No new or novel adverse drug effects were noted in the additional open label safety data for SD-809. No adverse drug effect increased over time with longer expose to SD-809. Following review of the clinical data, there was nothing to suggest that tolerance develops to the clinical efficacy of SD-809 or that withdrawal occurs on treatment cessation.

The balance between therapeutic benefit and the risk from taking SD-809 remains acceptable.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The additional safety data from the long term open label study C-16 are evaluated in this review. No new patients have been added to this study since the original NDA application.

At each visit during the open label study the safety evaluation included vital signs, clinical laboratory (chemistry, hematology and urine analysis), pregnancy test and the C-SSRS. An electrocardiogram was performed at weeks 4, and 8 and the end of treatment. A physical examination (including neurological examination) was to be performed at the end of treatment, which has not occurred for most patients enrolled in this study.

The sponsor also responded to requests to re-tabulate particular adverse events as described in Section 7.2, below.

7.1.2 Categorization of Adverse Events

As described in the first cycle review, the adverse events were collected and characterized in accordance with accepted ICH and FDA guidelines. The sponsor did this in an acceptable fashion. Adverse events were coded using MedDRA version 16.1 in C-15 and C-16 but other versions of MedDRA were used in the Phase 1 studies.

In the sponsor's safety update for this second cycle review, adverse event experience was presented in comparison to the first cycle AE data, as requested by the review team in the pre-submission meeting with the sponsor.

It is evident that the adverse event experience observed over this longer period is very much the same as described in the first cycle review. For the sake of clarity, the first cycle open label and second cycle open label adverse event data are combined for this safety review. Any pertinent changes are pointed out by the reviewer.

7.2 Adequacy of Safety Assessments

In the Complete Response Letter, the sponsor was asked to assemble the sections describing discontinuations due to adverse events, serious adverse events, and frequently reported adverse events, incorporate new safety data as follows:

- Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.

- Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- Present tabulations of the new safety data combined with the original NDA data. Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

- Review the characterization of certain adverse events and present a re-tabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from completed trials. Review all Psychiatry system-organ-class (SOC) adverse events in Study C-15 and Study C-16 for accuracy of the Preferred Term coding of the verbatim report of the adverse event. Provide a separate analysis for each study of all Psychiatry SOC events that led to an adverse event, a dose reduction, or a dose interruption regardless of whether the event was considered related to drug or not.

Reviewer's comment: while the sponsor fulfilled these requests, the findings were verified by the reviewer using the sponsor's own SDTM and ADaM datasets and, where

in agreement, the reviewer's tabulations are used. Any discrepancies between the sponsor's and reviewer's tabulations are noted.

7.2.1 Overall Exposure at Appropriate Doses/Durations

As submitted at the time of the first review cycle's 120 Day Safety Update, there were 229 persons who received at least one dose of SD-809. At the time of this submission, no additional patients received SD-809 in the HD development program. However, with continuation of the open label study C-16, there has been longer exposure to SD-809.

An additional 379 subjects have been exposed to SD-809 in 1 completed and 2 ongoing studies in patients with Tardive Dyskinesia and an additional 23 persons have been exposed to SD-809 in the completed study in subjects with Tourette's syndrome.

Exposure was calculated through the sponsor's cutoff date of March 31, 2016. First-HD had 45 patients who received drug in the active arm and an equal number received placebo. Of the 90 patients in First-HD, 82 rolled over into Study C-16 (ARC–Rollover). An additional 37 patients were switched from tetrabenazine to SD-809 (ARC-Switch), for a total of 119 patients in the open label long-term extension study.

In the first cycle the Phase 3 duration of exposure was described by this table derived from the sponsor's ADEX datasets (the double blind and open label populations were combined to derive this table):

Table 2 Duration of Exposure to SD-809 in combined Studies C-15 and C-16 in the first cycle review

Phase 3 Safety Population (N=121) - Duration of Exposure					
Epoch	≤ 3 months	≤ 6 months	≤ 9 months	≤ 12 months	>12 months
N	5	29	45	27	15

At the time of the data cut-off for this second cycle review of safety, 99 HD patients had had at least 1 year's exposure to SD-809. The average duration of treatment was 71 weeks and the longest duration of treatment for any HD patient is 75 weeks.

As of the data lock date for this submission, 90 of 119 participants remain in Study C-16. The sponsor's updated ADEX dataset in this submission shows that the number of patients in the ongoing C-16 open label study present at each visit is as follows:

Table 3 Study C-16 Patients remaining in the study by visit week

Visit Week	N reported
1	119
2	118
4	118
8	116
15	114
28	109
41	103
54	99
67	94
80	59
93	29
106	8

While the dose tested in First-HD was 48 mg/day (24 mg BID) or 36 mg/day (18 mg BID) if receiving a concomitant medication that was a CYP2D6 inhibitor, patients were titrated to best clinical response in the open label study at doses up to 72 mg/d. The first cycle review revealed 28 patients had been treated above 48 mg/d in Study C-16.

At the time of this submission, 119 patients had had1086 open label visits. At 283 (26%) of those visits, patients were taking more than 48 mg total daily dose (from the sponsor's ADEX dataset):

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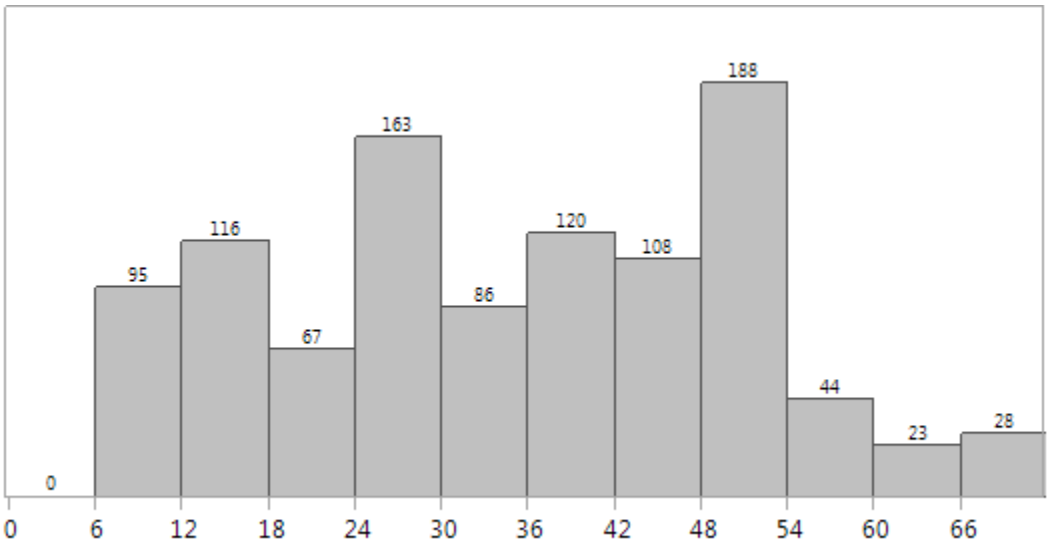
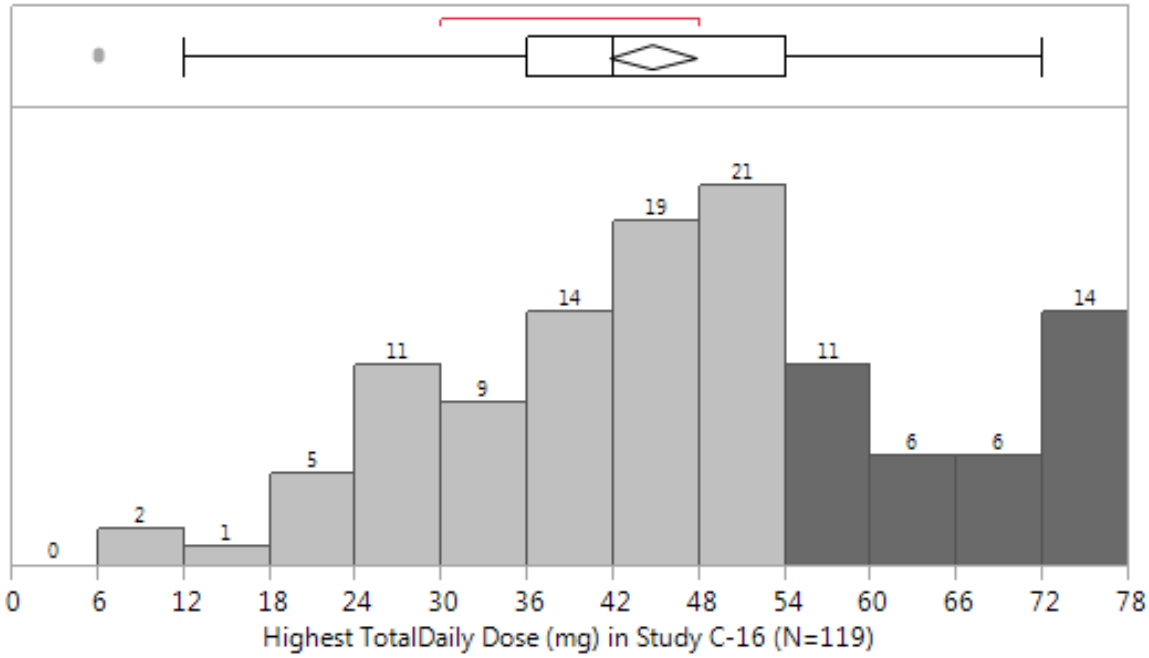
Figure 1 Study C-16 Number of visits at a given daily dose of SD-809



Of the 119 patients, 37 (31%) had their maintenance total daily dose above 48 mg/d. In this open label study the mean maintenance dose was 45 mg/d ± 16 mg/d SD (range 6 to 72 mg/d). Median dose was 42 mg /d with quartiles at 36 and 54 mg/d:

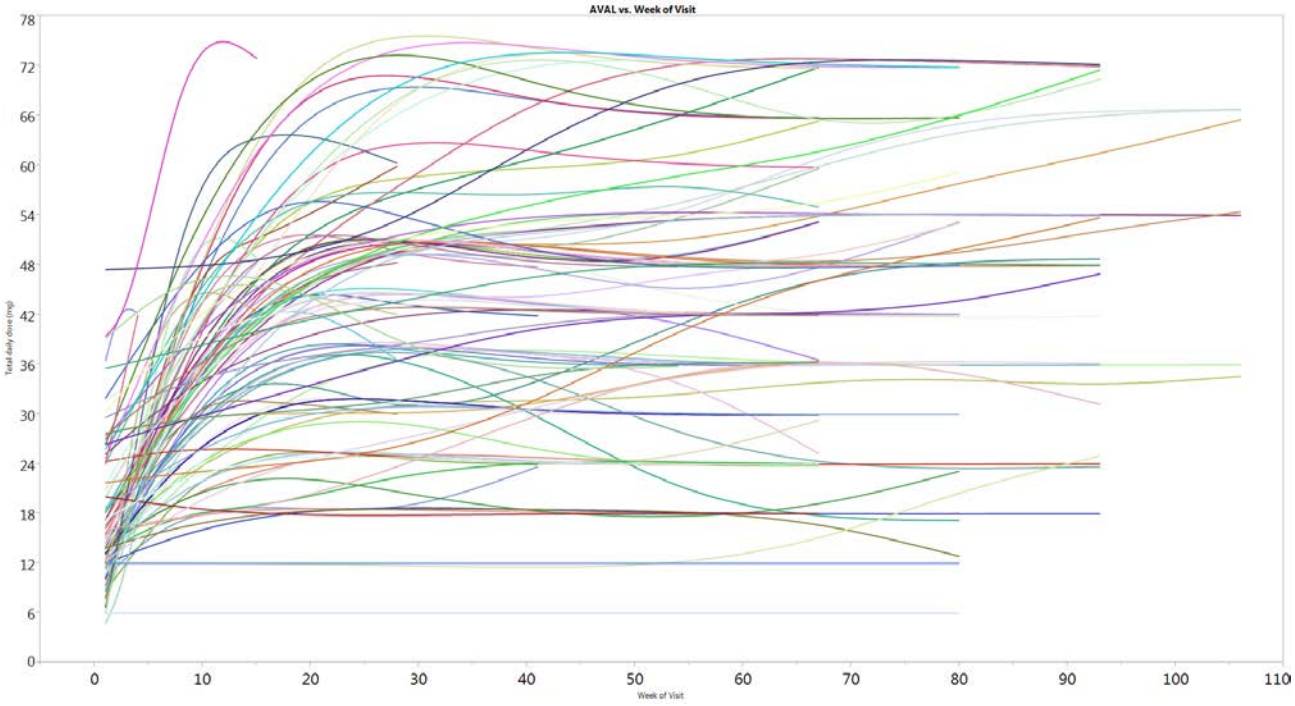
Figure 2 Study C-16 Maintenance dose (mg/d) by N (Sponsor's ADEX dataset)



Given the protocol-driven titration to best clinical response, it is interesting to note how long that took across the patient population. (Visits for this study took place at 1, 2, 4, 8, 15, 28, 41, 54, 676, 80, 93, and 106 weeks). Patients began at Week 0 with the dose they took in C-15 if they had been on active drug (up to 48 mg), or were titrated up from 0 mg, or were converted overnight from tetrabenazine (switch cohort).

As is evident from the total daily dose (Y axis) curves of each of the 119 patients, most patients were stabilized on their treatment dose by the Week 15 Visit (X axis) with lesser variation after that. This is consistent with the onset of drug effect of other catecholamine and indoleamine modulators of the central nervous system such as antipsychotic agents and antidepressants.

Figure 3 Study C-16 Total daily dose of SD-809 by patient by week



At the time of the data lock for this submission, 29 patients enrolled in Study C-16 have left the trial. The sponsor notes that “all of the early withdrawals due to adverse events occurred following at least 100 days of study participation.” The graphic representation of the titration of SD-809 in Study C-16 suggests that adverse events coincide with the onset of full drug effect after 15 weeks (105 days). This may explain why certain adverse drug effects begin to occur or occur more frequently in this study when compared to the C-15 placebo-controlled double-blind trial that lasted only 12 weeks (of which 8 were a titration phase).

7.3 Major Safety Results

The population of Studies C-15 and C-16 is described in the first cycle review. This clinical review addresses the newly submitted treatment emergent events but presents the safety experience of Study C-16 as a whole:

Table 4 Study C-16 Tally of important Treatment Emergent Adverse Events

Study C-16 TEAEs	First Cycle	Second Cycle	Total
SAE	19	13	32
Severe AE	26	24	50
AE leading to death	0	1	1
AE resulting in dose reduction	14	44	58
AE resulting in dose interruption	14	6	20
AE leading to withdrawal	4	5	9

Reviewer's Comment: It should be noted that the sponsor's Table 8 that summarizes TEAEs on page 30 of the Complete Response Safety update is entirely incorrect. The numbers in my table above are taken from the ADAE dataset. Checking this against my first cycle review, submitted CRFs, and narratives suggest that the SDTM and ADaM datasets are accurate.

7.3.1 Deaths

In the first cycle review, no deaths had occurred in the HD development program. There had been two deaths in the TD development program, both (appropriately) judged to have been unrelated to study drug.

There has now been a death in the HD program:

- Patient 029-3182, a 44-year-old man with no relevant medical history, died at home due to sudden cardiac death after receiving approximately 77 weeks of treatment with SD-809. An autopsy was not performed. At the time of enrollment, the patient had a QTcF of 403 ms and at Week 8, the subject had a QTcF of 400 ms while receiving 36 mg/day. The patient had been experiencing gradual worsening of his HD (dysphagia, dysarthria, gait disturbance, muscle rigidity, and somnolence) over 5 to 6 months before his death and SD-809 had been gradually reduced 18 mg/d two months before the patient's death. This death does not appear related to study drug.

Five additional deaths have been reported in the TD development program. The sponsor believes all are likely to be unrelated to SD-809:

- A 58-year-old woman discontinued study drug on day 241 as a result of an SAE of non-convulsive seizures. On day 260, she died as a result of brain stem infarction.

- A 73-year-old man, with a history of cardiac conduction disease had QTcF values of 405 to 451 msec on SD-809. A ventricular pacemaker was placed and his QTcF values increased to the 463 to 489 msec range. The patient was started on the prohibited medication sotalol on day 249 at 80 mg twice a day by his cardiologist, in an attempt to convert him to normal sinus rhythm from atrial flutter/fibrillation. On day 264, an ECG showed QT prolongation, with QTcF at 511 msec and on day 266 the sotalol dose was further increased by the subject's cardiologist to 120mg BID. On the merits of the QTcF changes alone, on day 270, study drug was suspended. On day 275, the subject died due to tachycardia. The site and medical monitor became aware of sotalol use after the subject's death.

  Reviewer comment: This event was assessed as unlikely related to study drug by the sponsor though it appears that a drug interaction cannot be ruled out.

- A 68-year-old woman with a family history of myocardial infarction had a fatal event of cardiopulmonary arrest that occurred 37 days after she started blinded study treatment.

- A 77-year-old man had a fatal event of sudden cardiac arrest that occurred 7 days after he started blinded study treatment. The patient had shown no signs of health deterioration the day before, and no AEs were noted.

- 71-year-old woman had a fatal event of cardiac arrest that occurred 243 days after she started the blinded study treatment.

7.3.2 Serious Adverse Events

Thirty-two SAEs occurred in 23 patients in Study C-16. Nineteen of these occurring in 13 participants have been previously reviewed. Two patients previously reported had new and unrelated SAEs. All resolved except for the patient who died and the patient with chronic moderate weight loss. Most are clearly unrelated to medication. The newly submitted SAEs are as follows:

Table 5 Study C-16 Serious Adverse Events

Patient	Age	Sex	Daily dose (mg)	Study day event began	Preferred Term	Severity	Outcome (All resolved except *)
SD809C15-007-	60	M	54	100	Penile cancer	Mild	Dose Unchanged

3047							
SD809C15-028-3582	64	F	42	158	Lethargy	Severe	Dose Unchanged
SD809C15-029-3181	60	F	24	522	Mental status changes	Severe	Withdrawn
SD809C15-029-3182	44	M	18	536	Sudden cardiac death	Severe	Fatal*
SD809C15-031-3621	47	F	48	286	Suicide attempt	Severe	Drug Suspended
SD809C15-031-3624	33	M	48	147	Appendicitis	Severe	Dose Unchanged
SD809C15-052-3323	45	M	60	287	Infection	Moderate	Dose Unchanged
SD809C15-052-3324	52	F	48	427	Deep vein thrombosis	Moderate	Dose Unchanged
SD809C15-052-3324	52	F	48	427	Pulmonary embolism	Moderate	Dose Unchanged
SD809C15-341-3841	53	M	66	416	Dehydration	Severe	Dose Unchanged
SD809C15-342-3863	52	F	60	176	Suicide attempt	Moderate	Dose Unchanged
SD809C16-007-7023	56	M	24	254	Pneumonia	Mild	Dose Unchanged
SD809C16-007-7023	56	M	24	316	Cellulitis staphylococcal	Mild	Dose Unchanged
SD809C16-020-7880	51	M	42	194	Intestinal obstruction	Moderate	Drug Suspended
SD809C16-020-7880	51	M	42	199	Weight decreased	Moderate	Dose Unchanged*
SD809C16-083-7329	46	F	36	517	Fall	Moderate	Dose Unchanged
SD809C16-083-7329	46	F	36	517	Laceration	Moderate	Dose Unchanged
SD809C16-093-7842	44	M	42	201	Pyelonephritis acute	Mild	Drug Suspended

7.3.3 Dropouts and/or Discontinuations

In study C-16, 29 of 119 patients (24%) have ended participation. The sponsor gives the following reasons for termination:

Table 6 Study C-16 Drop-outs and discontinuations (CR Safety Update, p 26)

Primary reason for withdrawal N = 29/119 (24%)	N (%)
Adverse event	12 (0.8)
Subject withdrawal	7 (5.9)
Investigator judgment	2 (1.7)
Lost to follow-up	1 (0.8)
Noncompliance with study drug dosing	1 (0.8)
Major violation or deviation of study protocol	1 (0.8)
Medication, potentially interfering with study	1 (0.8)
Death	1 (0.8)
Other	3 (2.5)

Some patients who developed adverse events were withdrawn from the study; 7 patients required no further treatment for the AE while 9 others required some further treatment before the event resolved:

Table 7 Study C-16 Adverse events leading to discontinuation

Patient	Age	Sex	Daily dose (mg)	Study day event began	Preferred Term	Severity	Additional AE-related treatment needed.
SD809C16-007-7021	56	F	54	553	Dysphagia	Moderate	N
SD809C16-007-7022	49	F	24	214	Sleep disorder, hypersomnia	Moderate	N
SD809C16-007-7023	56	M	18	536	Sudden cardiac death	Severe	N
SD809C16-020-7880	51	M	54	361	Communication disorder	Moderate	N
SD809C16-020-7881	54	F	54	361	Cognitive disorder	Moderate	N
SD809C16-031-7601	60	F	54	361	Chorea	Moderate	N
SD809C16-031-7602	61	M	30	213	Chorea	Severe	N
SD809C16-031-7603	53	M	48	250	Suicidal ideation	Mild	Y
SD809C16-031-7604	62	M	42	322	Anxiety	Moderate	Y
SD809C16-031-7605	60	M	42	322	Paranoia	Moderate	Y

SD809C16-052-7282	53	F	36	132	Major depression	Severe	Y
SD809C16-052-7284	32	F	24	522	Mental status changes	Severe	Y
SD809C16-054-7891	44	M	42	102	Depression	Mild	Y
SD809C16-057-7301	75	M	0	153	Anxiety	Moderate	Y
SD809C16-057-7302	49	F	36	256	Depression	Moderate	Y
SD809C16-057-7303	71	M	72	149	Failure to thrive	Severe	Y

7.3.4 Significant Adverse Events

Eighteen patients in C-16 had 50 adverse events considered severe. Three patients accounted for half of these; most patients had only one or two. Four patients were withdrawn from the study due to increasing depression, worsening chorea, altered mental state and "failure to thrive". Nine patients had doses reduced or interrupted for suicidal ideation or attempt (4) worsening mood (2), lumbar spine pain (2), weight loss, dysphagia, and restlessness (1, each). Three persons suffered falls, and the rest were either worsening of the patients underlying HD or incurrent illness (appendicitis, hip replacement, lacerations, degenerative joint disease, etc.)

Dose Reductions

Some patients with treatment emergent adverse events underwent dose reduction as part of the investigator's response, suggesting these AEs were considered by the investigator to be potentially related to SD-809. If the patient suffered an SAE or withdrew from the study, they are also considered in those relevant sections of this review:

Table 8 Study C-16 Adverse events leading to dose reduction

Patient	Age	Sex	Daily dose (mg)	Study day event began	Preferred Term
SD809C15-002-3003	71	M	36	234	Akathisia, anxiety, apathy, depression, dystonia, bradykinesia, rigidity, suicidal ideation
SD809C15-007-3041	62	F	36	547	Disturbance in attention
SD809C15-027-3163	69	F	60	378	Disturbance in attention
SD809C15-029-3181	60	F	30	379	Dysphagia, weight decreased

SD809C15-029-3182	44	M	36	347	Dysphagia, rigidity, dysarthria, dysphagia, somnolence, gait disturbance
SD809C15-031-3627	69	F	18	69	Psychomotor skills impaired
SD809C15-038-3701	59	F	24	26	Irritability, somnolence
SD809C15-040-3261	62	M	48	330	Restless legs syndrome
SD809C15-083-3362	58	M	54	253	Sedation
SD809C15-083-3369	61	F	48	114	Akathisia
SD809C15-083-3371	58	F	42	388	Akathisia, sedation
SD809C15-089-3681	30	F	30	30	Somnolence
SD809C15-160-3484	72	M	36	278	Fatigue, lethargy, somnolence, depression,
SD809C15-220-3521	31	F	36	35	Depression
SD809C15-333-3561	71	M	48	148	Agitation, depression, suicidal ideation
SD809C15-341-3841	53	M	72	161	Liver function test abnormal
SD809C15-342-3861	42	F	48	57	Fatigue
SD809C16-007-7022	49	F	36	486	Parkinsonism
SD809C16-007-7023	56	M	30	49	Suicidal ideation, depression, parkinsonism
SD809C16-031-7603	53	M	48	30	Akathisia
SD809C16-031-7605	60	M	60	378	Akathisia
SD809C16-057-7301	75	M	72	307	Fatigue
SD809C16-089-7632	63	M	48	51	Disorientation, somnolence
SD809C16-093-7841	46	F	24	24	Dizziness
SD809C16-199-7654	40	M	54	111	Muscular weakness, balance disorder
SD809C16-342-7822	40	F	72	127	Affective disorder

7.3.5 Submission Specific Primary Safety Concerns

With the increase in duration of exposure to SD-809, certain treatment emergent adverse events were looked at particularly closely as it was theoretically plausible that they could increase in severity or frequency. However, this did not appear to be the case:

Depression and Suicidality

The sponsor reports 34 patients have suffered with depression in Study C-16. Using the SDTM AE dataset reflecting the entire duration of Study C-16, with the Preferred Terms individually evaluated for depression and related terms (e.g.: mood disorder), there were 36 patients with depression. Seven adverse events of suicidal ideation and

2 suicide attempts were reported by the sponsor. An additional person with "depression suicidal" was found in the dataset.

In the first cycle review, in Study C-16, depression related Preferred Terms occurred in 26 patients and 5 had suicidal ideation as well. Given the additional exposure to SD-809 since the first cycle review, risk for this psychiatric disturbance does not appear to increase over time over time.

In response to a request from the review team, the sponsor reevaluated all psychiatric adverse event descriptions for correct mapping to Preferred Terms. They made three corrections which do not alter the safety profile for SD-809 in any way. Tables derived by the reviewer from the SDTM AE dataset for Study C-16 is below in section 7.4.1.

Table 9 Study C-15 Sponsor's summary of psychiatric adverse events (Response to information request, 1.11.4, Table 2, p 8)

Preferred Term	SD-809 (N=45) n (%)	Placebo (N=45) n (%)	Withdrawal/Dose Reduction/Dose Suspension
Abnormal dreams	1 (2.2)	1 (2.2)	
Agitated depression	1 (2.2)	0 (0.0)	Event led to dose suspension
Agitation	1 (2.2)	0 (0.0)	Led to withdrawal from study
Anxiety[a]	1 (2.2)	1 (2.2)	
Compulsions	0 (0.0)	1 (2.2)	
Depression	1 (2.2)	3 (6.7)	
Impulsive behaviour	0 (0.0)	1 (2.2)	
Insomnia	3 (6.7)	2 (4.4)	
Restlessness	1 (2.2)	0 (0.0)	
Sleep disorder	0 (0.0)	3 (6.7)	
Suicidal ideation	1 (2.2)	0 (0.0)	Led to dose suspension

Table 10 Study C-16 Sponsor's summary of psychiatric adverse events (Response to information request, 1.11.4, Table 3, p 9)

Preferred Term	Rollover Cohort (N=82) n (%)	Switch Cohort (N=37) n (%)
Affective disorder	0	1 (2.7)
Aggression	1 (1.2)	0
Agitation	3 (3.7)	1 (2.7)
Anxiety	16 (19.5)	9 (24.3)
Apathy	4 (4.9)	1 (2.7)
Communication disorder	1 (1.2)	0
Confusional state	0	1 (2.7)
Delirium	1 (1.2)	0
Delusion	1 (1.2)	0
Depressed mood	0	1 (2.7)
Depression	24 (29.3)	7 (18.9)
Depression suicidal	1 (1.2)	0
Disorientation	0	1 (2.7)
Dysphoria	1 (1.2)	0
Insomnia	18 (22.0)	4 (10.8)
Intermittent explosive disorder	1 (1.2)	0
Major depression	1 (1.2)	0
Mental status changes	1 (1.2)	0
Mood altered	1 (1.2)	1 (2.7)
Negative thoughts	1 (1.2)	0
Obsessive thoughts	1 (1.2)	0
Paranoia	2 (2.4)	0
Perseveration	2 (2.4)	0
Sleep disorder	4 (4.9)	1 (2.7)
Sleep disorder due to general medical condition, hypersomnia type	1 (1.2)	0
Suicidal ideation	5 (6.1)	2 (5.4)
Suicide attempt	2 (2.4)	0
Tic	1 (1.2)	0

Akathisia
In the first cycle review, in Study C-16, akathisia occurred in 5% of the participants. In Study C-16 overall, 8 patients (6.7%) have experienced this restlessness to date.

Parkinsonism
While 3 patients had reported Parkinsonism in C-16, the overall tally in this review is 5 patients (4.2%) to date.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events occurring in the open label Study C-16 were tabulated. The Preferred Terms found in the sponsor's SDTM AE dataset were reviewed and edited by the reviewer for accuracy prior to tabulation. For example, nausea and vomiting were combined into a single event as were all terms related to affect and depression.

Virtually all patients (116 of 119) had at least one AE. Of the 800 AEs occurring in this C-16 cohort, 50 AEs were characterized as severe, 234 as moderate, and 516 as mild. Most moderate and severe AEs occurred in the Nervous System and Psychiatric SOCs:

Table 11 Study C-16 Moderate and severe AEs by SOC

System Organ Class	N (AEs, MODERATE)	N (AEs, SEVERE)
Psychiatric disorders	64	16
Nervous system disorders	43	10
Injury, poisoning and procedural complications	25	7
Gastrointestinal disorders	16	3
Infections and infestations	22	3
Metabolism and nutrition disorders	5	3
Musculoskeletal and connective tissue disorders	9	3
Reproductive system and breast disorders	4	2

Outside of the adverse events discussed in Deaths and SAEs above, no new or novel adverse events occurred in this Complete Response update.

The tables below list all Nervous System and Psychiatry SOC AEs. It is clear that with the longer duration of exposure some AEs developed that were not seen in the shorter duration pivotal trial. These include Parkinsonism, depression and suicidality that had been previously noted in the first cycle review. The two patients with suicidal attempts are in addition to the occurrences of suicidal ideation.

Table 12 Study C-16 Nervous system disorders SOC AEs

System Organ Class	Preferred Term	N (Head Count)	%
Nervous system disorders	Somnolence	27	22.7
	Chorea	12	10.1
	Akathisia	8	6.7

	Cognitive disorder	5	4.2
	Memory impairment	5	4.2
	Parkinsonism	5	4.2
	Disturbance in attention	3	2.5
	Dizziness	3	2.5
	Drooling	3	2.5
	Dysarthria	3	2.5
	Headache	3	2.5
	Lethargy	3	2.5
	Sedation	3	2.5
	Bradykinesia	2	1.7
	Dyskinesia	2	1.7
	Encephalopathy	2	1.7
	Syncope	2	1.7

Table 13 Study C-16 Psychiatric SOC AEs

System Organ Class	Preferred Term	N (Head Count)	%
Psychiatric disorders	Depression	36	30.3
	Anxiety	25	21.0
	Insomnia	24	20.2
	Suicidal ideation	8	6.7
	Sleep disorder	6	5.0
	Apathy	5	4.2
	Agitation	4	3.4
	Paranoia	2	1.7
	Perseveration	2	1.7
	Suicide attempt	2	1.7

The sponsor in this Study C-16 update separated the adverse events in the C-15 rollover population from those that occurred in the overnight switch population of Study C-16. However, given the duration of exposure remote from the switch portion of the study at this time and the lack of a qualitative difference in the AEs in these two study populations they are considered as one population in this review. (The overnight switch from tetrabenazine to SD-809 is discussed in the first cycle review.)

Table 14 Study C-16 Most frequent relevant AEs by Preferred Term occurring in the Rollover and Switch cohorts.

Study C-16: Rollover Cohort N=82; Switch Cohort N=37				
AE Preferred Term	ROLLOVER AE Head Count	ROLLOVER %	SWITCH AE Head Count	SWITCH %
Depression	25	30.5	7	18.9
Fall	24	29.3	14	37.8
Insomnia	19	23.2	5	13.5
Anxiety	16	19.5	9	24.3
Somnolence	16	19.5	11	29.7
Fatigue	8	9.8	2	5.4
Irritability	8	9.8	3	8.1
Chorea	7	8.5	5	13.5
Akathisia	5	6.1	3	8.1
Sleep disorder	5	6.1	1	2.7
Suicidal ideation	5	6.1	2	5.4
Apathy	4	4.9	1	2.7
Agitation	3	3.7	1	2.7
Cognitive disorder	3	3.7	2	5.4
Dysarthria	3	3.7		
Gait disturbance	3	3.7	2	5.4
Lethargy	3	3.7		

7.4.2 Laboratory Findings

No safety signals related to clinical laboratory findings were observed in the updated results provided for Study C-16 as of the visit cut-off for the NDA complete response. There are no clinically meaningful shifts in urine, hepatic, or hematological indices. There were sporadic elevations of liver function (2 patients) increased blood lipids (4 patients), increased creatinine (1 patient) and I patient with increased BUN. These were not of clinical significance.

7.4.3 Vital Signs

Vital signs (heart rate and blood pressure measurement) demonstrated no pattern of clinically meaningful change over the course of the open label study.

7.4.4 Electrocardiograms (ECGs)

No meaningful events related to electrocardiograms occurred in this study except coincident to cardiac events in individuals described above.

7.6 Additional Safety Evaluations

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There had not been concern about habituation in the RLD tetrabenazine for this 505(b)(2) application, but the issue has been raised by the Controlled Substance Staff for SD-809. This topic was initially discussed in the first cycle review.

Abuse or the intentional nontherapeutic use of SD-809 was not encountered in the SD-809 development program. This was ascertained by compliance measures, which included the return of used pill containers and tablet counts. The recorded instances of non-compliance are due to reduced medication use.

Adverse events suggesting abuse potential include euphoria, hallucinations, perceptual disorders, altered cognition and disordered mood. In this study population mood and cognitive disorders are confounded by the underlying disease process. Nevertheless these events did not occur in the placebo controlled pivotal C-15 trial. In Study C-16, no instances of hallucination, euphoria or other elevation of mood occurred.

No instances of overdose were encountered in the HD development program.

While the development of tolerance for SD-809 was not directly investigated, Figure 3 above illustrates the maintenance dose of SD-809 (dictated by clinical response) over the course of the open label study. The dose curves of individual patients do not suggest that there was any need for increasing the dose to maintain the therapeutic effect over periods of observation of up to two years. In actual calculation, at the Week 15 visit when a stable maintenance dose had been achieved, 114 participants had a mean total daily dose of 40.5 ± 13.8 mg SD. At Week 54, 99 remaining participants had a mean total daily dose of 42.8 ± 15.8 mg SD. Of the 59 participants having reached Week 80, the mean total daily dose was 43.9 ± 16.6 mg SD.

Dependence was investigated by looking at patients' individual responses at the end of Study C-15. Study drug was withdrawn from the patient for 1 week prior to rolling over to the open label extension study C-16. The 44 patients who had been on active drug and completed study C-15 provide an opportunity to observe for any physiological signs of withdrawal. The placebo arm had 43 completers.

The sponsor, in response to requests from CSS performed a search for events relating to drug abuse, drug dependence, and drug withdrawal, as well as euphoric mood, using

standardized MedDRA query (SMQ) terms; no such adverse events were found in Studies SD-809-C-15 and SD-809-C- 16. They note that the studies in the SD-809 clinical development program did not reveal any tendency for drug-seeking behavior and that abuse has not been reported from the postmarketing experience of the RLD, tetrabenazine.

Concern has been raised by CSS that scales reflecting the disease state may have worsened beyond baseline measurements and that this represents a withdrawal state. The sponsor addressed this by looking at scores for the Total Motor Score (TMS) for the UHDRS, the Barnes Akathesia Rating Scale, the Berg Balance Test and the dysarthria item on the UHDRS. (1.11.3 Response to FDA Request for Information)

The mean TMS in SD-809 treated patients improved at Week 12 and returned nearly to baseline following washout of the study drug however the Week 13 score does not exceed the Baseline score and does not demonstrate rebound. (Table 2, page 5)

Table 15 Study C-16 TMS score before and after SD-809 washout at study end (Sponsor's CR safety update, Table 2, p 5)

		SD-809 (N=45)		Placebo (N=45)	
Visit	**Statistic**	**Value**	**Change from Baseline[a]**	**Value**	**Change from Baseline[a]**
Baseline[a]	n	45	-	45	-
	Mean	34.06	-	38.82	-
	SD	13.174	-	15.162	-
Week 12	n	45	45	43	43
	Mean	28.04	-6.01	36.07	-2.69
	SD	16.259	7.910	16.072	6.269
Week 13	n	44	44	43	43
	Mean	33.43	-0.68	39.60	0.16
	SD	16.006	6.253	16.372	6.221

The same is true of the akathisia score, though there is no physiological reason why it should rebound (worsen) as it is a potential treatment-related adverse effect. It is also not clear what a clinically important difference in the Barnes Scale might be in this population (the mean variation was approximately 0.7 points (between 0.7 and 1.4) over the course of the trial) within the active treatment arm. This is also true of the Berg Balance Test score which varied narrowly on average between 51.3 and 53 over the course of the trial

Vital signs (heart rate, systolic and diastolic blood pressure) are autonomic indices that can indicate a physiological state of withdrawal. To this end, measurements of systolic and diastolic blood pressure and heart rate taken in the supine position were compared for each patient in Study C-15 between the active and placebo groups at Visit 12 (the last visit with drug treatment) and Visit 13, one week after treatment cessation.

Unfortunately, the sponsor had vital signs taken when the patient was supine and standing at Visit 12 but only sitting at Visit 13. Paired comparisons for the supine to sitting measurements were made for [Week 12 Supine-Week 13 Sitting] parameters and grouped for the active and placebo arms of Study C-15.

Table 16 Study C-15 Vital signs before and after SD-809 washout at study end

Vital signs 1 week after treatment cessation (Matched Pairs comparison by patient)				
	SD-809 (n=44) Placebo (n=42)	Mean Mean	Mean difference from Week 12 to Week 13	p
Heart Rate (bpm)	SD-809	68.3	-3.7	Within pairs p = 0.5174
	Placebo	70.7	-2.4	Among pairs p = 0.1641
Systolic BP (mmHg)	SD-809	119.3	0.1	Within pairs p = 0.9376
	Placebo	122	0.4	Among pairs p = 0.3209
Diastolic BP (mmHg)	SD-809	73.2	0.5	Within pairs p = 0.8113
	Placebo	74.4	1	Among pairs p = 0.4992

No elevation of these autonomic parameters occurred and there is no suggestion of a withdrawal state one week after drug withdrawal.

Reviewer's comment: With reliance upon what is known about the RLD for this application, in addition to the lack of any indication of withdrawal one week following drug cessation in a placebo controlled study, this reviewer has not found data to support the need for additional safety studies related to habituation of SD-809 and does not have further concern about the abuse potential of SD-809.

9 Appendices

9.2 Labeling Recommendations

Label changes made by the clinical team throughout this review cycle have been shared with the sponsor. Major items of importance include:

Boxed warning
Depression and suicidality
Dosing and Administration:
Dose titration,
Conversion from tetrabenazine treatment
Maximum dose considerations in CYP2D6 poor metabolizers or with CYP2D6 inhibitors.
Warnings and Precautions
Depression and suicidality
Neuroleptic Malignant Syndrome
Akathisia
Dysphagia and pneumonia
Sedation and somnolence

6 Clinical Trial Experience
Preliminary table of adverse events in Trial C-15 is as follows:
Adverse Reactions in a 12-Week, Double-Blind, Placebo-Controlled Trial Experienced by at Least 4% of Patients on AUSTEDO and Greater than Placebo

Adverse Reaction	SD-809 (N=45) n (%)	Placebo (N=45) n (%)
Somnolence	11.	4
Diarrhea	9	0
Dry mouth	9	7
Insomnia	7	4
Fatigue	7	4
Irritability	7	13
Depression	4	7
Dizziness	4	9
Constipation	4	2
Urinary tract infection	4	2
Contusion	4	2

(b) (4)

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/s/

KENNETH J BERGMANN
03/20/2017

GERALD D PODSKALNY
03/28/2017

Office of Drug Evaluation-I: Decisional Memo

Date:	May 27, 2016
From:	Ellis F. Unger, M.D., Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject:	Office Director Decisional Memo
NDA #:	208082
Applicant Name:	Teva Pharmaceuticals, Inc.
Date of Submission:	May 29, 2015
PDUFA Goal Date:	May 29, 2016
Proprietary Name:	Austedo
Established (USAN) Name:	Deutetrabenazine (SD-809)
Dosage Forms/ Strengths:	Oral tablets: 6 mg, 9 mg, and 12 mg
Indication:	Treatment of chorea in patients with Huntington's disease.
Action:	*Complete Response*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Stacy Metz
Medical Officer Clinical Review	Ken Bergmann
Clinical Pharmacology Review	Kristina Dimova; Angela Men; Xiaofeng Wang; Kevin Krudys; Jeffrey Kraft; Christian Grimstein
Statistical Review	Xiangmin Zhang; Kun Jin; Hsien Ming Hung
Pharmacology Toxicology	Chris Toscano; Lois Freed; Paul Brown
Chemistry Manufacturing and Controls	Wendy Wilson-Lee; Martha Heimann; Gene Holbert; Sherita McLamore-Hines; Masih Jaigirdar; Don Obenhuber
Office of New Drug Quality Assessment Biopharmaceutics Review	Jing Li; Okpo Eradiri; Angelica Dorantes
Controlled Substance Staff	Alicja Lerner; Michael Klein
Office of Scientific Investigation	Antoine El Hage; Susan Thompson; Kassa Ayalew
Division of Medication Error Prevention and Analysis	Deborah Myers; Danielle Harris
Division of Risk Management	Jasmine Kumar; Jamie Wilkins Parker
QT Interdisciplinary Review Team	Moh Jee Ng; Qianyu Dang; Dinko Rekic; Jiang Liu; Michael Li; Norman Stockbridge
Office of Surveillance and Epidemiology Project Managers	Ermias Zerislasse; Corwin Howard
Epidemiology Reviewer	Lockwood Taylor; Elisa Braver
Cross-Discipline Team Leader	Gerald (Dave) Podskalny
Deputy Director, Division of Neurology Products	Eric Bastings
Director, Division of Neurology Products	Billy Dunn

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Deutetrabenazine is a deuterated form of tetrabenazine, a drug approved in 2008 for the treatment of chorea associated with Huntington's disease. The activity of both drugs is related to their metabolites, α- and β-dihydrotetrabenazine. Deuteration affects the metabolism and pharmacokinetics of the drug, such that for equivalent doses, exposure to the active metabolites of deutetrabenazine is approximately twice that of tetrabenazine, and the half-life is longer. This 505(b)(2) NDA relies on tetrabenazine for pharmacology/ toxicology studies, including a fertility and early embryonic development study, an embryofetal developmental study, a pre- and post-natal development study, and an assessment of carcinogenic potential.

The efficacy of deutetrabenazine was established in a 12-week placebo-controlled study that used a well-accepted measure of chorea, the total maximal chorea (TMC) score, as the 1° endpoint. The change from baseline in TMC score was significantly higher (a drug-placebo difference of 2.5 points on a 24-point scale) for deutetrabenazine than for placebo ($p<0.0001$). These results were supported by statistically significant effects on 2° outcome measures: the Patient Global Impression of Change and the Clinical Global Impression of Change.

The deutetrabenazine safety database was closely examined with consideration of tetrabenazine's known safety issues. These issues include sedation and somnolence, akathisia, depression, and suicidality. Notwithstanding the usual limitations of cross-study comparisons, the frequency of these events appears similar for the two drugs. Huntington's Disease (HD) is an orphan disease, and this was a small safety database. Given the size of the database and lacking a head-to-head study, it is impossible to reach any definitive conclusions regarding comparative safety, but there are no obvious new safety concerns. A QT prolongation signal is known and labeled for tetrabenazine. The TQT study conducted by the applicant did not reach sufficiently high exposures of deutetrabenazine to rule out QT prolongation at supratherapeutic concentrations that would likely occur in patients who are CYP2D6 poor metabolizers, as well as patients taking CYP2D6 inhibitors. As was the case for tetrabenazine, this can be addressed by labeling.

Unfortunately, the clinical pharmacology studies were not adequate to determine whether all major human metabolites of deutetrabenazine have been identified. Such information is needed to assess whether the bridge to the reference listed drug (Xenazine) is scientifically justified to address the toxicity of all deutetrabenazine's major metabolites.

In terms of whether these data need to be generated before approval (vs. after approval), my opinion is the same as that of Dr. Bastings. Tetrabenazine is already marketed for the same indication as that proposed for deutetrabenazine. Deutetrabenazine's only clear advantage over tetrabenazine is the need for less frequent dosing (BID instead of TID) at the higher end of the dosing range. Although this convenience could represent a significant aid to caregivers of patients with HD, it does not justify marketing approval prior to obtaining needed data on deutetrabenazine's metabolites.

The applicant has proposed a method to obtain the necessary information. Unfortunately, an amendment containing all of the necessary information was not submitted before the action date. Finally, there are three product quality deficiencies (test for [redacted] (b) (4), commitment for long-term stability assessments, and categorical exclusion) that need to be addressed. Therefore, this application will receive a *Complete Response*.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. HD has an estimated prevalence of 5/100,000 in the US. HD is an orphan disease. The affected gene codes for a cytosine-adenine-guanine (CAG) repeat expansion that produces abnormal Huntingtin protein. Patients with a CAG repeat length ≥ 37 become symptomatic. The length of the CAG repeat influences the severity of the disease and the age of onset (longer is worse). The disease is characterized by progressive dementia, motor impairment, and psychiatric symptoms, beginning most often between 30 and 50 years of age. Death usually occurs within 20 years of symptom onset.	HD is a serious and profoundly disabling disorder. HD essentially represents a death sentence. There is currently no treatment that is known to delay the progression of the disease.
Current Treatment Options	Tetrabenazine is the only drug approved for the treatment of HD, specifically, for the treatment of chorea associated with HD. Tetrabenazine may cause side effects, including sedation, worsening depression, suicidality and drug-induced Parkinsonism. Antidepressants and antipsychotics are used to treat the psychiatric and behavioral aspects of HD	Tetrabenazine is the only available treatment for patients with HD. The drug has no effect on the progression of the disease, but is indicated to reduce chorea.
Benefit	Benefit was established in a mostly US, multicenter, randomized, double-blind, placebo-controlled study in 90 patients (Study C-15). The study used a well-accepted measure of chorea as the 1° outcome measure: the Total Maximal Chorea (TMC) score. There was a statistically significant difference between deutetrabenazine and placebo for the primary endpoint (difference in score change from baseline of -2.5, $p<0.0001$). This effect size was similar to that seen with tetrabenazine. The meaningfulness of the benefit of deutetrabenazine to patients was supported by statistically significant improvements on 2°	Efficacy of deutetrabenazine appears similar to that of tetrabenazine, which is approved for the treatment of chorea in HD patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	endpoints, the Patient Global Impression of Change and the Clinical Global Impression of Change, compared with placebo.	
Risk	Deutetrabenazine has a safety profile similar to that of tetrabenazine. The clinical pharmacology studies were not adequate to determine whether all of deutetrabenazine's major human metabolites have been identified. This information is needed to assess whether the bridge to the listed drug (Xenazine) is scientifically justified to address the toxicity of all major metabolites of deutetrabenazine.	It is unclear whether bridging to tetrabenazine is scientifically appropriate to assess the potential toxicities of these metabolites.
Risk Management	As it is for tetrabenazine, the risks associated with deutetrabenazine can be managed by labeling. Routine pharmacovigilance is recommended.	As with tetrabenazine, deutetrabenazine should include a Boxed Warning for increased risk for suicidality and depression in patients with HD.

2. Background

Huntington's disease (HD) is a genetic neurodegenerative disorder characterized by progressive dementia, motor impairment, and psychiatric symptoms. Patients with the adult form of the disease typically become symptomatic between 30 and 50 years of age, with death ensuing 15 to 20 years after symptom onset. The Huntingtin gene is located on the short arm of chromosome 4, and inheritance is autosomal dominant. The gene mutation codes for a cytosine-adenine-guanine (CAG) triplet repeat that produces abnormal huntingtin protein. Patients with a CAG repeat length of 37 or more become symptomatic. Despite discovery of the genetic basis of the disease some 23 years ago, no treatment is known to affect the inexorable progression of the disease. Prevalence is estimated at 5/100,000 in the US. HD was the subject of a public patient-focused drug development meeting at FDA on September 22, 2015. Patients made it clear that although tetrabenazine can be helpful, they are hoping for the availability of a drug that will prevent progression of the disease.

Tetrabenazine is the only approved treatment for HD. Initially approved in 2008, the drug is indicated for the treatment of chorea associated with Huntington's disease, but does not affect disease progression. Tetrabenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Its anti-chorea effect is believed to be mediated by decreased uptake of monoamines into synaptic vesicles with depletion of monoamine stores (e.g., dopamine, serotonin, norepinephrine, and histamine).

Deutetrabenazine is a deuterated form of tetrabenazine that is proposed for the same indication: treatment of chorea associated with Huntington's disease.

The NDA is a 505(b)(2) submission, with tetrabenazine (NDA 21894) as the Reference Listed Drug (RLD). Clinical development was conducted under IND 112975. This application relies on the RLD for various pharmacology-toxicology studies, including a fertility and early

embryonic development study, a pre- and postnatal development study, and an assessment of carcinogenic potential.

Deutetrabenazine has not been approved in any country, and has orphan drug designation.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends a complete response on this NDA because of 3 unresolved issues:

Drug Substance: The drug substance specification did not include a test for (b) (4) (b) (4) The applicant committed to adding a test and acceptance criterion (b) (4) for (b) (4) as part of the drug substance specification and amending the NDA with the test, acceptance criterion, and method validation by March 22, 2016. The test method was not submitted until April 14, 2016, however, and validation data were not provided.

Drug Product: The applicant indicated that at least one production batch of the product in the commercial packaging will be placed on long-term stability annually. As the registration stability batches were not manufactured at full commercial scale, OPQ is requesting that the applicant change their post-approval stability commitment to include placing the first 3 commercial batches of each strength of the drug product on long-term stability through the proposed shelf life and on accelerated stability for 6 months, as per ICH Q1A(R2).

Environmental: Per 21 CFR 25.15(d), OPQ is asking the applicant to revise their claim for categorical exclusion to include a statement that no extraordinary circumstances exist to the applicant's knowledge.

Per the Overall Manufacturing Inspection Recommendation (May 24, 2016), all manufacturing facilities are considered acceptable, and there are no facility-related deficiencies to preclude approval.

Sufficient data have been presented to support a 32-month expiry.

4. Nonclinical Pharmacology/Toxicology

According to the pharmacology/toxicology review, the applicant provided adequate nonclinical information to support the proposed specifications for deutetrabenazine's *known* impurities.

Importantly, however, there is uncertainty regarding the adequacy of the available information on the human metabolism of deutetrabenazine; therefore, it is unknown whether all major human metabolites (MHMs) of the drug have been adequately tested (MHMs are those that comprise greater than 10% of total drug in the circulation).

As stated by Dr. Toscano, "It is not possible to determine if the nonclinical studies submitted in the application support bridging to the available nonclinical information for the RLD without a determination of the status of SD-809 metabolites as major or minor, as defined by ICH

M3(R2), by the Clinical Pharmacology review team. If it is determined that the metabolite profile for SD-809 is similar to the RLD and that there are no new MHMs of SD-809, then the current nonclinical package would support the approval of the NDA. However, if the available information on human metabolism of SD-809 is not adequate to determine the status of the metabolites in humans or if it is determined that there are major human metabolites of SD-809 that are not MHMs of TBZ, then the sponsor would need to demonstrate that the level of each MHM was qualified in nonclinical studies in order to support the level of exposure in humans."

His view is supported by Dr. Lois Freed, Supervisory Pharmacologist, and Dr. Paul Brown, ODE Associate Director for Pharmacology and Toxicology.

In general, the pharmacokinetics/absorption, distribution, metabolism, and excretion of deutetrabenazine are similar to those of tetrabenazine. The major active metabolites quantified were d_6 α- and β-dihydrotetrabenazine (d_6 α- and β-HTBZ).

In Sprague-Dawley rats, oral doses of deutetrabenazine resulted in up to 2.4-fold higher plasma exposure (assessed as area under the time-concentration curve) for the parent and metabolites (d_6 α- and β-HTBZ), compared to tetrabenazine and metabolites at the same doses. The pattern of tissue distribution, including brain penetration in Lister Hooded or Sprague-Dawley rats, was also similar following acute oral doses of radiolabeled deutetrabenazine and tetrabenazine.

Non-clinical *in vivo* metabolism studies were not conducted. The applicant stated "None are planned as human exposure to the metabolites of the listed tetrabenazine will be used to qualify the SD-809 metabolites."

The Office of Clinical Pharmacology/Biopharmaceutics review team has concluded, however, that because of deficiencies in the evaluation of the *in vivo* metabolic profile in humans, it is unknown whether all major circulating metabolites of deutetrabenazine in humans have been identified (see Section 5, below).

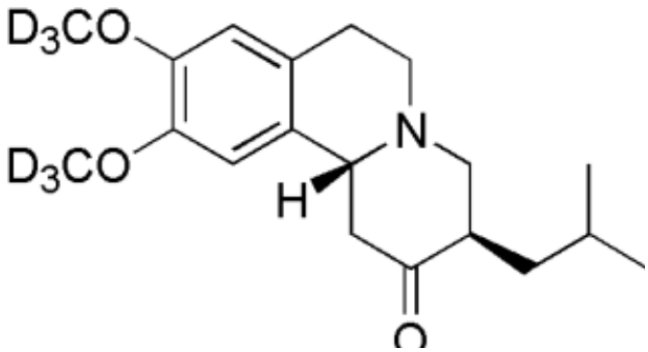
The nonclinical reviewer finds that, compared with tetrabenazine, deutetrabenazine exhibited no unique toxicities in the limited battery of nonclinical studies conducted. Deutetrabenazine and metabolites, d_6 α- and β-HTBZ, were negative in genotoxicity assays *in vitro* (Ames and chromosomal aberration assay in human peripheral blood lymphocytes).

On multiple occasions during clinical development, the sponsor was reminded of the need to provide an adequate comparison of the *in vivo* metabolic profiles of deutetrabenazine and the RLD. Despite this advice, the Office of Clinical Pharmacology/Biopharmaceutics review team has concluded that the applicant has not adequately characterized the *in vivo* metabolic profile of deutetrabenazine in humans. The need for additional nonclinical data will depend on data to be generated from a human mass balance study. Lacking this information at the present time, the pharmacology/toxicology review team cannot assess the adequacy of the nonclinical data, and Drs. Toscano, Freed, and Brown agree that the issue should be addressed prior to approval. Drs. Podskalny and Bastings agree with their conclusion, as do I.

5. Clinical Pharmacology

Deutetrabenazine is a deuterated form of tetrabenazine in which the two O-linked methyl groups of the tetrabenazine molecule have been replaced by two trideuteromethyl groups.

Figure 1: Structure of Deutetrabenazine



Pharmacokinetics of deutetrabenazine (and of tetrabenazine): As discussed in the clinical pharmacology review, over 80% of an orally administered dose of deutetrabenazine is absorbed. The deutetrabenazine (and tetrabenazine) parent is rapidly metabolized by hepatic carbonyl reductase to its active metabolites, α-HTBZ and β-HTBZ, which are inhibitors of VMAT2 in the central nervous system and thought to mediate the biological effects of deutetrabenazine (and tetrabenazine). Of note, the applicant based the 2:1 tetrabenazine to deutetrabenazine dose ratio on comparative (α + β)-HTBZ plasma concentrations.

Because of extensive metabolism, concentrations of deutetrabenazine are generally below the limit of detection 3 hours post-dose, whereas peak plasma concentrations (C_{max}) of α-HTBZ and β-HTBZ are reached in this time frame, with a half-life of 7 to 10 hours. Both α-HTBZ and β-HTBZ are subsequently metabolized, principally by CYP450 enzymes (largely CYP2D6 with a minor contribution of CYP1A2). Metabolites are primarily excreted in the urine (over 80% of the dose). Systemic exposure to total (α+β) HTBZ following deutetrabenazine administration is approximately twice as high as following tetrabenazine administration.

At least two major circulating metabolites, α-HTBZ (M6) and monohydroxy tetrabenazine (M4), have been identified after oral administration of deutetrabenazine; however, the metabolite profiling and identification results of the mass balance study are inconclusive.

The C_{max} and area under the time-concentration curve (AUC) for the active metabolites (α+β) HTBZ are linear/dose-dependent following single or multiple doses of deutetrabenazine.

Intrinsic factors: According to the tetrabenazine label, exposure to (α+β) HTBZ is 30 to 39% greater with hepatic impairment and the mean tetrabenazine C_{max} in patients with hepatic impairment was 7- to 190-fold higher than in healthy subjects. The clinical pharmacology reviewer recommends contraindication of deutetrabenazine in patients with hepatic impairment, consistent with the labeling of tetrabenazine.

Extrinsic factors: Strong CYP2D6 inhibitors markedly increase exposure to the active tetrabenazine metabolites (tetrabenazine label). The applicant proposes to omit this restriction for deutetrabenazine because of their belief that CYP2D6 metabolism of deuterated (α+β) HTBZ is attenuated relative to non-deuterated (α+β) HTBZ. The results of an *in vivo* drug-drug interaction (DDI) study conducted with deutetrabenazine and a strong CYP2D6 inhibitor (paroxetine) nevertheless showed a 3-fold increase in total (α+β) HTBZ exposures when the two drugs were co-administered. In light of this DDI, the deutetrabenazine dose was limited to 18 mg BID in patients taking strong CYP2D6 inhibitors in the development program. Labeling will note, therefore, that the daily dose of deutetrabenazine should not exceed 36 mg in CYP2D6 poor metabolizers and in patients taking strong CYP2D6 inhibitors.

Bridging of deutetrabenazine to tetrabenazine: Bridging is a critical issue that is well covered by the Clinical Pharmacology/Biopharmaceutics Review, the CDTL, and the Deputy Division Director.

As noted above, this is a 505(b)(2) application that relies, in part, on FDA's prior finding of safety and efficacy for tetrabenazine. Demonstration of strict bioequivalence between deutetrabenazine and tetrabenazine was neither required nor expected, because the applicant conducted a safety and efficacy study with deutetrabenazine. The bridging studies showed that, at highest proposed dose, the C_{max} of deutetrabenazine is no higher than that of tetrabenazine.

The applicant needed to provide an adequate PK bridge to the tetrabenazine NDA in order to permit an assessment of the bioavailability of both drugs, as well as an evaluation of the comparability of their metabolic profiles/metabolites. In particular, it was imperative to determine whether there are any major human metabolites unique to deutetrabenazine.

The metabolic profile of deutetrabenazine has been the subject of extensive discussions with the applicant during the development program. According to the applicant, deuteration does not alter the metabolic pathway of deutetrabenazine relative to that of tetrabenazine, and all of the 22 metabolites of deutetrabenazine are among the 24 metabolites of tetrabenazine. At least 2 major human metabolites (defined as >10% of total circulating deutetrabenazine-related radioactivity) have been identified: α-HTBZ (M6) and monohydroxy tetrabenazine (M4).

The available data suggest that M4 (monohydroxy tetrabenazine) is a major human metabolite of deutetrabenazine and tetrabenazine; however, M4 is not identified as a major human metabolite in labeling for tetrabenazine and was not quantified in nonclinical studies. Thus, if M4 is confirmed to be a major human metabolite, additional nonclinical data will be needed to determine if bridging to tetrabenazine is scientifically justified.

The Clinical Pharmacology review team finds inconclusive the results of the mass balance study intended to compare the metabolism of deutetrabenazine and tetrabenazine, and does not believe that the applicant has adequately characterized the metabolic profile of deutetrabenazine. As summarized by others, the issues include:

- Inconsistent results were obtained for assessment of metabolite M1, the 2-methylpropanoic acid metabolite of β-HTBZ. Given the inconsistent results, it is unknown whether M1 is a

major metabolite in humans. (M1 was not identified as a major human metabolite of tetrabenazine, either by the applicant or in tetrabenazine labeling.) If M1 were a major metabolite, additional nonclinical studies would be required.

- The applicant's inability to demonstrate, using semi-quantitative methods, that a known (based on tetrabenazine labeling) major human metabolite of tetrabenazine, 9-O-desmethyl-β-HTBZ, is a major human metabolite of tetrabenazine. The applicant's inability to reproduce these findings increases general concern regarding the adequacy of the applicant's methods, as noted for M1.

The clinical pharmacology reviewer states: "It is recommended that the sponsor assess the concentration of circulating SD-809-related metabolites for the purpose of determining if there are major metabolites in humans dosed with SD-809. Whether this could be done post approval will be decided by the non-clinical and clinical teams."

The team has discussed this issue extensively, and has concluded that the data should be obtained and reviewed *prior* to approval. Clearly, the data on human metabolism are needed to identify the major human metabolites, which will inform the need for additional nonclinical pharmacology/toxicology studies.

If this drug offered an important clinical advantage over available therapy, we would consider completing the evaluation of the metabolites and the necessary nonclinical pharmacology/ toxicology evaluations as Post-Marketing Requirements. But tetrabenazine is already marketed for the same indication as proposed for deutetrabenazine. Other than convenience, i.e., less frequent need for deutetrabenazine administration compared to tetrabenazine administration, we see no advantage of deutetrabenazine over tetrabenazine. The drugs were not studied head-to-head, and there is no evidence that deutetrabenazine is superior to marketed tetrabenazine. The review team is in alignment in favor of having the applicant conduct the mass balance study *prior to* marketing, to be followed by other studies as needed.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Considering the similarities in the PK profile of tetrabenazine and deutetrabenazine, the division agreed to rely on a single efficacy study for deutetrabenazine.

The clinical study is well described in the reviews of Drs. Bergmann, Zhang, Podskalny, and Bastings.

Study C-15 was a multi-national (US and Canada), randomized, double-blind, placebo-controlled study to evaluate the efficacy of deutetrabenazine for the treatment of chorea associated with HD. The trial was performed in the to-be-marketed patient population, defined as having manifest HD and genetic testing that confirmed ≥ 37 abnormal CAG repeats on

chromosome 4. Enrollment criteria were usual and appropriate. Patients had to have a Total Maximal Chorea (TMC) score ≥ 8 and a Total Functional Capacity (TFC) Score ≥ 5. (The TMC and TFC are subscales of the Unified Huntington Disease Rating Scale [UHDRS]). Patients needed to be able to walk 20 yards unassisted.

Ninety (90) patients were planned to be randomized to placebo or deutetrabenazine in a 1:1 ratio.

The overall treatment duration was 12 weeks. The study included a screening period of up to 4 weeks, an 8-week titration period, a 4-week maintenance period, and a 1-week washout.

Patients were started on deutetrabenazine 6 mg per day (or placebo), and titrated weekly up to a tolerated dose level at which adequate chorea control had been achieved, or to a maximum dose of 48 mg daily. (For patients receiving strong CYP2D6 inhibitors, the total daily dose was capped at 36 mg.)

The 1° efficacy endpoint was change from Baseline to Maintenance in TMC score. The TMC score is derived from 7 items of the Unified Huntington's Disease Scale. Each item measures the maximal chorea of a body part, with individual scores ranging from 0 to 4 (0 representing no chorea and 4 representing marked or prolonged chorea). TMC scores, therefore, can range from 0 (best) to 28 (worst). The Baseline TMC score was defined as the mean of the TMC scores obtained at the Screening and at Day 0 visits. The maintenance TMC score was defined as the mean of the TMC scores obtained at Weeks 9 and 12.

Secondary efficacy endpoints included the following:

- The proportion of patients considered a ‘treatment success’ at the end of therapy, based on the Patient Global Impression of Change (PGIC). This was analyzed as a binary variable, i.e., the proportion of patients "Much Improved" or "Very Much Improved" at Week 12.

- The proportion of patients considered a treatment success at the end of therapy, based on the Clinical Global Impression of Change (CGIC), analyzed as per the PGIC.

- Change from Baseline (Day 0) to Week 12 in the Short Form 36 Health Survey (SF-36) Physical Functioning score.

- Change from Baseline (Day 0) to Week 12 in the Berg Balance Test (BBT) score.

The 1° analysis was performed using an analysis of covariance (ANCOVA) model with treatment as a factor and Baseline TMC as the covariate. The analysis was performed on the modified intent-to-treat (mITT) population, defined as all randomized patients who received the test drug and had at least one post-baseline assessment of their TMC score.

The statistical reviewer notes that 123 patients were screened to randomize 90 (45 to placebo and 45 to deutetrabenazine). All but 3 patients completed the study (43 completed in the placebo group; 44 completed in the deutetrabenazine group).

Mean age was 54; 56% of patients were male. Eleven percent (11%) of patients in the placebo group were African American, versus 0% in the deutetrabenazine group.

The two groups were fairly well balanced for demographic characteristics, although there were more males in the placebo group (62%) than in the deutetrabenazine group (49%), and the difference in race as just noted. The baseline TMC scores were 12.1 ± 2.7 (mean ± standard deviation) in the deutetrabenazine group and 13.2 ± 3.5 (slightly worse) in the placebo group – probably not an important difference.

Efficacy results are summarized in Table 1. The change from baseline in TMC score was statistically significantly higher for deutetrabenazine than for placebo (p<0.0001).

Table 1: Efficacy results (adapted from Table 11 in the applicant's Clinical Study Report, verified by statistical review)

	Change in Total Maximal Chorea Score			
	deutetrabenazine (N=45)	placebo (N=45)	Difference in Means (deutetrabenazine - placebo) (95% CI)	*p*-value
Least Squares Mean (SD)	-4.4 (3.0)	-1.9 (2.7)	-2.5 (-3.7, -1.3)	<0.05
95% CI for Mean	(-5.2, -3.5)	(-2.8, -1.2)		

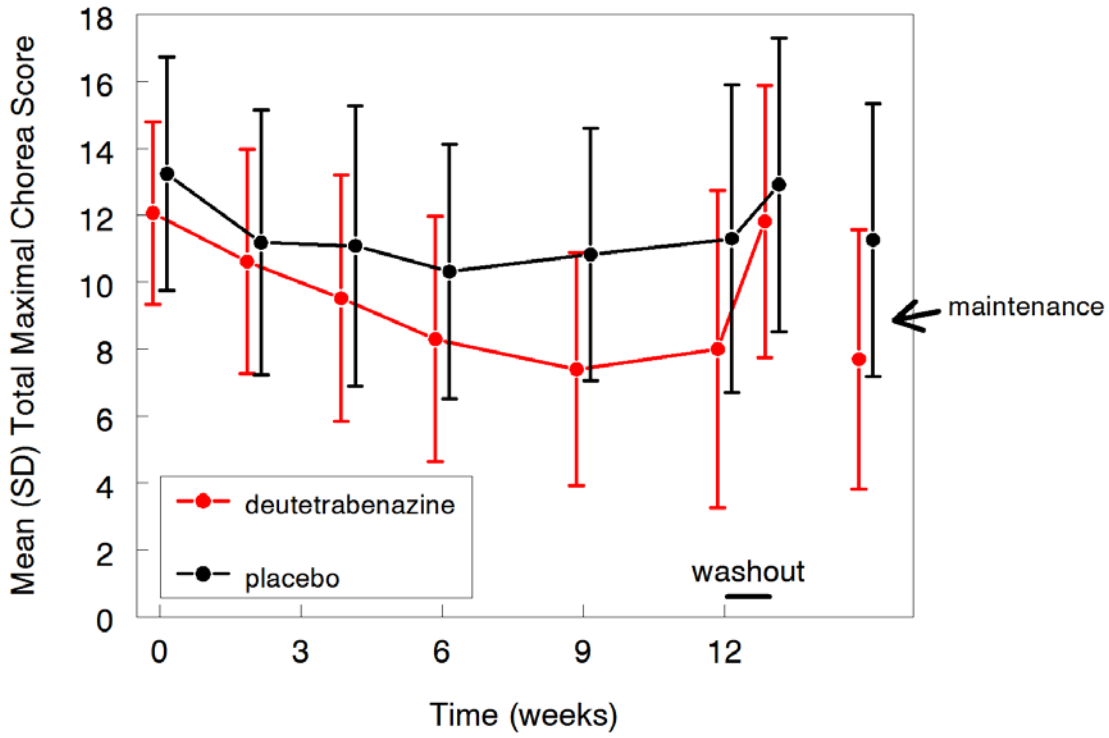
Table 2 is adapted from figure 19 of the applicant's clinical study report, and shows the change in Total Maximal Chorea Scores over time for the intent-to-treat population (n=90).

Table 2: Study C-15: Change in Total Maximal Chorea Over Time (adapted from applicant's clinical study report, verified by statistical review)

	deutetrabenazine (n=45)			placebo (n=45)		
	n	mean (SD)	mean Δ from baseline	n	mean (SD)	mean Δ from baseline
Screening	45	11.9 (2.7)	-	45	13.0 (3.7)	-
Day 0	45	12.2 (3.1)	-	45	13.5 (3.8)	-
Baseline	45	12.1 (2.7)	-	45	13.2 (3.5)	-
Week 2	45	10.6 (3.4)	-1.4 (2.1)	45	11.2 (4.0)	-2.1 (2.8)
Week 4	44	9.5 (3.7)	-2.4 (2.8)	45	11.1 (4.2)	-2.2 (3.0)
Week 6	44	8.3 (3.7)	-3.7 (2.7)	44	10.3 (3.8)	-2.8 (2.8)
Week 9	45	7.4 (3.5)	-4.7 (2.8)	42	10.8 (3.8)	-2.2 (2.9)
Week 12	45	8.0 (4.7)	-4.1 (3.8)	43	11.3 (4.6)	-1.9 (3.2)
Maintenance	45	7.7 (3.9)	-4.4 (3.0)	45	11.3 (4.1)	-2.0 (2.7)
Week 13	44	11.8 (4.1)	-0.3 (2.7)	43	12.9 (4.4)	-0.5 (2.7)

These values are also plotted in Figure 2. After the washout period, the mean TMC scores at Week 13 of both treatment groups appeared to return to the baseline levels (Figure 2).

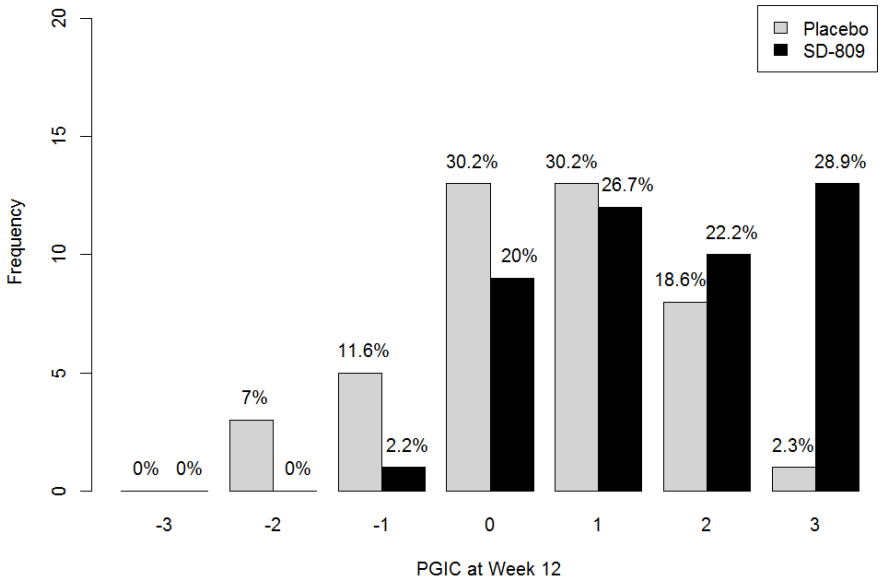
Figure 2: Study C-15: Total Maximal Chorea Over Time



The statistical reviewer considered subgroups of sex and age and found "…no compelling evidence…." of differential efficacy. The vast majority of patients were from the US, and so there was no need to consider geographical differences. There were too few blacks (none in the deutetrabenazine group) upon which to base an analysis by race.

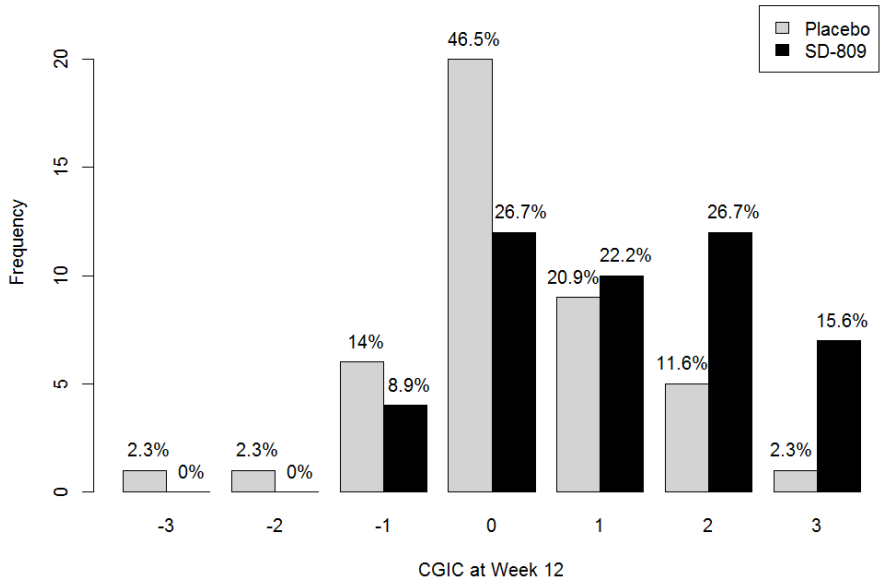
Figures 3 and 4 show the distributions of results for the PGIC and the CGIC.

Figure 3: Distribution of Patient Global Impression of Change at Week 12 (source: statistical review of Dr. Zhang)



-3: Very Much Worse; -2: Much Worse; -1: Minimally Worse; 0: Not Change; 1: Minimally Improved; 2: Much Improved; 3: Very Much Improved.

Figure 4: Distribution of Clinical Global Impression of Change at Week 12 (source: statistical review of Dr. Zhang)



-3: Very Much Worse; -2: Much Worse; -1: Minimally Worse; 0: Not Change; 1: Minimally Improved; 2: Much Improved; 3: Very Much Improved.

8. Safety

The tetrabenazine label is germane to the review of this NDA. The clinical reviewer notes that the main safety concerns expected for deutetrabenazine, based on the tetrabenazine label, are sedation and somnolence, akathisia, depression/ suicidality, and QT prolongation.

This safety database for deutetrabenazine consists of 6 phase 1 studies and a double-blind efficacy study (C-15) with an open-label long-term extension (C-16). The phase 1 studies evaluated 178 healthy adult subjects, where most of the exposure was limited to a single dose.

For patients with HD in the phase 3 studies, the applicant counted 121 subjects with any deutetrabenazine exposure, including 119 subjects with exposure $\geq$ 8 weeks, 111 $\geq$ 15 weeks, 65 $\geq$ 28 weeks, and 16 $\geq$ 52 weeks.

The open-label long-term extension study (C-16) also included a cohort of patients who were switched from tetrabenazine to deutetrabenazine according to a 2:1 conversion paradigm (e.g., 100 mg tetrabenazine was switched to 48 mg deutetrabenazine). As discussed above, the maximum dose in Study C-15 was 48 mg/day, except for patients receiving a potent CYP2D6 inhibitor whose daily dose was limited to 36 mg. In Studies C15 and C16, weekly dose increases were $\leq$ 6 mg/day. Most patients (76%) reached a maintenance dose of $\geq$ 36 mg/day.

The applicant also submitted summary safety information from Study C-18, a study of deutetrabenazine for the treatment of tardive dyskinesia. Study C18 randomized 56 patients to deutetrabenazine (at the same dose range as in Study C-15) and 57 to placebo.

The clinical reviewer focused on Studies C-15 and C-16.

Deaths: No deaths have been reported in the HD development program. There were 2 deaths in the tardive dyskinesia study, neither of which appears to be drug-related, according to the clinical reviewer.

Serious adverse events: Through the 120-day safety update, 19 serious adverse events were reported in 13 patients. I agree with the clinical reviewer that none of the serious adverse events is likely to be drug-related, with the possible exception of depression (2 events) and suicidality (1 event, which was reported in one of the subjects with depression). Depression and suicidality occur frequently in the HD population, and it would be difficult to reach a conclusion of causality here. Having inspected the list of serious adverse events, I believe that some are not plausibly drug-related (chronic cholecystitis, COPD, lumbar spinal stenosis), and the others are few in number and lack any unifying pathophysiologic themes.

All adverse events: As shown in Table 3, somnolence was the most commonly reported adverse event in Study C-15 (11% for deutetrabenazine vs. 4% on placebo). Somnolence occurred primarily during the initial up-titration, and led to a dose reduction in 4 cases. Of note, somnolence is also the most frequent adverse event in the tetrabenazine label: 31% on drug, vs. 3% on placebo.

Fatigue, a closely related event, was also more frequent on deutetrabenazine (9%) than on placebo (4%). Fatigue is the second most frequent event for tetrabenazine, according to its label.

Table 3: Adverse events in Study C-15 (source: Dr. Bergmann's clinical review)

System Organ Class	Preferred Term	SD-809 (N)	SD-809 %	Placebo (N)	Placebo %
Nervous system disorders	Somnolence	5	11.1	2	4.4
Gastrointestinal disorders	Dry mouth	4	8.9	3	6.7
General disorders and administration site conditions	Fatigue	4	8.9	2	4.4
Gastrointestinal disorders	Diarrhoea	4	8.9	0	0.0
Nervous system disorders	Dizziness	3	6.7	4	8.9
Injury, poisoning and procedural complications	Fall	3	6.7	9	20.0
Psychiatric disorders	Insomnia	3	6.7	2	4.4
General disorders and administration site conditions	Irritability	3	6.7	6	13.3
Psychiatric disorders	Anxiety	2	4.4	1	2.2
Musculoskeletal and connective tissue disorders	Back pain	2	4.4	1	2.2
Gastrointestinal disorders	Constipation	2	4.4	1	2.2

Diarrhea, which was reported more commonly on deutetrabenazine (9% vs. 0%), is not included in tetrabenazine's label as an adverse reaction. As noted by Dr. Bastings, diarrhea is common in the general population, and may be a chance finding here.

Finally, as noted by Dr. Bastings, there were excess adverse events of anxiety, back pain, and constipation for deutetrabenazine, but I do not believe that a difference of 1 adverse event between groups can be interpreted as a difference.

Adverse Events of Interest:

Depression and suicidality: Tetrabenazine has a boxed warning for depression and suicidality. In Study C-15, 4% of deutetrabenazine-treated subjects and 7% of placebo-treated subjects experienced depression adverse events. Similarly, there was no difference between deutetrabenazine and placebo on the Hospital Anxiety and Depression Scale Depression Subscale (HADS-D), a scale assessing anxiety and depression, and no signals for suicidal ideation or behavior in the study.

As discussed by the review team and Dr. Bastings, the background rate of depression and suicide in HD is so large that it would be very difficult to assess whether deutetrabenazine adds to that risk in a pre-marketing study, unless the effect were large. No signal was detected here; nevertheless, the warning in the label for tetrabenazine should probably carry over to deutetrabenazine.

Akathisia: In contrast to the large difference between tetrabenazine and placebo included in tetrabenazine's labeling (19% vs. 0%), the clinical reviewer found that restlessness occurred in only 5% of deutetrabenazine-treated patients in the open-label study.

Parkinsonism: Parkinsonism was not reported as an adverse event in Study C-15, but was reported in 3 patients in the open-label study (C-16). These events resolved with dose-reduction. As for akathisia, the absence of this adverse event contrasts with a large difference between tetrabenazine and placebo in tetrabenazine's labeling (9% vs. 0%).

Dysphagia/Swallowing: The tetrabenazine label notes that dysphagia is a component of HD, and that drugs that reduce dopaminergic transmission can cause esophageal dysmotility and dysphagia. Swallowing was evaluated by the Swallowing Disturbance Questionnaire in the deutetrabenazine studies. In the open-label Study C-16, dysphagia was reported as an adverse event in 5 patients (4.2%). In the double-blind Study C-15, none of the deutetrabenazine patients reported dysphagia.

Switching patients from tetrabenazine to deutetrabenazine: The applicant evaluated the safety and tolerability of switching subjects from tetrabenazine to deutetrabenazine using a 2:1 dose conversion ratio. A total of 37 patients taking a mean dose of 42 mg tetrabenazine daily (range 12.5 to 100 mg) were switched to deutetrabenazine, with a mean 20.3 mg dose daily (range 6 to 48 mg). No safety issues were apparent with treatment switching, but increases in the dose of deutetrabenazine were often necessary after the switch.

QTc prolongation: No significant QTc prolongation was detected in a TQT study that evaluated 12 and 24 mg of deutetrabenazine. The study used tetrabenazine as an active control and moxifloxacin to establish assay sensitivity. Tetrabenazine produced a marginal QT effect at 50 mg, consistent with the 8 msec increase reported in the tetrabenazine label. Assay sensitivity was established with moxifloxacin.

For the "worst case" scenario (a CYP2D6 poor metabolizer taking a strong CYP2D6 inhibitor), deutetrabenazine exposure is projected to be $>$ 3-fold higher than the exposure achieved in the TQT study. Thus, the QT Interdisciplinary Review Team concluded that the TQT study was not conducted at sufficiently high concentrations to rule out QT prolongation at supratherapeutic or therapeutic concentrations. The reviewer expects that clinically relevant QT prolongation might occur in some patients at the highest therapeutic dose of 24 mg BID, especially in CYP2D6 poor metabolizers or in patients co-administered a strong CYP2D6 inhibitor. The tetrabenazine label includes a Warning about QT effects. The QT Interdisciplinary Review Team recommends similar language for the deutetrabenazine label. The Division concurs with their recommendation, and I also support their view.

9. Advisory Committee Meeting

The NDA was not presented to the Peripheral and Central Nervous System Drugs Advisory Committee. This is a 505(b)(2) application without novel or controversial safety or efficacy issues.

10. Pediatrics

Deutetrabenazine is an orphan drug, and therefore, no pediatric obligations exist.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Audits: Two domestic clinical investigator sites were inspected. Minor deviations were reported that do not adversely impact data acceptability.

Controlled Substances Staff (CSS): Tetrabenazine is not a scheduled drug. The CSS reviewer notes that there were no preclinical or clinical studies designed to evaluate abuse potential and dependence of deutetrabenazine; therefore, the abuse potential is unknown.

The reviewer believes that clinical data comparing adverse events with deutetrabenazine and tetrabenazine are too limited to allow any conclusions about the abuse potential of deutetrabenazine relative to tetrabenazine, although the reviewer notes that there appear to be excess neuro-psychiatric adverse events with deutetrabenazine. The reviewer also notes that the data raise the possibility of a rebound phenomenon, although there is not alignment with the Division with respect to this concern.

The reviewer recommends evaluation of clinical dependence at the end of a trial lasting 4 weeks or more.

12. Labeling

Labeling is deferred until the open issues are addressed by the applicant. It seems clear, however, that much of the safety information in the tetrabenazine label will need to be recapitulated to the deutetrabenazine label.

13. Postmarketing

No REMS has been proposed. The need for Postmarketing Requirements and Commitments will be assessed once the open issues are addressed by the applicant.

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/s/

ELLIS F UNGER
05/27/2016

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD, Deputy Director, DNP.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208082
Applicant	Teva Pharmaceuticals, Inc.
Date of Submission	May 29, 2015
PDUFA Goal Date	May 29, 2016
Proprietary Name / **Non-Proprietary Name**	Austedo/ Deutetrabenazine (deutetrabenazine)
Dosage Form(s) / Strength(s)	Oral tablets / 6 mg, 9 mg, and 12 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of chorea in patients with Huntington's disease.
Recommended Action	Complete Response
Recommended Indication/Population(s)	N/A

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Stacy Metz
Medical Officer Clinical Review	Ken Bergmann
Clinical Pharmacology Review	Kristina Dimova; Angela Men; Xiaofeng Wang; Atul Bhattaram; Kevin Krudys; Jeffrey Kraft; Christian Grimstein
Statistical Review	Xiangmin Zhang; Kun Jin; Hsien Ming Hung
Pharmacology Toxicology	Chris Toscano; Lois Freed
Chemistry Manufacturing and Controls	Wendy Wilson-Lee; Martha Heimann; Gene Holbert; Sherita McLamore-Hines; Masih Jaigirdar; Don Obenhuber
ONDQA Biopharmaceutics Review	Jing Li; Okpo Eradiri; Angelica Dorantes
CSS	Alicja Lerner; Michael Klein
OSI	Antoine El Hage; Susan Thompson; Kassa Ayalew
OSE/DMEPA	Deborah Myers; Danielle Harris
OSE/DRISK	Jasmine Kumar; Jamie Wilkins Parker
QT/IRT	Moh Jee Ng; Qianyu Dang; Dinko Rekic; Jiang Liu; Michael Li; Norman Stockbridge
OSE PMs	Ermias Zerislasse; Corwin Howard
OSE/DEPI	Lockwood Taylor; Elisa Braver
Cross-Discipline Team Leader	Gerald (Dave) Podskalny

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

APPEARS THIS WAY ON ORIGINAL

1. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

The 505(b)(2) application under review is for deutetrabenazine (Austedo), a deuterated form of tetrabenazine, proposed for the treatment of chorea associated with Huntington's disease. The applicant proposes using tetrabenazine, which is approved for the same indication, as reference listed drug. This application relies on the tetrabenazine NDA for some pharmacology/toxicology studies that were not conducted by the applicant, including a fertility and early embryonic development study, an embryofetal developmental study, a pre- and post-natal development study, and carcinogenicity assessment.

Both deutetrabenazine and tetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors. The mechanism of action of deutetrabenazine and tetrabenazine on chorea is believed to be related to their effect as reversible depletors of monoamines (e.g., dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

The efficacy of deutetrabenazine was established in a 12-week placebo-controlled efficacy study that used a well-accepted measure of chorea, the total maximal chorea (TMC) score. The change from baseline in TMC score was significantly higher (drug-placebo difference of 2.5 points, on a 24-point scale) for deutetrabenazine than for placebo ($p<0.0001$). The meaningfulness of the TMS results was supported by statistically significant effects on the Patient Global Impression of Change and the Clinical Global Impression of Change.

The safety profile of deutetrabenazine is acceptable. There were no unique toxicities identified for deutetrabenazine, as compared with tetrabenazine. A close examination of the deutetrabenazine safety database was conducted for the safety issues known for tetrabenazine. These issues include sedation and somnolence, akathisia, depression, and suicidality. Notwithstanding the usual limitations of cross-study comparisons, the frequency of these events appears no higher for deutetrabenazine than for tetrabenazine. Absent a head to head comparative study, it is impossible to make any definitive conclusions about the comparative safety profile between tetrabenazine and deutetrabenazine, but there are no new safety concerns identified. A QT prolongation signal is known and labeled for tetrabenazine. The TQT study conducted by the applicant did not use sufficiently high concentrations of deutetrabenazine to rule out QT prolongation at supratherapeutic or therapeutic concentrations. As for tetrabenazine, this can be addressed by labeling.

Unfortunately, M1, a human metabolite of deutetrabenazine, has been inadequately characterized by the applicant, and it is yet to be determined whether M1 is a major human metabolite of deutetrabenazine. M1 was not identified as a major metabolite of tetrabenazine. Therefore, it is unclear whether bridging to tetrabenazine is scientifically appropriate to assess the potential toxicity of M1.

It appears that M4 is a major human metabolite of both deutetrabenazine and tetrabenazine. Because it was not identified as a major human metabolite at the time tetrabenazine was approved, M4 was not quantitated in the nonclinical studies. Therefore, it is unknown if M4 has been adequately assessed in the appropriate nonclinical studies. However, since M4 is present with tetrabenazine, possibly at higher levels, nonclinical bridging studies may be conducted as PMRs.

Tetrabenazine is already marketed for the same indication as that proposed for deutetrabenazine, and deutetrabenazine does offer as only clear advantage over tetrabenazine that, at high end of the dosing range, tetrabenazine must be taken two to three times a day, while deutetrabenazine may be taken just twice a day. The lower frequency of drug administration can be a significant aid to caregivers of Huntington's disease patients, but does not justify, in my opinion, a delay to the post-marketing period in obtaining the necessary information about deutetrabenazine metabolites. The applicant has proposed a method to obtain the necessary information on metabolites. Unfortunately, an amendment containing that information has not been submitted before the action date. In addition, there are product quality deficiencies (test for (b) (4), commitment for long-term stability assessments, and categorical exclusion) that need to be addressed prior to approval. Therefore, I recommend a complete response action for this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. HD has an estimated prevalence of 5/100,000 in the US. • The affected gene codes for a trinucleotide (CAG) repeat expansion producing abnormal Huntingtin protein (Huntingtin). Patients with a CAG repeat length of 37 CAG repeats or more become symptomatic. The length of the CAG repeat also influences the age of onset. Long repeat sequence lengths are associated with an onset of symptoms at a younger age. • The disease is characterized by progressive dementia, motor impairment and psychiatric symptoms, beginning most often between ages 30 to 50 years. Death usually occurs within 20 years of symptoms onset. • A less common juvenile form of HD does also exist.	HD is a serious and profoundly disabling disorder. There is currently no treatment that can delay the progression of the disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Tetrabenazine (Xenazine) is the only drug approved for the treatment of HD (specifically, for the treatment of chorea associated with HD). Tetrabenazine may cause side effects, including sedation, worsening depression, suicidality and drug-induced Parkinsonism. • Antidepressants, and antipsychotics are used to treat the psychiatric and behavioral aspects of HD.	Tetrabenazine is the only available symptomatic treatment of chorea in HD patients.
Benefit	• Benefit was established in a double-blind, placebo-controlled clinical study in 90 patients (Study C-15). The study used a well-accepted measure of chorea as primary outcome measure: the Total Maximal Chorea (TMC) score. • There was a highly significant difference between deutetrabenazine and placebo for the primary endpoint (difference in score change from baseline of -2.49, $p<0.0001$). This effect size is similar to that seen with tetrabenazine. • The meaningfulness of the benefit of deutetrabenazine to patients was supported by statistically significant improvements on the Patient Global Impression of Change and the Clinical Global Impression of Change, compared with placebo.	Efficacy of deutetrabenazine appears similar to that of tetrabenazine, which is approved for the treatment of chorea in HD patients.
Risk	• Deutetrabenazine has a safety profile similar to that of tetrabenazine. • M1, a human metabolite of deutetrabenazine, has been inadequately characterized by the applicant, and it is yet to be determined whether M1 is a major human metabolite of deutetrabenazine. M1 was not a major metabolite of tetrabenazine. Therefore, it is unclear whether bridging to tetrabenazine is scientifically appropriate to assess the potential toxicity of M1. • It appears that M4 is a major human metabolite of both	Deutetrabenazine has a safety profile similar to that of tetrabenazine. However, it is unclear whether bridging to tetrabenazine is scientifically appropriate to assess the potential toxicity of metabolite M1. In addition, it appears that M4 is a major human metabolite of both deutetrabenazine and tetrabenazine. It is unknown if M4 has been adequately assessed in the appropriate nonclinical studies. Because

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	deutetrabenazine and tetrabenazine. Because it was not identified as a major human metabolite at the time tetrabenazine was approved, M4 was not quantitated in the nonclinical studies. Therefore, it is unknown if M4 has been adequately assessed in the appropriate nonclinical studies.	M4 is also present with tetrabenazine, possibly at higher levels, bridging studies could be conducted as PMRs.
Risk Management	• As for tetrabenazine, the risks associated with deutetrabenazine can be managed by labeling. • Routine pharmacovigilance is recommended.	As tetrabenazine, deutetrabenazine should include a Boxed Warning for increased risk for suicidality and depression in patients with HD.

APPEARS THIS WAY ON ORIGINAL

2. Background

Huntington's disease is an autosomal dominant inherited neurodegenerative disorder characterized by progressive dementia, motor impairment and psychiatric symptoms. The 505(b)(2) application under review is for deutetrabenazine (Austedo), a deuterated form of tetrabenazine, proposed for the treatment of chorea associated with Huntington's disease. Chorea has been defined[1] as "a state of excessive, spontaneous movements, irregularly timed, non-repetitive, randomly distributed and abrupt in character. These movements may vary in severity from restlessness with mild intermittent exaggeration of gesture and expression, fidgeting movements of the hands, unstable dance-like gait to a continuous flow of disabling, violent movements."

The applicant proposes using Xenazine (tetrabenazine), which is approved for the treatment of chorea associated with Huntington's disease, as reference listed drug. This application relies on the Xenazine NDA for some pharmacology/toxicology studies that were not conducted by the applicant, including a fertility and early embryonic development study, an embryofetal developmental study, a pre- and postnatal development study, and carcinogenicity studies.

Both deutetrabenazine and tetrabenazine are vesicular monoamine transporter 2 (VMAT2) inhibitors. The mechanism of action of deutetrabenazine and tetrabenazine on chorea is believed to be related to their effect as reversible depletors of monoamines (e.g., dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

Deutetrabenazine is an active moiety that has not yet been previously approved in any new drug application, and has orphan drug designation.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends a complete response action.

There are three unresolved issues:

1. The drug substance specification does not include a test for (b) (4). The applicant committed to adding a test and acceptance criterion (b) (4) part per million (ppm) for (b) (4) as part of the drug substance specification and to amending the NDA with the test, acceptance criterion, and method validation. However, the amendment came too late to allow FDA review in this cycle.

2. The applicant indicated that at least one production batch of the product in the commercial packaging will be placed on long-term stability annually. As the

[1] Barbeau A, Duvoisin RC, Gerstenbrand F, Lakke JP, Marsden CD, Stern G. Classification of extrapyramidal disorders. Proposal for an international classification and glossary of terms. J Neurol Sci. 1981 Aug. 51(2):311-27

registration stability batches were not manufactured at full commercial scale, OPQ is requesting that the applicant change their post-approval stability commitment to include placing the first 3 commercial batches of each strength of the drug product on long-term stability through the proposed shelf life and on accelerated stability for 6 months, as per ICH Q1A(R2).

3. Per 21 CFR 25.15(d), OPQ is asking the applicant to revise their claim for categorical exclusion to include a statement that, to the applicant's knowledge, no extraordinary circumstances exist.

Sufficient data have been presented to support a 32-month expiry.

4. Nonclinical Pharmacology/Toxicology

The only pivotal studies of deutetrabenazine that were conducted by the applicant are a 3-month oral toxicity study and an embryofetal development study in rat. The nonclinical reviewer finds that, compared with tetrabenazine, deutetrabenazine exhibited no unique toxicities in the limited battery of nonclinical studies conducted. The nonclinical reviewer also notes that the pharmacokinetics and absorption, distribution, metabolism, and excretion (ADME) of deutetrabenazine were similar to those of tetrabenazine. The major active metabolites quantified by the applicant were α- and β-dihydrotetrabenazine. Deutetrabenazine and its α- and β- metabolites were negative when tested in *in vitro* genetic toxicity assays (Ames and chromosomal aberration assay in human peripheral blood lymphocytes).

As discussed below under "Clinical Pharmacology", there are inadequacies in the applicant's evaluation of the *in vivo* metabolic profile of deutetrabenazine in humans, and it remains unclear whether all major circulating metabolites of deutetrabenazine in humans have been identified. As a result, the nonclinical reviewer (and supervisor) conclude that it is not possible to determine whether bridging to the nonclinical studies conducted with tetrabenazine is appropriate for this 505(b)(2) application, i.e., whether all major circulating metabolites of deutetrabenazine have been adequately evaluated in nonclinical studies. Without this information, the adequacy of the nonclinical data cannot be determined. The need for additional nonclinical data will depend on new human mass balance data being collected by the sponsor. The nonclinical team believes that this issue should be addressed prior to approval. I concur.

5. Clinical Pharmacology

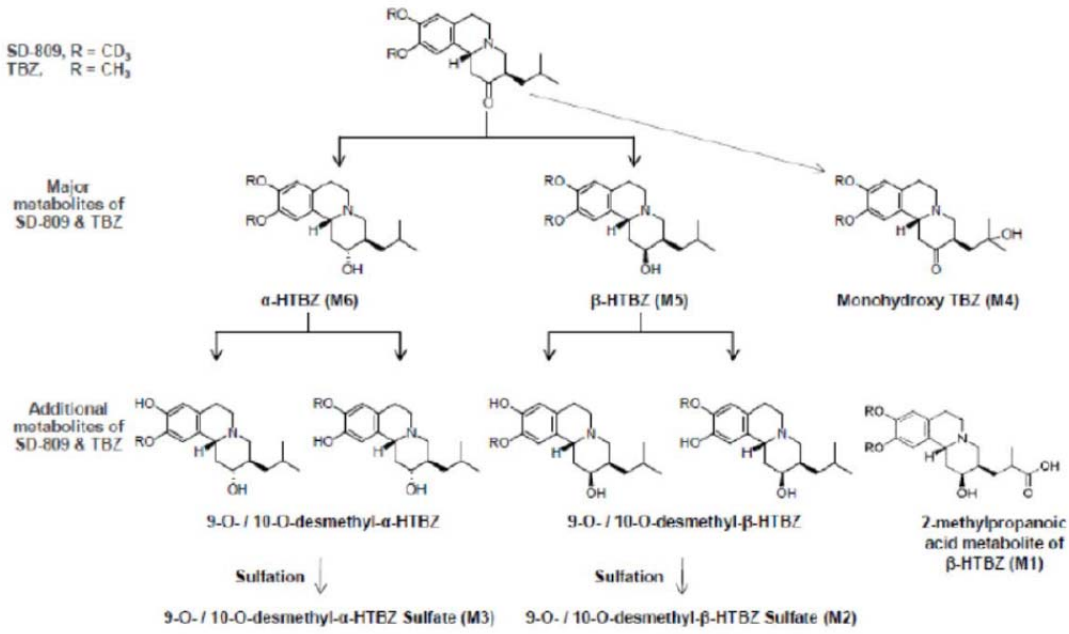
Deutetrabenazine is a selectively deuterated form of tetrabenazine in which the two O-linked methyl groups (CH3) of the tetrabenazine molecule have been replaced by two trideuteromethyl groups (CD3).

Pharmacokinetics of deutetrabenazine (and of tetrabenazine)

About 80 % of an oral dose of deutetrabenazine is absorbed from the gastrointestinal tract.

As discussed by the clinical pharmacology reviewer, both deutetrabenazine and tetrabenazine, the reference listed drug relied upon for this 505(b)(2) application, are rapidly converted in the liver by carbonyl reductase to their active metabolites, alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ). These two metabolites are thought to mediate the efficacy of deutetrabenazine and tetrabenazine. After oral dosing, plasma concentrations of deutetrabenazine are generally below the limit of detection by 3 hours post-dose, while peak plasma concentrations (Cmax) of α-HTBZ and β-HTBZ are reached within 3 to 4 hours after dosing, with a half-life of about 11 hours. Both α-HTBZ and β-HTBZ are subsequently metabolized principally by CYP450 enzymes, principally CYP2D6 (with minor contribution of CYP1A2), to form 9- and 10-desmethyl- α- and β-DHTBZ (**Figure 1**). Subsequently, 9- and 10-desmethyl-α- and β-DHTBZ are metabolized to sulfate or glucuronide conjugates. Systemic exposure to total (α+β) HTBZ following deutetrabenazine administration is approximately twice as high as following tetrabenazine administration.

Figure 1: Metabolism of deutetrabenazine and of tetrabenazine



Food had no effect on the area under the curve (AUC) of the α-HTBZ and β-HTBZ metabolites, but Cmax of those metabolites was increased by approximately 50% with food.

Deutetrabenazine was administered with food in all clinical studies, and the applicant recommends deutetrabenazine to be administered with food. The clinical pharmacology reviewer agrees with that dosing strategy.

Deutetrabenazine is primarily renally eliminated in the form of metabolites (over 80% of the dose recovered in the urine). The half-life of total (α+β)-HTBZ is approximately 9 to 10 hours.

The pharmacokinetics of deutetrabenazine and its primary metabolites have not been formally studied in specific populations (i.e., pediatric patients, geriatric patients, and patients with renal or hepatic impairment). The clinical pharmacology reviewer saw no apparent effect of gender on the PK of α-HTBZ or β-HTBZ. The clinical pharmacology reviewer notes that, according to the Xenazine label, the exposure to α-HTBZ and β-HTBZ was 30 to 40% greater in patients with hepatic impairment and the mean tetrabenazine C_{max} in patients with hepatic impairment was between 7- to 190-fold higher than in healthy subjects. As for tetrabenazine, the clinical pharmacology reviewer recommends that deutetrabenazine be contraindicated for patients with hepatic impairment.

Bridging of deutetrabenazine to tetrabenazine

As discussed above, this 505(b)(2) application relies, in part, on FDA's prior finding of safety and efficacy for Xenazine (tetrabenazine). Therefore, an adequate PK bridge had to be provided to the Xenazine NDA, in order to allow a comparison of the bioavailability of both drugs, and the comparability of their metabolic profiles and metabolites. In particular, it was critical to know how the metabolites levels compare for both drugs, and whether there is any major metabolite unique to deutetrabenazine.

Of note, the demonstration of strict bioequivalence between deutetrabenazine and tetrabenazine was not required or expected, as the applicant conducted a safety and efficacy study with deutetrabenazine (see Clinical/Statistical-Efficacy and Safety below). The bridging studies showed that, at highest proposed dose, the Cmax of deutetrabenazine is no higher than that of tetrabenazine.

An important aspect of the bridging studies was to compare the exposures to tetrabenazine and deutetrabenazine metabolites to ensure that no new major metabolite is seen with deutetrabenazine. The metabolic profile of deutetrabenazine has been the subject of extensive discussion with the applicant during the development program. According to the applicant, deuteration does not change the metabolic pathway of deutetrabenazine, relative to that of tetrabenazine, and all 22 metabolites of deutetrabenazine are among the 24 metabolites of tetrabenazine. At least two major circulating metabolites (defined as >10% of total circulating deutetrabenazine related radioactivity), α-HTBZ (M6) and monohydroxy tetrabenazine (M4), have been identified by the applicant. It appears that M4 is a major human metabolite of both deutetrabenazine and tetrabenazine. Because it was not identified as a major human metabolite at the time tetrabenazine was approved, M4 was not quantitated in the nonclinical studies. Therefore, it is unknown if M4 has been adequately assessed in the appropriate nonclinical

studies. However, since M4 is present with tetrabenazine, possibly at higher levels, nonclinical bridging studies may be conducted as PMRs.

The OCP review team, however, believes that the applicant has not adequately characterized the *in vivo* metabolic profile of deutetrabenazine in humans, and finds the results of the mass balance study (SD-809-C-12) intended to compare the metabolism of deutetrabenazine to that of tetrabenazine inconclusive, for the following reasons:

a. Inconsistent results were obtained for metabolite M1, resulting in an inability to determine whether M1 is a major metabolite in humans (M1was not identified as a major human metabolite of tetrabenazine, either by the applicant or in Xenazine labeling, and if M1 is thought to be a major metabolite, further nonclinical studies would be required).
b. The applicant was unable to demonstrate, using semi-quantitative methods, that a known (based on Xenazine labeling) major human metabolite of tetrabenazine, 9-odesmethyl-β-dihydrotetrabenazine, is a major human metabolite of tetrabenazine. This deficiency increases the overall concern of the clinical pharmacology reviewer regarding the adequacy of the applicant's analytical methods.

The clinical pharmacology reviewer recommends that the applicant reassess the concentration of circulating deutetrabenazine-related metabolites. The clinical pharmacology reviewer proposes that "whether this could be done post approval will be decided by the non-clinical and clinical teams." The team has extensively discussed this issue, and has concluded that the data should be requested prior to approval, because it is not possible to determine whether all major circulating metabolites have been adequately evaluated in the appropriate nonclinical studies without an adequate understanding of the *in vivo* metabolic profile of deutetrabenazine in humans. In addition, tetrabenazine is already marketed for the same indication as proposed for deutetrabenazine, and deutetrabenazine does offer as only clear advantage over tetrabenazine that, at the high end of therapeutic doses, tetrabenazine must be taken two to three times a day, while deutetrabenazine may be taken just twice a day. A lower dosing frequency can be a significant aid to caregivers of Huntington's disease patients, but does not justify, in my opinion, not obtaining the necessary information about deutetrabenazine safety information before marketing the product.

Drug-drug interactions

The tetrabenazine label indicates that strong CYP2D6 inhibitors markedly increase exposure to the active metabolites of tetrabenazine. Tetrabenazine has a maximum recommended daily dose of 100 mg, and the maximum recommended single dose is 37.5 mg. The tetrabenazine label recommends that patients who require doses of tetrabenazine greater than 50 mg per day should first be tested and genotyped to determine if they are poor or extensive metabolizers by their ability to express CYP2D6. The tetrabenazine label also indicates that the daily dose of tetrabenazine should not exceed 50 mg per day in in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers, with single doses not exceeding 25 mg.

The deuteration of deutetrabenazine was intended to reduce the impact of CYP2D6 status due to genotype or concomitant medication usage. The clinical pharmacology reviewer discusses

that the applicant proposed not to include in the deutetrabenazine label the CYP2D6 restrictions part of the tetrabenazine label. However, the clinical pharmacology reviewer notes that the results of an *in vivo* drug-drug interaction study conducted with deutetrabenazine showed a 3-fold increase in total (α+β)-HTBZ exposure when a strong CYP2D6 inhibitor (paroxetine) was co-administered with deutetrabenazine. In addition, the clinical pharmacology reviewer notes that, in clinical trials, the deutetrabenazine dose was capped at 18 mg twice daily (36 mg total daily dose) in patients taking strong CYP2D6 inhibitors, and recommends that, similarly, the daily dose of deutetrabenazine not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers. This recommendation appears reasonable to me.

Conversion from tetrabenazine to deutetrabenazine

Of note, the applicant based a 2:1 tetrabenazine to deutetrabenazine dose ratio on comparative [α-HTBZ + β-HTBZ] plasma concentrations. Following administration of equal doses of deutetrabenazine and tetrabenazine, systemic exposure to total (α+β)-HTBZ was approximately twice as high for deutetrabenazine than for tetrabenazine. However, in the face of CYP2D6 inhibition, the Cmax and half-life of β-HTBZ were affected to a greater extent than those of α-HTBZ. The clinical relevance of this finding is unclear.

Other issues

The clinical pharmacology reviewer also recommends that the activity (VMAT2 and off-target binding) of metabolites M1 and M4 be evaluated, but would find it acceptable to have this conducted as a Post-Marketing Requirement.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Considering the similarities in the PK profile of tetrabenazine and deutetrabenazine, the division accepted to rely on a single efficacy study for deutetrabenazine.

Study C-15 was a double-blind, placebo-controlled, randomized, 2-arm, parallel-group, multi-center study to evaluate the efficacy of deutetrabenazine as a treatment of chorea associated with Huntington's disease. A total of 90 patients were planned to be randomized in a 1:1 ratio to placebo or deutetrabenazine. The study was conducted in the United States and Canada.

The study consisted of a screening period of up to 4 weeks, an 8-week titration period, a 4-week maintenance period, and a 1-week washout. The overall treatment period was 12 weeks.

Patients were started on deutetrabenazine 6 mg per day (or placebo), and progressively (weekly) titrated up to a tolerated dose level at which adequate chorea control had been achieved, or until a 48 mg daily dose was reached. If the patient was receiving a strong CYP2D6 inhibitor, the maximal total daily dose was limited to 36 mg.

The primary efficacy endpoint was change from Baseline to Maintenance in total maximal chorea (TMC) score. The TMC score is derived from seven items of the Unified Huntington's Disease Scale. Each of the seven items measures the maximal chorea of a body part, with scores ranging from 0 to 4 (0 representing no chorea and 4 representing marked or prolonged chorea). TMC scores, therefore, can range from 0 to 28. The Baseline TMC score was defined as the mean of the TMC scores at the Screening and at Day 0 visit. The maintenance TMC score was defined as the mean of the TMC scores at Week 9 and at Week 12.

Secondary efficacy endpoints included the following:

- The proportion of patients who were a treatment success at the end of therapy, based on the Patient Global Impression of Change (PGIC). This was analyzed as a binary variable, i.e., the proportion of patient "Much Improved" or "Very Much Improved" at the Week 12 visit.

- The proportion of patients who were a treatment success at the end of therapy, based on the Clinical Global Impression of Change (CGIC), analyzed the same way as for the PGIC.

- Change from Baseline (Day 0) to Week 12 in the Short from 36 Health Survey (SF-36) Physical Functioning score.

- Change from Baseline (Day 0) to Week 12 in the Berg Balance Test (BBT) score.

The primary analysis was performed on the modified intent-to-treat (mITT) population using an analysis of covariance (ANCOVA) model with treatment as a factor and Baseline TMC as the covariate. The mITT population was defined as all randomized patients who received treatment and had at least one post-baseline assessment of the TMC score.

The statistical reviewer notes that a total of 123 patients were screened, of which 90 were randomized (45 to placebo and 45 to deutetrabenazine). A total of 87 patients completed the study (43 in the placebo group and 44 in the deutetrabenazine group). There were more males than females in the placebo group (62%) but more females than males in the deutetrabenazine group (49%). The TMC score at baseline was slightly higher in the placebo group than in the deutetrabenazine group.

Efficacy results are summarized in **Table 1**. The change from baseline in TMC score was significantly higher for deutetrabenazine than for placebo ($p<0.0001$). The proportion of patients meeting the treatment success criterion for the PGIC and for the CGIC was significantly higher for deutetrabenazine than for placebo (**Table 1**).

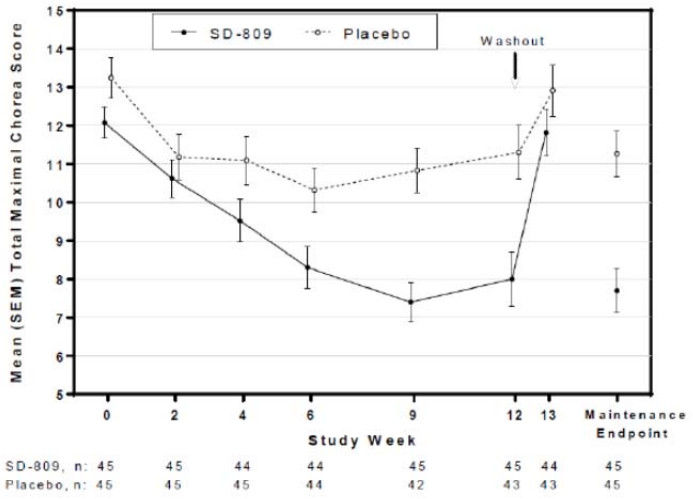
Table 1: Efficacy results (copied from page 13 of statistical review)

Endpoint	SD-809 (N=45)	Placebo (N=45)	Difference (95% CI) (SD-809 – Placebo)	p-value
Primary Endpoint				
Total Maximal Chorea Score[a], LS Mean (SD)	-4.42 (2.953)	-1.93 (2.666)	-2.49 (-3.69, -1.29)	<0.0001
Key Secondary Endpoints				
PGIC Treatment Success[b], n (%)	23 (51.1)	9 (20.0)	31.1[c] (12.4, 49.8)	0.0020
CGIC Treatment Success[b], n (%)	19 (42.2)	6 (13.3)	28.9[c] (11.4, 46.4)	0.0022
SF-36 Physical Functioning[d], LS Mean (SD)	0.74 (9.773)	-3.61 (9.669)	4.34 (0.41, 8.27)	0.0308
Berg Balance Test[d], LS Mean (SD)	2.2 (3.47)	1.3 (4.04)	1.0 (-0.3, 2.3)	0.1415
Additional Prespecified Endpoints				
Change in UHDRS Total Motor Score[a]	-7.35 (6.344)	-3.36 (5.469)	-3.99 (-6.52, -1.46)	0.0023
Percentage Change in Total Maximal Chorea Score[a]	-36.97 (25.704)	-16.17 (19.646)	-20.80 (-30.47, -11.13)	<0.0001
Change in Total Maximal Chorea Score Based on Video Rating[a]	-2.3 (2.55)	-0.4 (2.54)	-1.9 (-3.0, -0.9)	0.0005

Abbreviations: CGIC, Clinical Global Impression of Change; CI, confidence interval; LS, least squares; PGIC, Patient Global Impression of Change; SD, standard deviation; UHDRS, Unified Huntington's Disease Rating Scale.
[a] Change from Baseline to maintenance therapy. Baseline was defined as the mean of values from Screening and Day 0. Maintenance therapy was defined as the mean of values from the Week 9 and Week 12 visits.
[b] Treatment success at Week 12 defined as "much improved" or "very much improved".
[c] Difference in percentages of treatment success.
[d] Change from Baseline to Week 12.

Figure 2 illustrates the time course of treatment response for the TMC score. After the washout period, the mean TMC scores at Week 13 of both treatment groups appeared to return to the Baseline levels (**Figure 2**).

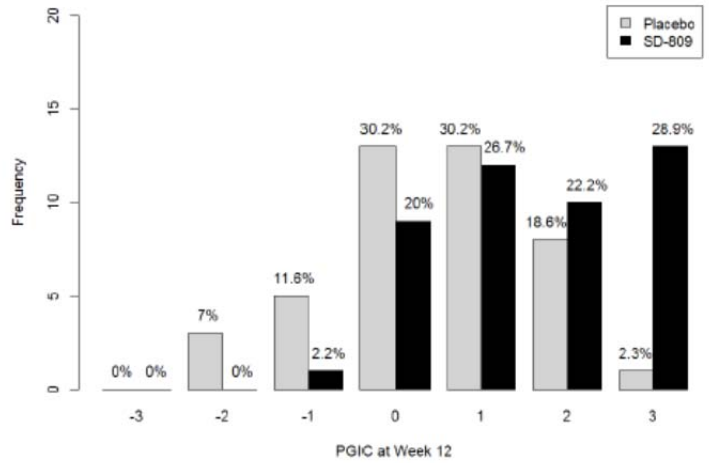
Figure 2: Primary endpoint results in Study deutetrabenazine-C-15



Source: Table 14.2.8.2 and Listing 16.2.6.1.1.
Abbreviations: SEM, standard error of the mean; TMC, Total Maximal Chorea score.
Notes: TMC is determined from Item 12 of the Unified Huntington's Disease Rating Scale. The Baseline value (defined as the mean of the values from the Screening and Day 0 visits) is graphed for Week 0. Maintenance endpoint is the mean of values of the Week 9 and Week 12 visits. Higher scores indicate more chorea. TMC score ≥8 was an inclusion criterion.

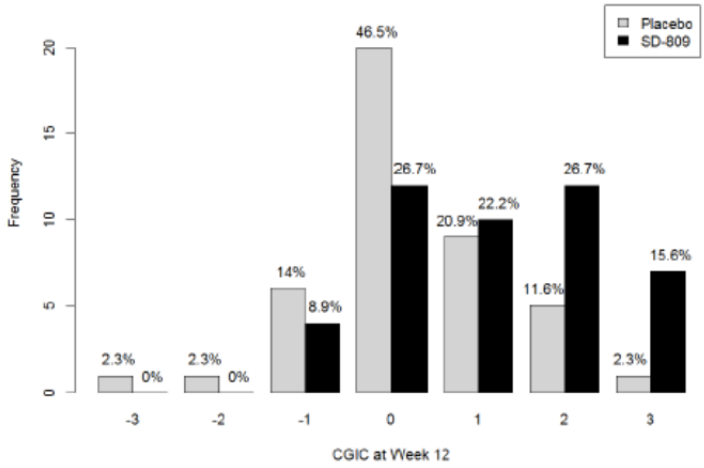
Figure 3 and
Figure **4** show the distribution of results for the PGIC and the CGIC.

Figure 3: Distribution of Patient Global Impression of Change at Week 12 (copied from page 12 of statistical review)



-3: Very Much Worse; -2: Much Worse; -1: Minimally Worse; 0: Not Change;
1: Minimally Improved; 2: Much Improved; 3: Very Much Improved.

Figure 4: Distribution of Clinical Global Impression of Change at Week 12 (copied from page 12 of statistical review)



-3: Very Much Worse; -2: Much Worse; -1: Minimally Worse; 0: Not Change;
1: Minimally Improved; 2: Much Improved; 3: Very Much Improved.

The statistical reviewer notes that there is no compelling evidence from subgroup analyses that a specific gender, race, age, or geographic region subgroup benefits differently from deutetrabenazine.

8. Safety

The clinical reviewer notes that, based on the tetrabenazine label, the main safety concerns expected for deutetrabenazine were sedation and somnolence, akathisia, depression/suicidality, and a risk of QT prolongation.

The safety database for deutetrabenazine comes from six Phase 1 studies and one single double-blind efficacy study (C-15) with open-label long term extension (C-16). The Phase 1 studies evaluated 178 healthy adult subjects, mostly for single dose exposures (24 healthy subjects received multiple doses). The open-label long-term extension study (C-16) also included a cohort of patients who were switched from tetrabenazine to deutetrabenazine overnight, according to a pre-specified dose conversion schedule (e.g., 100 mg tetrabenazine was converted to 48 mg deutetrabenazine). As discussed above, the maximum dose in Study C-15 was 48 mg/day, except for patients receiving a potent CYP2D6 inhibitor, who had a 36 mg daily limit. In Study C15 and C16, weekly dose increases were not to exceed 6 mg/day. In clinical studies, most patients (76%) reached a maintenance dose of 36 mg/day or above. Some patients received doses up to 72 mg/day in Study C-16, and 28 patients were exposed to doses greater than 48 mg/day. Doses were taken approximately 10 hours apart during the day, with meals.

The clinical reviewer focused his review on Study C-15 and Study C-16. The applicant also submitted safety information from Study C-18, which investigated deutetrabenazine for the treatment of tardive dyskinesia (TD). Study C-18 included a 6-week titration period, a 6-week maintenance period, and a 1-week washout. Only summary information of adverse events occurring in Study C-18 was submitted to this NDA. In Study C18, 56 patients received active drug (and 57 received a placebo) at the same dose range as in Study C-15. **Table 2** shows the overall safety database for deutetrabenazine.

Table 2: Overall safety database (copied from page 71 of clinical review)

Study	Any SD-809 Exposure	≥8 Weeks	≥15 Weeks	≥28 Weeks	≥52 Weeks
Phase 3 (Subjects With Chorea Associated With Huntington's Disease)					
First-HD	45	45	--	--	--
ARC-HD (120 day update)[a]					
ARC-Rollover	82	79	71	33	8
ARC-Switch	37	36	32	19	1
Total HD Subjects Exposure[b]	**121**	**119**	**111**	**65**	**16**
Phase 1 (Healthy Volunteer Subjects)					
Total Healthy Volunteer Subjects Exposure	**178**	--	--	--	--

Deaths

No death has occurred in the HD development program. There have been two deaths in the tardive dyskinesia study, neither of which appears related to study drug, according to the clinical reviewer.

Serious adverse events

There were 19 events (in 13 patients) labelled as serious in the safety database. The clinical reviewer believes none of the events is likely to be related to the drug, with the possible exception of depression and suicidality (which is frequent in that population, and difficult to assess for causality). All events clinically improved or resolved with treatment. Only one patient who experienced a serious adverse event (hip fracture) was a poor metabolizer of CYP 2D6.

Adverse dropouts

Adverse events leading to withdrawal or requiring dose reductions were reported in both Study C-15 and Study C-16.

In the controlled study experience, 1 patient in the deutetrabenazine group withdrew from Study C-15 due to an adverse event, vs. 1 patient in the placebo group. Five additional patients in Study C-16 had AEs that led to withdrawal (2 cases of akathisia and 3 cases of depression). The clinical reviewer notes that the cases of akathisia appear to have a temporal relationship to drug.

The clinical reviewer notes that 17 additional patients had dose reductions during clinical studies. Events were primarily related to somnolence, dizziness, depression, akathisia, and fatigue.

Common adverse events

As shown in Table 3, somnolence was the most commonly reported adverse event in Study C-15 (11% for deutetrabenazine vs. 4% on placebo). Somnolence occurred primarily during the initial (up-titration) weeks, and in 4 cases (on deutetrabenazine) led to a dose reduction. Of note, somnolence was also the most frequent adverse event seen with tetrabenazine (31% of drug, vs. 3 % on placebo), according to the drug label.

A closely related event, fatigue, was also more frequent for patients on deutetrabenazine (9%) than for patients on placebo (4%). Fatigue was also the second most frequent event for tetrabenazine, according to the label.

Table 3: Adverse events in Study C-15 (copied from page 84 of the clinical review)

System Organ Class	Preferred Term	SD-809 (N)	SD-809 %	Placebo (N)	Placebo %
Nervous system disorders	Somnolence	5	11.1	2	4.4
Gastrointestinal disorders	Dry mouth	4	8.9	3	6.7
General disorders and administration site conditions	Fatigue	4	8.9	2	4.4
Gastrointestinal disorders	Diarrhoea	4	8.9	0	0.0
Nervous system disorders	Dizziness	3	6.7	4	8.9
Injury, poisoning and procedural complications	Fall	3	6.7	9	20.0
Psychiatric disorders	Insomnia	3	6.7	2	4.4
General disorders and administration site conditions	Irritability	3	6.7	6	13.3
Psychiatric disorders	Anxiety	2	4.4	1	2.2
Musculoskeletal and connective tissue disorders	Back pain	2	4.4	1	2.2
Gastrointestinal disorders	Constipation	2	4.4	1	2.2

Diarrhea, which was seen more commonly on deutetrabenazine, was not an adverse reaction noted for tetrabenazine. It is a common event in the general population, and may be a chance finding.

Finally, there was a slight excess of anxiety, back pain, and constipation for deutetrabenazine compared with placebo. Again, the numbers are small, and the apparent difference between drug and placebo may be a chance finding.

Laboratory findings

There are no noteworthy laboratory findings.

Vital signs

There are no noteworthy vital signs findings.

Events of Interest

Depression and suicidality

Tetrabenazine has a boxed warning for depression and suicidality. In Study C-15, 4% of deutetrabenazine-treated subjects and 7% of placebo-treated subjects experienced adverse events related to depression. There was a lack of a difference between deutetrabenazine and placebo on the HADS-D (a scale assessing anxiety and depression), and no signal for suicidal ideation or behavior in the study.

As discussed by the clinical reviewer, the background rate of depression and suicide in Huntington's disease is so large that it would be very difficult to assess whether deutetrabenazine adds to that risk in a pre-marketing study, unless the effect is large. No signal was detected for that event in the deutetrabenazine database.

Akathisia
The clinical reviewer notes that motor restlessness occurred in 5% of the treated population of the open-label study, but only one of the participants taking deutetrabenazine in the double-blind study experienced akathisia. This contrasts with a large difference between drug and placebo reported for tetrabenazine in labeling (19% vs. 0%).

Parkinsonism
Parkinsonism was not reported as an adverse event in any patient in controlled Study C-15. Parkinsonism was reported in 3 patients in open-label Study C-16. These events resolved with dose reduction. Again, this observation contrasts with a large difference between drug and placebo reported for tetrabenazine in labeling (9% vs. 0%).

Dysphagia
The tetrabenazine label discusses that dysphagia is a component of Huntington's disease, and that drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. There was a slight excess of dysphagia in tetrabenazine studies (4% vs. 3% on placebo).

Swallowing was evaluated by the Swallowing Disturbance Questionnaire in deutetrabenazine studies. In the open -label Study C-16, dysphagia was reported as an adverse event in 5 patients (4.2%). In the double-blind Study C-15, none of the deutetrabenazine-treated patients had dysphagia as an adverse event, while 1 placebo-treated patient did.

In summary, there is no signal for dysphagia seen in the deutetrabenazine database.

Switching patients from tetrabenazine to deutetrabenazine
The applicant evaluated the safety and tolerability of switching subjects from tetrabenazine to deutetrabenazine overnight using a 2:1 dose conversion ratio. A total of 37 patients taking a mean dose of 42 mg tetrabenazine daily (range 12.5 to 100 mg) were converted to deutetrabenazine, with a mean 20.3 mg dose daily (range 6 – 48 mg). There was no safety issue noted with this treatment switch, but increases in the dose of deutetrabenazine were often necessary after the switch.

Thorough QT Study Review

Tetrabenazine has a Warning for QTc prolongation.

No significant QTc prolongation effect of deutetrabenazine 12 and 24 mg was detected in a TQT study. The study used tetrabenazine as an active control; a marginal QT effect of tetrabenazine 50 mg was seen. This is consistent with an increase in the QT interval of approximately 8 ms reported in the Xenazine Prescribing Information. Assay sensitivity was established with moxifloxacin.

As, in the predicted worst case clinical scenario (CYP2D6 poor metabolizer administered a strong CYP2D6 inhibitor), deutetrabenazine exposure is projected to more than 3-fold higher than studied in this TQT study, the QT study reviewer concludes that the TQT study was not conducted at sufficiently high concentrations to rule out QT prolongation at supratherapeutic or therapeutic concentrations. The reviewer expects that clinically relevant QT prolongation might occur in some patients at the highest therapeutic dose of 24 mg b.i.d., especially in CYP2D6 poor metabolizers or in patients co-administered a strong CYP2D6 inhibitor.

The tetrabenazine label includes a Warning about QT effects. The QT reviewer recommends similar language for the deutetrabenazine label. I concur.

9. Advisory Committee Meeting

No advisory committee meeting was held for this 505(b)(2) application.

10. Pediatrics

As the product has orphan exclusivity, PREA was not triggered by this application.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Audits

Two domestic clinical investigator sites were inspected. They revealed minor deviations that would not adversely impact data acceptability.

Controlled Substances Staff (CSS)

The CSS reviewer notes that there were no preclinical and clinical studies designed to evaluate abuse potential and dependence of deutetrabenazine. The reviewer believes that clinical data comparing adverse events following administration of deutetrabenazine and tetrabenazine are too limited to allow any conclusions about the abuse potential of deutetrabenazine, although the reviewer believes that the data seem to show more neuro-psychiatric adverse events for deutetrabenazine. The reviewer recommends evaluation of clinical dependence at the end of a trial lasting at least 4 weeks. This can be requested from the applicant, but is not a reason for a complete response action, considering the reliance on tetrabenazine as a reference listed drug, which should be largely be adequate to address the the potential for abuse and dependence of deutetrabenazine .

12. Labeling

Labeling review is deferred to the next cycle.

13. Postmarketing

As for Xenazine, no Postmarketing Risk Evaluation and Mitigation Strategy should be necessary for this product.

The need for Postmarketing Requirements and Commitments will be assessed in the next review cycle.

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/s/

ERIC P BASTINGS
05/27/2016

Cross-Discipline Team Leader Review

Date	May 24, 2016
From	Gerald D. Podskalny, DO, MSPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208082
Applicant	Teva
Date of Submission	May 29, 2015
PDUFA Goal Date	May 29, 2016
Proprietary Name / Non-Proprietary Name	Austedo (deutetrabenazine)
Dosage form(s) / Strength(s)	6 mg, 9mg, and 12mg oral tablets
Applicant Proposed Indication(s)/Population(s)	The treatment of chorea associated with Huntington's disease
Recommendation on Regulatory Action	***Complete Response***
Recommended Indication(s)/Population(s) (if applicable)	The treatment of chorea associated with Huntington's disease

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Huntington's disease is an inherited neurodegenerative disorder that follows an autosomal dominant pattern of inheritance. It is an uncommon disorder with an estimated prevalence of 5/100,000 in the US (Kay C., 2014). The disease causes progressive dementia, motor disability including chorea and psychiatric symptoms. Symptoms begin most often between ages 30 to 50 years. Disease related disability causes death in 15-20 years after the onset of symptoms, most often due to pneumonia but suicide is also more frequent among patients with HD (Roos, 2014). Although it is possible to detect the genetic abnormality in utero, there are no treatments that alter the progression of the disease. Tetrabenazine (Xenazine) was approved on August 15, 2008, (NDA 21894) for the treatment of HD associated chorea. It is remains the only drug approved for treatment of HD.

Tetrabenazine is rapidly and extensively metabolized to α-HTBZ and β-HTBZ metabolites, which are active and bind reversibly to VMAT2. The

α-HTBZ and β-HTBZ metabolites of tetrabenazine are potent inhibitors of VMAT2 in the central nervous system and deplete presynaptic monoamines, including dopamine, which reduces chorea in patients with HD. Austedo (deutetrabenazine, aka. SD-809) is a deuterated form of tetrabenazine and it follows the same metabolic pathway and tetrabenazine. Systemic exposure (AUC) to total (α+β)-HTBZ following deutetrabenazine administration is approximately 2-fold greater than with tetrabenazine, which is the rationale for administering a lower dose of deutetrabenazine compared to Xenazine.

The proposed indication for deutetrabenazine is the same as the indication for Xenazine. The evidence of safety and effectiveness observed in study SD-809-C-15, and supporting evidence of effectiveness from the Agency's finding of safety and effectiveness for the reference drug (Xenazine), meet the statutory requirement showing deutetrabenazine is safe and effective for treating chorea associated with HD. The safety profile of deutetrabenazine similar clinical safety profile as Xenazine. There is an increased risk for depression, suicidality, a need for dose reduction in poor CYP2D6 metabolizers and in patients taking CYP2D6 inhibiting agents, Parkinsonism, neuroleptic syndrome and mildly prolonged QTc associated with deutetrabenazine and approved Xenazine.

It is uncertain whether deutetrabenazine has two unique major human metabolites (M1 and M4) that are not described in Xenazine label. The exposure to the M1 and M4 metabolites resulting from deutetrabenazine has not been determined with certainty during drug development. Importantly, the sponsor has not shown that M1 and M4 were adequately represented in the 3-month bridging toxicology study, or in the embryofetal development study of deutetrabenazine. Until it is shown that human exposure to M1 and M4 from deutetrabenazine does not exceed the level associated with Xenazine, and there was adequate exposure to M1 and M4 in the sponsor's bridging toxicology studies, the safety of deutetrabenazine cannot be fully assessed. The sponsor needs to provide quantitative assessments of the human exposure to M1 and M4 associated with deutetrabenazine using validated methods. Patients with HD may conceive children while taking deutetrabenazine; therefore, the toxicology and embryofetal development study to evaluate the effect of M1 and M4 are of greatest concern.

The sponsor's Thorough QTc (TQT) study was limited to a single dose of deutetrabenazine. It did not adequately assess the effects of the highest doses of deutetrabenazine administered to patients in the open label clinical study. Dosing in the open label study showed that some patient may need more than the proposed maximum recommended dose of 24 mg bid to adequately control their chorea, up to 36 mg bid. If patients treated with higher doses with impaired CYP2D6 function could be exposed to 3 times the level of the active α- and β-HTBZ metabolites compared to individuals with normal CPY2D6 function. In the TQT study, the sponsor did not evaluate levels of the M1 and M4 in the study subjects. The combined effect of high doses of deutetrabenazine and CYP2D6 inhibition could greatly exceed the exposure to α- and β-HTBZ assessed in the TQT study. A single dose of deutetrabenazine 24 mg, prolonged QTcF by an average of 4.6 ms in the sponsor TQT study.

Deutetrabenazine does not appear to offer a significant advantage over Xenazine for efficacy or safety although; the two drugs were not compared in the same study. Considering the uncertainties and the potential safety risks, I recommend a Complete Response action until the sponsor can provide information to address the uncertainties concerning the M1 and M4 metabolites, and provide labeling to inform prescribers and patients about any unique risks with using deutetrabenazine.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Huntington's disease is an inherited neurodegenerative disorder. The gene is on the short arm (of chromosome 4 giving rise to an autosomal dominant pattern of inheritance. HD is uncommon with an estimated prevalence of 5/100,000 in the US(Kay C., 2014). The affected gene codes for a trinucleotide (CAG) repeat expansion producing abnormal Huntingtin protein (Huntingtin). Patients with a CAG repeat length of 37 CAG repeats or more become symptomatic. The disease causes progressive dementia, motor impairment and psychiatric symptoms beginning most often between ages 30 to 50 years. HD causes death in 15-20 years after the onset of symptoms. The juvenile form of HD (onset <21 years) is uncommon and it is more likely to present with rigidity and dystonia rather than chorea. The length of the CAG repeat influence the age of onset. Individuals with long repeat sequence length are associated with a younger onset of symptoms(Roos, 2014).	HD is a serious, eventually fatal neurodegenerative disorder. Although it is possible to detect the genetic abnormality in utero, there are no treatments that alter the progression of the disease.
Current Treatment Options	• Tetrabenazine (Xenazine) is the only drug approved (8/15/2008) for the treatment of patients with HD. Tetrabenazine is approved for the treatment of chorea associated with HD(FDA, 2015). There are no criteria to determine when chorea should or needs to be treated. Approved medications (e.g., antidepressants, antipsychotics mood anticonvulsants) are often used off label to treat the psychiatric and behavioral aspects of HD(Killoran & Biglan, 2014). Tetrabenazine may cause side effects including sedation, worsening depression and suicidality and drug induced Parkinsonism.	Tetrabenazine is the only available for symptomatic treatment of chorea associated with HD.
Benefit	• The evidence of effectiveness is provided from the results of clinical study SD-809-C-15. Ninety patients were enrolled in this DB, PC trial (N=45 SD-809 and N=45 Placebo). The study compared the effects of SD-809 up to 48 mg to placebo on reducing the Total Maximal Chorea (TMC) score The LSmean treatment difference (SD-809 minus placebo) in the pivotal efficacy show a statically significant reduction in the TMC (primary endpoint) scores in HD patients treated with SD-809 of -2.49 (P<0.0001). The benefit to patients is supported by the statistically significant improvement	The evidence of safety and effectiveness observed in study SD-809-C-15, and supporting evidence of effectiveness from the Agency's finding of safety and effectiveness for the reference drug (Xenazine), meets the statutory requirement showing SD-809 is safe and effective for treating chorea associated with HD. On face, SD-809 does not appear to offer a significant advantage over approved Xenazine although; the two drugs were not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	shown for SD-809 compared to placebo on the patient and investigator rated CGI. The effect of SD-809 on the TMC score is similar to the reduction seen with non-deuterated tetrabenazine (-3.5)(Huntington Study, 2006). Other than a small sample size and that the study did not assess dose response, there were no specific design limitations in the pivotal efficacy study. The sponsor did not seek SPA agreement and the sponsor decided to use a different trial design from the one discussed at the EOP2 meeting.	compared in the same study.
Risk	• SD-809 has similar clinical safety profile as non-deuterated tetrabenazine. An increased risk for depression, suicidality, the need for dose reduction in poor CYP2D6 metabolizers, and in patients taking CYP2D6 inhibiting agents, Parkinsonism, neuroleptic syndrome and prolonged QTc, are concerns with SD-809 and approved tetrabenazine. • SD-809 has an unknown risk associated with potential major human metabolites (M1 and M4), unique to SD-809 that were not assessed during development of the reference product (Xenazine) or in the SD-809 development program. • The Sponsor's Thorough QTc (TQT) study did not adequately assess the effects of SD-809for clinical doses administered in the open label clinical studies. • The sponsor needs to submit a limit for (b) (4) allowed in the drug substance and a validated testing method for review by the Agency.	I recommend a Complete Response Action until it can be determined that M1 and M4 are, or are not new major human metabolites using quantitative methods. The sponsor must establish that their nonclinical studies bridge to the existing nonclinical toxicology, embryofetal toxicity and carcinogenicity information. The sponsor has treated patients with as much as 36 mg bid of SD-809, which is high than the maximum dose tested in the completed TQT. The open label data suggests that some patients may require doses that are higher than the sponsor planned maximum recommended dose of 24 mg bid.
Risk Management	The risks associated with somnolence, Parkinsonism, depression and suicidality can be managed in labeling. Xenazine was originally approved with a Communication Plan REMS to inform prescribers and dispensers about the risk of higher exposure to the active metabolites in patients with impaired CYP2D6 function and the increased risk for suicidality. The REMS was removed after 7 years. The risk of QTc prolongation caused by SD-809 has not been adequately assessed and needs to be studied at doses that produce exposures that patients with impaired CYP2D6 function may experience if prescribed a dose of 36	A REMS is not necessary for Xenazine or SD-809. The need to clarify the status M1 and M4 as MHM needs to be addressed in the premarket period with the assessment of potential embryofetal toxicity being the highest priority. A Postmarketing requirement should be imposed for the sponsor to conduct an adequate TQT study with a supramaximal dose that covers the levels of exposure to deuterated

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mg bid. SD-809 is associated with depression and suicidality. The sponsor's clinical studies are not designed to adequately show differences for the risk of depression and suicidality between SD-809 and placebo. Patients with HD are at higher risk for depression and suicidality, SD-809 and Xenazine may increase these risks.	α- and β-HTBZ that exceed those associated with a single dose SD-809 dose of 36 mg in poor CYP2D6 metabolizers. If marketed, the SD-809 label needs to include the same Boxed Warning that appears in the Xenazine label. It describes an increased risk for suicidality and depression in patients with HD. Labeling was not discussed with the sponsor during this review cycle.

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2. Background

Austedo (deutetrabenazine, aka. SD-809) is a deuterated form of tetrabenazine. Non-deuterated tetrabenazine (Xenazine) is approved in the US for the treatment of for the treatment of chorea associated with Huntington's disease (HD) (August 15, 2008). Auspex Pharmaceuticals developed SD-809 up to the late IND stage of development then Teva Pharmaceuticals acquired Auspex. On May 29, 2015, Teva Pharmaceuticals submitted a 505(b)(2) NDA for Austedo (deutetrabenazine). The 505(b)(2) application relies on pharmacology/toxicology studies necessary for labeling of deutetrabenazine that were not conducted by Auspex/Teva, data described in the Xenazine Prescribing Information (Section 1.14.3.3) including fertility and early embryonic development, embryofetal developmental, pre- and postnatal development, and carcinogenicity studies.

SD-809 is included in the pharmaceutical class of vesicular monoamine transporter 2 (VMAT2) inhibitors. The proposed indication is for "the treatment of chorea associated with Huntington's disease", which the same as the indication for the reference listed drug (RLD). SD-809 was assessed in adult patients with HD but it was not studied in children with HD. SD-809 is manufactured in 6 mg, 9 mg, and 12 mg oral tablets.

HD is an inherited neurodegenerative disorder. The Huntingtin gene (HTT) is located (locus IT15) on the short arm of chromosome 4 (4p16.3) giving rise to an autosomal dominant pattern of inheritance. The gene mutation codes for a trinucleotide (CAG) repeat expansion producing abnormal huntingtin protein (Hughes A., 2014). Patients with a CAG repeat length of 37 repeats or more become symptomatic. Manifest HD causes progressive dementia, motor impairment and psychiatric symptoms. The adult form of HD typically becomes symptomatic between 30-50 years, and death occurs 15-20 years after the onset of symptoms (Roos 2014).

Tetrabenazine (Xenazine) was approved on August 15, 2008, (NDA 21894) for the treatment of HD associated chorea. It remains the only drug approved for treatment of HD. Xenazine is associated with an increased risk for suicidality and depression; however, HD causes an increased risk for depression and suicidal ideation, and this was a small study and it may be difficult to attribute these effects to any drug in these circumstances. There are no treatments known to slow the progression of HD.

Regulatory background and marketing history

The FDA Office of Orphan Product Development granted Auspex orphan status on November 5, 2014, for deutetrabenazine (d_6-tetrabenazine), for the treatment of chorea associated with Huntington's disease. On July 31, 2015, the CDER Exclusivity Board concluded, "tetrabenazine and deutetrabenazine are not the same active moiety under FDA's regulations and precedent. Therefore, deutetrabenazine and tetrabenazine are not the "same drug" under the statute and regulations governing orphan drugs and it is appropriate to grant orphan drug designation to deutetrabenazine without a plausible theory of superiority to tetrabenazine. In addition, the Agency commented that the active moiety deutetrabenazine has not yet been previously approved in any new drug application (NDA)."

Auspex requested Fast Track Designation and Breakthrough Designation (BTDR), both requests were denied on April 2, 2015. Fast Track Designation Request was denied because the sponsor did not show that deutetrabenazine addressed an unmet medical need. The sponsor submitted the BTDR at the Pre-NDA stage of development without preliminary clinical evidence indicating deutetrabenazine may demonstrate substantial improvement over existing treatments on a clinically significant endpoint(s).

Bridging Strategy

The sponsor was unable to obtain Xenazine from the innovator to conduct its Phase 1 bioavailability (BA) and bioequivalence (BE) studies. The sponsor's PK bridging strategy did not follow a typical approach because they could not obtain a sufficient supply of the RLD (Xenazine) to complete the necessary BA and BE studies. Instead, the sponsor evaluated exposure to the active α-HTBZ and β-HTBZ metabolites of SD-809 and tetrabenazine in their Phase 1 studies using tetrabenazine as unformulated powder-in-capsule and a commercially available tetrabenazine drug (tablet) sourced from Australia and Northern Ireland. The second part of the strategy compared human PK samples from patients enrolled in study SD-809-C-16, patients entered the study taking a stable dose of Xenazine sourced from their personal supply purchased from their pharmacy. After switching patients to a dose of SD-809 predicted to be equivalent to their stable Xenazine dose, levels of the active α-HTBZ and β-HTBZ metabolites from both products were compared. The details of the PK sampling plan and results of the PK analysis from study SD-809-C-16 are discussed in the Clinical Pharmacology section of this review.

The application included results from clinical pharmacology studies that are not typically included in a b2 application. The sponsor submitted information from their human Mass Balance Recovery study, in vitro and in vivo drug-drug interaction studies, and the sponsor's clinical safety and efficacy study information. This approach provided multiple levels of support for the sponsor's bridge to the reference listed drug. The approach relied upon information from studies conducted by the b2 applicant rather than simply demonstrating bioequivalence. In this individual application, the review Division, OCP and Office of Regulatory Policy (ORP) considered sponsor's unique bridging strategy acceptable.

There are several regulatory interactions that involve advice about specific review issues that include:

- Information that clearly determines if M1 and M4 are or are not major human metabolites
- The ability to rely on the safety experience for Xenazine (nonclinical carcinogenicity and embryofetal toxicity studies) if there are major human metabolites that are unique to SD-809,
- Submission of a revised specification and analytical method for (b) (4)

These review specific issues are discussed in detail in the relevant review sections.

Foreign Regulatory Status

SD-809 is not marketed in any country.

Review Conduct
There were no differences of opinion regarding the recommended action or review issues that required alignment during the course of this review.

Table 1: FDA Personnel Involved in the Review of NDA 208082

Quality Review Team	Listed in the Product Quality Section
Christopher Toscano, PhD Lois Freed, PhD	Nonclinical Reviewer Nonclinical Supervisor (Memo)
Kristina Dimova, PhD	Primary Reviewer Office of Clinical Pharmacology
Xiaofeng Wang, Ph.D.	Office of Clinical Pharmacology Pharmacometrics Reviewer
Kenneth Bergmann, MD	Clinical Reviewer
Xiangmin Zhang, PhD	Division of Biometrics I
Alicja Lerner, MD, PhD	Medical Officer Controlled Substance Staff
Xingfang Li, MD	Division of Generic Drug Bioequivalence Evaluation Office of Study Integrity and Surveillance (OSIS)
Hasan A. Irier, PhD	Division of Generic Drug Bioequivalence Evaluation Office of Study Integrity and Surveillance Office of Translational Sciences
Antoine El-Hage, PhD	Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
Deborah Myers, RPh, MBA (Label and Labeling Review)	Division of Medication Error Prevention and Analysis (DMEPA) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) Center for Drug Evaluation and Research (CDER)

3. Product Quality

Table 2: The Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Gene Holbert	Branch1/DNDAPI/ONDP
Drug Product	Sherita Mclamore Hines	Branch 1/DNDP 1/ONDP
Process	Masih Jaigirdar	Branch 1/DPAI/OPF
Microbiology	Masih Jaigirdar	Branch 1/DPAI/OPF
Facility	Don Obenhuber	Branch1/DIA/OPF
Biopharmaceutics	Jing Li	Branch 1/DB/ONDP
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heimann	Branch 1/DNDP 1/ONDP

Recommendation for NDA 208028 (Austedo)

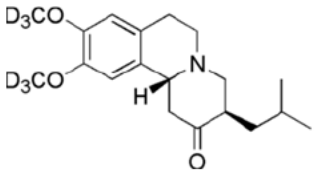
OPQ recommends a **COMPLETE RESPONSE** action for this application.

Drug Substance Manufacture

The Drug Substance (DS) reviewer for this NDA is Gene W. Holbert, Ph.D. At the present time, there are two pending issues that have potential to impact a recommendation for approval

from OPQ. Teva has agreed to, but has yet to submit a suitable test method and limit for (b) (4) a potential genotoxic impurity, the limits for this (b) (4) impurity need to be below the threshold for toxicological concern (1.5 µg/person/day), based on the maximum recommended daily dose of SD-809 of 48 mg daily. Second, the manufacturing facilities inspection recommendation for a drug substance release testing site not previously inspected by FDA, needs to be received before OPQ can make their final recommendation regarding this NDA.

Austedo (Deutetrabenazine) is the deuterated version of the FDA approved drug Xenazine (Tetrabenazine).



Deutetrabenazine
$C_{19}H_{21}D_6NO_3$

The primary metabolites of tetrabenazine are α-dihydrotetrabenazine (α-HTBZ) and β-dihydrotetrabenazine (β-HTBZ). These active metabolites reversibly inhibits human vesicular monoamine transporter type 2 (VMAT2), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. α and β-HTBZ are metabolized by CYP2D6 in humans. (b) (4)

(b) (4)

(b) (4)

Key DS properties of deuterated tetrabenazine (d-tetrabenazine) are:

- SD-809 has two chiral centers and the DS is a racemic mixture of the RR and SS enantiomers.
- It is poorly soluble in water, solubility increases with decreasing pH reaching peak

(b) (4)

Drug Substance Manufacture

(b) (4)

(b) (4)

Synthesis

There are 4 stages in the DS synthesis. The DS reviewer concluded that (b) (4) demonstrated adequate control of the critical steps in manufacture, identified and created specifications of the intermediates. The reviewer concluded the specifications, acceptance criteria and analytical testing procedures "were adequately described in the NDA. "

The (b) (4) impurities are controlled at levels below ICH (Q3A (R2) recommendations at acceptable limits, or they have been qualified at levels that are levels that are (b) (4) than the proposed limits.

There are no (b) (4) used in the manufacture of the DS. The DS reviewer noted that the levels of all the (b) (4) are below the level of detection. (b) (4) (b) (4)) impurities were within acceptable limits.

There are 6 potential impurities that may be present in the finished DS these include, (b) (4) (b) (4). A QSAR evaluation for the impurities (b) (4) was requested from the CDER Computational Toxicology Consultation Service. None of the four impurities was positive for mutagenicity. The sponsor provided the results of an in silico assessment requested by OPQ, which was also negative.

(b) (4)

(b) (4)

However, the NDA did not include a DS specification to control for (b) (4). Following a request from the Agency, the sponsor has "agreed to include a suitable test method and a limit for (b) (4) that is lower than the threshold for toxicological concern based on the maximum recommended dose of deutetrabenazine. The DS reviewer commented that the test for (b) (4) would resolve this issue; however, "a final determination regarding the acceptability of the applicant's controls cannot be made prior to submission and review of the revised specification."

On February 22, 2016, the sponsor committed to adding a test and acceptance criteria (b) (4) as part of the specification for the final drug substance, as requested by the Agency on 02/17/2016. The sponsor proposed an acceptance criteria limit for (b) (4) for the final drug substance of not more than (b) (4). The sponsor committed to submitting the test acceptance criteria, and method validation information to the NDA "on or before March 22, 2016".

On April 14, 2016, Teva submitted an update to the following sections with respect to (b) (4) content:

3.2.S.4.1 Specification
3.2.S.4.2 Analytical Procedures
3.2.S.4.5 Justification of Specification
2.3.S.4 Control of Drug Substance

However, the Method Validation section **has not** been amended. **Teva states that the validation report will be submitted within the next two to three weeks.** Their response is incomplete and a Complete Response action is therefore recommended.

CDTL Comment:
The outstanding information for (b) (4) is not expected to arrive until April 29 to May 5, 2016 (2-3 weeks), this does not leave sufficient time to review the information prior to the PDUFA deadline.

Batch Analyses
All validation batches were manufactured at the intended commercial scale of approximately (b) (4) The reference standards produced by the DS manufacturer were acceptable to the DS reviewer. The (b) (4) content was monitored on stability testing for developmental purposes and no changes were observed. The DS reviewer concluded; "the proposed specification includes tests and acceptance criteria. The Analytical procedures validated for their intended use. The methods were shown to be stability-indicating."

(b) (4)

(b) (4)

DS Recommendation

The applicant has not provided sufficient information to ensure the identity, quality and purity of the drug substance. **A Complete Response action** is recommended by the DS reviewer based on the incomplete information on the potential (b) (4).

Drug Product

The drug product (DP) is manufactured as 6, 9 and 12 mg round, film-coated tablets. The 6 mg tablets are purple with "SD" over "6" printed on one side of the tablet. The 9 mg tablets are blue with "SD" over "9" printed on one side of the tablet, and the 12 mg tablets are beige with "SD" over "12" printed on one side of the tablet. All tablets strengths are the same size, (b) (4)

The DP reviewer concluded the "applicant has provided a clear description of the drug product including the shape, color, printing and size. The applicant provided reference standards as well as the function for each of the excipients, and the excipients used in the color coatings. All excipients used are compendial, commonly used in solid oral dosage forms and are present at a levels below the maximum potency listed in the IIG. The information provided is adequate to support the approval of this application as there are no scientific or regulatory concerns pertaining to the proposed composition of the drug product."

The commercial container closure system for the drug product is a (b) (4) HDPE bottles with a (b) (4) closure. (b) (4) (b) (4).

Batch Analyses Data
The DP reviewer commented that batch analyses were provided for nine registration batches (3 batches of each strength). All nine batches were manufactured at the (b) (4) developmental scale (which represents (b) (4)% of the proposed commercial batch size) and packaged in (b) (4) (b) (4) HDPE bottles count. All batches were tested according to and met the acceptance criteria outlined in the drug product specification.

The DP reviewer concluded, "the proposed DP specification was consistent with ICH Q6A. The DP specifications addressed all critical quality attributes and there was adequate to control the drug product."

The analytical methods and validation procedures to evaluate related substances and content uniformity, identification, and dissolution 6, 7.5, 12 and 18 mg tablets was found to be adequate by the DP reviewer. The data for the 7.5 and the 12 mg tablets bracketed the 9 mg tablet which was acceptable.

Stability
The sponsor provided 24 months of real-time stability data within 12 months in the original application, and a 24-month update provided during the review cycle. All batches were manufactured at the commercial site according to the process controls and operating principles proposed for the commercial process and packaged into the commercial container closure system. However, the stability batches submitted in the NDA were not manufactured at commercial scale; therefore, the applicant was asked to revise the post-approval commitment to include the first three commercial batches. The applicant responded in the amendment received April 14, 2016. The DP reviewer concluded "the sponsor matrix for stability testing, which included reduced testing at 3, 6, 9 and 18 month and full testing at 12, 24 and 36 months was adequate. The results of all batches tested fell within the drug product release specification with microbial limits, (b) (4) content and (b) (4) activity tested for informational/developmental purposes only."

The results from the primary stability study indicate the drug product is stable under long-term and accelerated conditions and shows no sensitivity to heat, base, light or oxidative conditions. The stability data demonstrated very little change over time, and very little variability under long term conditions or forced degradation conditions (b) (4) (b) (4).

The DP Reviewer concluded that "in accordance with ICH Q1E, sufficient data has been presented to support the 32 month expiry and that the 32 month expiry should be granted."

However, the DP reviewer found the sponsor's proposed post-approval stability program was **NOT ACCEPTABLE**. The sponsor committed to placing "at least one production batch of the product in the commercial packaging will be placed on long term stability annually". OPQ

will advise the sponsor that" the post approval stability commitment should be updated to include placing the first three commercial batches of each strength of the drug product on long term stability through the proposed shelf life and on accelerated stability for 6 months as per ICH Q1A(R2)."

Recommendation on Expiry
The DP reviewer agreed that the data supports the requested 32 month expiry, and recommended granting a 32 month expiry.

Drug Product Manufacture

Masihuddin Jaigirdar was the OPQ Drug Product Manufacturing (DPM) reviewer for this application.

Table 3: Sites and Responsibilities in Manufacture of SD-809

Site/Facility	Responsibility
	(b) (4)

SD-809 (Austedo), 6 mg, 9 mg, and 12 mg tablets are manufactured using the following process steps:

(b) (4)

The sponsor identified the [redacted] as two critical steps in the DP manufacture.

1. [redacted]
2. [redacted]

The DPM reviewer considered the sponsor's exploration and refinement of the manufacturing process during product development satisfactory. The DPM reviewer also concluded the sponsor's selection of [redacted] controls and DP critical quality attributes (CQAs) were also satisfactory.

The DP manufacturer does not employ [redacted] technologies. The DP manufacturer performed [redacted] The DPM reviewer concluded this [redacted] is acceptable.

Scale up of Commercial Batches

Following the sponsor's selection of dosage strengths, three clinical bioavailability batches were manufactured at the [redacted] scale for clinical trial C-11. Subsequently, two scale up batches [redacted] scale) and 9 registration batches [redacted] scale) to supply drug for the pivotal clinical trials.

Following production of the registration batches, the DP manufacturer made minor process scale improvements. Manufacture of the commercial scale of [redacted] the size of the registration batches by 2 fold to an approximate yield of [redacted] dosage units [redacted] coated tablets). Two batches (one placebo, one [redacted] active) were manufactured at commercial scale. The DPM reviewer concluded the equipment used to manufacture commercial scale batches is acceptable.

Batch Analysis

The sponsor submitted information for two [redacted] batches, one placebo (E458190 core tablets/E458421coated tablets) to assess physical and mechanical tablet manufacturing properties, and one active (N458417 core tablets/N458496 coated tablets) to demonstrate that the process developed for the [redacted] batch size can be scaled up to the commercial scale of [redacted] using the selected commercial manufacturing equipment.

During the review, the DPM reviewer asked the sponsor to provide the Master Batch Records of deutetrabenazine (b) (4), coated tablets for 6mg and 9mg tablet strengths, in addition to the 12 mg tablet. On November 2, 2015, the sponsor provided the proposed Master Batch Records for the 6 mg and 9 mg tablets, which the DPM reviewer concluded were satisfactory.

In Process Controls and Specifications
The DPM reviewer concluded the In-Process Controls and Specification for the commercial batches are acceptable. The attributes, assessments and acceptance specifications included (b) (4) (b) (4) are acceptable. The control of critical steps and intermediates in the manufacture of commercial batches of SD-809 tablets from (b) (4) (b) (4) process and tablet printing are also satisfactory. The sponsor adequately described and validated the analytical procedures.

The individual strengths are differentiated by (b) (4) coat color and imprint as follows:

6 mg: purple tablets with "SD" over "6" printed on one side
9 mg: blue tablets with "SD" over "9" printed on one side
12 mg beige tablets with "SD" over "12" printed on one side

Microbiological quality assessment of the drug product
(b) (4). performed microbial limit testing on the (b) (4) drug product for the registration batches of SD-809 tablets, at release and on stability. Microbial limit testing included total aerobic microbial and total yeasts and molds count. Identification testing included Escherichia coli and Salmonella species. The test results showed that all microbial counts were well below the acceptable limits and all identification tests were negative.

Biopharmaceutics

Jing Li, Ph.D., is the Biopharmaceutical (BP) Reviewer for this application.

There were no Biowaiver requests included in this application. The BCS classifications for the drug substance and drug product are not established.

Dissolution Method and Method Development
The DP is designed to release SD-809 in the acidic pH of the upper gastrointestinal tract. The BP reviewer commented that the acid pH (3.0) of the medium selected for dissolution testing was adequate. The volume of the medium used in testing, and the sponsor's selection of the apparatus were justified. The BP reviewer found the discriminating ability of the dissolution method was adequate for testing variations (b) (4) (b) (4) was not observed to have a large effect on the dissolution profile. The BP reviewer concluded the dissolution method and criteria were acceptable.

(b) (4)

Dissolution Acceptance Criteria

Table 4: Proposed Dissolution Acceptance Criteria for SD-809 Tablets

Time	Acceptance Criteria
1 hour	(b) (4) %
2 hour	%
5 hour	NLT (b) (4) %

Source: Biopharmaceutics Reviewer

The Dissolution Acceptance Criteria proposed by the sponsor were adequate.

Rationale for Absence of Extended Release Claim

Throughout the IND phase of development, the sponsor referred to the product as SD-809 extended release (ER) but the sponsor did not request designation as an extended release tablet in the NDA. The BP reviewer asked the sponsor to submit their rationale (b) (4) (b) (4) (b) (4) The BP reviewer concluded (b) (4) (b) (4) (b) (4) is not sufficient to designate SD-809 as an extended release product.

Bridging of Different Formulations and Scales

The to-be-marketed formulation of SD-809 differed from the Phase 1 formulation (b) (4) (b) (4). The tablet compositions of the registration and commercial batches do not differ. The BP reviewer noted that ordinarily, the (b) (4) is not expected to impact drug release or absorption. The dissolution data provided by the sponsor supported the in vitro similarity of the (b) (4) tablets. The biopharmaceutics reviewer concluded, "The Phase 1 formulation was adequately bridged to the to-be-marketed formulation."

Environmental Assessment

The sponsor requested categorical exclusion "under 21 CFR25.31 (b)…entry into the aquatic environment less than 1ppb) and provided the necessary calculations based on a production scale of (b) (4) to support this claim."

Although the primary reviewer, Dr. McLamore-Hines, concluded the sponsor's "claim for categorical exclusion is acceptable" on secondary review, Dr. Wilson-Lee the Acting Branch Chief, found the sponsor request was inadequate.

Dr. Wilson-Lee commented, "The categorical exclusion is not complete as the applicant did not include the required statement regarding extraordinary circumstances per 21 CFR 25.15(d). After discussion, the primary and secondary reviewers and the Application Technical Lead (ATL) agreed that the following deficiency would be included in the complete response letter:

> "Per 21 CFR 25.15(d), revise your claim for categorical exclusion to include a statement that to the applicant's knowledge, no extraordinary circumstances exist."

Until this issue is resolved, the environmental assessment is INADEQUATE.

Facilities Inspections

Donald C. Obenhuber, Ph.D. completed the Facilities Inspections portion of the OPQ review.

Table 5: Drug Substance Facilities Review/Inspection

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)								

(b) (4)

CDTL Comments:

OPQ recommends a **Complete Response** action for the following reasons:

1. The sponsor requested categorical exclusion under 21 CFR25.31 (b) categorical exclusion is not complete. The applicant did not include the required statement regarding extraordinary circumstances per 21 CFR 25.15(d).

2. The sponsor committed to placing "at least one production batch of the product in the commercial packaging will be placed on long term stability annually". The post approval stability commitment should be updated to include placing the first three

commercial batches of each strength tablet on long term stability through the proposed shelf life and on accelerated stability for 6 months as per ICH Q1A(R2).

3. Teva has recently (5/9/2016) submitted an update to the following sections with respect to (b) (4) content:
   - 3.2.S.4.1 Specification
   - 3.2.S.4.2 Analytical Procedures
   - 3.2.S.4.5 Justification of Specification
   - 2.3.S.4 Control of Drug Substance

An amendment to correct the deficiencies that include a test and acceptance criteria for (b) (4) in the drug substance will not be submitted to the NDA in sufficient time for review in this cycle.

The facilities inspection result for (b) (4), the drug substance testing facility, is still pending at this time. The facility has no prior inspection history.

The NDA resubmission will include updated stability information. OPQ will assign a shelf-life after OPQ considers the updated stability data in the resubmission.

3. Nonclinical Pharmacology/Toxicology

Christopher Toscano, Ph.D., was the primary Nonclinical reviewer for this application. Dr. Lois Freed, Ph.D. provided a Nonclinical Supervisory Memo.

The conclusions of the nonclinical review team are reflect the need for conclusive information regarding the status of the M1 and M4 as major human metabolites. If M1 and/or M4 are shown to be major human metabolite, the bridging nonclinical studies may not provide adequate information to allow the sponsor to rely on the Agency's finding of safety and effectiveness for Xenazine. Dr. Freed concluded, "Without this information, the adequacy of the nonclinical data cannot be determined. The need for additional nonclinical data will depend on the new human mass balance data being collected by the sponsor (cf. Memorandum of Teleconference Minutes, March 23, 2016). This issue should be addressed prior to approval."

Nonclinical Pharmacology Studies Submitted in support of the NDA for SD-809

This 505(b)(2) NDA for SD-809 references the nonclinical information in the Xenazine (the RLD) product label. The sponsor submitted results from a 3-month oral toxicity study and an embryofetal development study in rat, to bridge to the existing nonclinical information for Xenazine, the reference drug.

Dr. Toscano's review included the reports of the following pivotal studies of SD-809 for:

- Pharmacology
- PK/ADME
- Toxicology

- 3-month oral toxicity study of SD-809 and tetrabenazine in rat
- Embryofetal development study of SD-809 and tetrabenazine in rat

- Genetic toxicology
  - Ames, in vitro mammalian clastogenic assay in human peripheral blood lymphocytes, with SD-809 and d_6 α- and β-HTBZ
  - In vivo micronucleus assay in mouse, with SD-809

Primary Pharmacology

As shown in Table 6, deuteration does not substantially change binding affinity of the two active metabolites α-HTBZ and β-HTBZ to VMAT2.

Table 6: Inhibition of VMAT2 Binding by Deuterated and Nondeuterated α-HTBZ and β-HTBZ; Ki and IC50 Values, Study SD-809-NC-008.

	α-HTBZ		β-HTBZ		Reference Compounds	
	Deuterated	Nondeuterated	Deuterated	Nondeuterated	DHTBZ	Reserpine
K_i	3.8 nM	3.1 nM	22 nM	20 nM	0.8 nM	280 nM
IC50	8.2 nM	6.7 nM	47 nM	43 nM	15 nM	598 nM

Section 2.6.3.2; Reference: SD-809-NC-008.
Results are expressed as K_i or IC50 mean of duplicate determinations.
DHTBZ: Dihydrotetrabenazine (α-HTBZ and β-HTBZ)

Source: Teva

As shown in Table 7, deuteration does not cause a significant difference in the off-target receptor binding profile compared to tetrabenazine. The results show no significant differences for the α-HTBZ and β-HTBZ metabolites, for targets with > 50% inhibition, with the exception of β-HTBZ at the opioid receptor.

Secondary Pharmacology

Table 7: Percentage Inhibition of Radioligand Binding to Off-target Receptors by 10 µM of Deuterated and Nondeuterated α-HTBZ-and β-HTBZ, Study SD-809-NC-009

	α-HTBZ		β-HTBZ	
Receptor	Deuterated	Nondeuterated	Deuterated	Nondeuterated
Adrenergic, Alpha 1, non-selective	16	35	77	60
Adrenergic, Alpha 2, non-selective	60	65	88	75
Dopamine, (D1)h	13	11	55	56
Dopamine, (D2s)h	83	81	96	95
Opioid, non-selective	18	-1.1	72	50
Serotonin, non-selective	41	35	63	73
Sigma, non-selective	91	93	100	99

Section 2.6.3.3; Reference SD-809-NC-009.
Results are expressed as % inhibition, mean of duplicate determinations.

Source: Teva

The off-target binding was confirmed in a separate series of in vitro studies for each of the targets listed in the sponsor's Table 7. The IC50 for both deuterated and non-deuterated α-

HTBZ and β-HTBZ are provided in Table 8 below. Deuteration had little impact on off target binding affinity.

Table 8: Inhibition of Radioligand Binding to Off-target Receptors by Deuterated and Nondeuterated α-HTBZ and β-HTBZ; IC50 Values

Receptor	α-HTBZ		β-HTBZ		Positive control ligand
	Deuterated	Nondeuterated	Deuterated	Nondeuterated	
Adrenergic, Alpha 1, non-selective [a]	Not tested	Not tested	8.07 µM	3.32 µM	0.026 µM
Adrenergic, Alpha 2, non-selective [b]	10.6 µM	9.87 µM	3.87 µM	3.24 µM	0.084 µM
Dopamine, (D2s)h [c]	1.72 µM	1.75 µM	0.59 µM	0.90 µM	0.001 µM
Opioid, non-selective [d]	Not tested	Not tested	8.80 µM	13.7 µM	0.002 µM
Serotonin, non-selective [a]	Not tested	Not tested	13.7 µM	14.0 µM	0.036 µM
Sigma, non-selective [c]	1.20 µM	1.84 µM	0.11 µM	0.08 µM	0.005 µM

Results are expressed as IC_{50}, mean of duplicate determinations.
[a] Section 2.6.3.3; Reference SD-809-NC-012. Positive control for Adrenergic, Alpha 1: phentolamine; Positive control for Serotonin: methylsurgide maleate.
[b] Section 2.6.3.3; Reference SD-809-NC-013. Positive control for Adrenergic, Alpha 2: phentolamine.
[c] Section 2.6.3.3; Reference SD-809-NC-010. Positive control for Dopamine and Sigma: haloperidol.
[d] Section 2.6.3.3; Reference SD-809-NC-011. Positive control for opioid: naloxone HCl.

In Vitro Safety Pharmacology Studies

An in vitro assessment of hERG inhibition was performed with 10 µM of the deuterated and non-deuterated forms of α- and β-HTBZ; inhibition < 50% was considered to be below the level of clinical concern. The sponsor did not conduct in vivo cardiovascular safety pharmacology studies of SD-809.

Pharmacokinetic and ADME Studies

PK/ADME studies of SD-809 and tetrabenazine were conducted mouse and rat. In vitro metabolism studies in rat and human liver preparations (S9, microsomes, or hepatocytes). In Sprague-Dawley rat, acute oral dosesSD-809 resulted in up to 2.4- fold higher plasma AUCs for parent and metabolites, d6 α- and β-HTBZ, compared to tetrabenazine and its' metabolites, α- and β-HTBZ, at the same doses. The results of the sponsor's ADME studies are described in Dr. Toscano's review.

The sponsor did not conduct in vivo metabolism studies in animals. The sponsor stated, "None are planned, as human exposure to the metabolites of listed tetrabenazine will be used to qualify the SD-809 metabolites" (Pharmacokinetics Written Summary, pg. 8 of 25).

Impurities/Degradants of Concern

With the exception of (b) (4), the proposed specification for each individual impurity is less than the qualification threshold of 0.15%. There is no concern regarding the mutagenic potential of (b) (4). However, two of the impurities in the drug substance are carried over to the drug product, (b) (4). Dr. Toscano concluded, "Based on the MRHD of 48 mg/day, the qualification threshold for drug product impurities, according to ICH Q3B(R2), is 0.5% or 200 µg total daily intake, whichever is

lower. The proposed drug product specification for (b) (4) is NMT (b) (4)%; therefore, this specification is acceptable."

The sponsor has proposed a drug product specification of NMT (b) (4)% for the (b) (4) (b) (4) To support this drug product specification, the sponsor refers to the results of the 90-day study conducted in rat (SD- 809-NC-025), the mouse micronucleus study (SD-809-NC-044), the bacterial reverse mutation assay conducted with (b) (4) (SD-809-NC-056), and the in vitro chromosomal aberration study conducted with (b) (4) (SD-809-NC-057). Dr. Toscano concluded, "Based on the information provided in the sponsor's table below, (b) (4) was present at sufficient levels in the 90-day rat study, and in the micronucleus study to be considered qualified at (b) (4)% of the drug product."

Toxicology Studies

Single Dose Toxicology Study in Rat Study SD-809-NC-004
This was an exploratory toxicity and toxicokinetic study of tetrabenazine and d6-tetrabenazine (SD-809). Animals (5 groups, 6/sex) in the study received a single oral (gavage) dose of 2.5 mg/kg or 15 mg/kg of tetrabenazine, SD-809 or placebo. According to the protocol, the animals were euthanized 14 days after dosing. SD-809 was associated with increased the circulating levels of α- and β-HTBZ but the study did not assess levels of other known metabolites (including the known human metabolites M1 and M4). The 2.5 mg/kg dose was identified as the NOAEL of 2.5 mg/kg tetrabenazine or SD-809 for SD0809 and tetrabenazine based on lethargy observed in the high dose animals (males and females).

14 Day Repeat Dose Toxicity Study SD-809-NC-006
This was a 14-day, comparative dose range-finding and toxicokinetic study of SD-809 (d6-tetrabenazine) in male Sprague-Dawley rats (Toxicology: 5 /group; Toxicokinetic: 6 /group). Animals received 0, 15, 30, 50 mg/kg/day divided BID, or SD-809; or 50 mg/kg/day (divided BID) of tetrabenazine, both administered by oral gavage. All of the animals in all SD-809 dose groups and in the tetrabenazine group survived to the scheduled terminal sacrifice.

Clinical observations included intermittent tremor and flattened body in all SD-809 groups and in the tetrabenazine group. WBCs were reduced by approximately 20% for all of the SD-809 dose groups and for animals in the tetrabenazine (50 mg/kg/day) group. Platelets were reduced 18% and 16% in the low and mid-dose SD-809 groups with a 28% reduction in platelets observed in the 50 mg/kg/day SD-809 group. Platelets were reduced by 37% in the tetrabenazine 50 mg/kg/day group.

Dr. Toscano notes that liver enzymes were elevated in rats dosed with SD-809 or tetrabenazine. ALT was increased in the mid-dose (21%) and high dose (46%) SD-809 animals, and it was increased by 27% in the tetrabenazine group, relative to control. AST was increased in mid-dose (36%) and high dose (57%) SD-809 animals and by 31% in the tetrabenazine group compared to control animals. However, there were no test article related findings on necropsy.

Dr. Toscano reported the key findings in this study as:

- "The NOAEL was < 7.5 mg/kg BID (15 mg/kg/day) SD-809. Clinical signs (tremors, flattened body, and palpebral closure), decreased BW, and decreased WBC parameters occurred at all doses of SD-809 or tetrabenazine."
- "Exposure to the alpha and beta metabolites was higher in rats dosed with the deuterated tetrabenazine, relative to the non-deuterated form."

A 14-Day Twice-Daily Oral Gavage Toxicity and Toxicokinetic Study of an Impurity (b) (4) of SD-809 in Sprague Dawley Rats (Study SD-809-NC-076)

Three groups of animals (20 per group, 10 per sex) received vehicle, SD-809 alone or 5% (b) (4) (b) (4) for 14 days, dosed b.i.d.

Table 9: Study SD-809-NC-076 Design

Toxicology Groups ((b) (4)-847043M, (b) (4)-847043F)

Group Number	Treatment	Dosage Level (mg/kg/day)[a]	Dosage Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals Males	Number of Animals Females
1	Vehicle	0	0	5	10	10
2	95% SD-809/(b) (4)	9.5 SD-809, (b) (4)	4.75 SD-809, (b) (4)	5	10	10
3	SD-809	10	5	5	10	10

[a] = The total daily dosages were split into 2 equally divided sub-doses, with each dose administered approximately 6 hours apart.

Toxicokinetic Groups ((b) (4)-847043A, (b) (4)-847043B)

Group Number	Treatment	Dosage Level (mg/kg/day)[b]	Dosage Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals Males	Number of Animals Females
1A	Vehicle	0	0	5	3	3
2A	95% SD-809/(b) (4)	9.5 SD-809, (b) (4)	4.75 SD-809, (b) (4)	5	9	9
3A	SD-809	10	5	5	9	9

[b] = The total daily dosages were split into 2 equally divided sub-doses, with each dose administered approximately 6 hours apart, except on blood sample collection day 0, when the doses were given 12 hours apart.

Source: Teva

A single female animal in the 95% 809 and (b) (4) toxicokinetic group was found dead on day 12. The death did not appear to be related to the test article. All of the remaining animals in the toxicokinetic group survived until scheduled necropsy. All toxicology animals survived to the scheduled necropsy. There were no test article-related clinical signs in any of the dose groups.

Dr. Toscano commented that Inclusion of 95% SD-809 and (b) (4) did not result in unique adverse effects in male or female rats, relative to SD-809 alone.

A 3-Month (Twice-Daily) Oral Gavage Toxicity and Toxicokinetic Study of Deuterated Tetrabenazine in Sprague Dawley Rats Study SD-809-NC-025

This study is the pivotal toxicology bridging study.

Table 10: Design and Dosing Plan for Study SD-809-NC-025

Toxicology Groups ((b) (4)-847005M and (b) (4)-847005F)

Group Number	Treatment [a]	Dosage Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals [b] Males	Females
1	Vehicle	0	5	25	25
2	Low-Dose SD-809	2.5	5	25	25
3	Mid-Dose SD-809	5	5	25	25
4	High-Dose SD-809	15	5	25	25
5	High-Dose Comparator Tetrabenazine	15	5	25	25

[a] = The doses were administered twice daily approximately 8 hours apart, except on study days 3, 36, and 37 when the doses were administered 12 hours apart ± 1 hour.

[b] = 10 animals/sex/group were euthanized at the interim necropsy following a minimum of 28 consecutive days of dose administration; the remaining 15 animals/sex/group were euthanized at the primary necropsy following a minimum of 91 consecutive days of dose administration.

Toxicokinetic Groups ((b) (4)-847005A and (b) (4)-847005B)

Group Number	Treatment [a]	Dosage Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals [b] Males	Females
1A	Vehicle	0	5	4	4
2A	Low-Dose SD-809	2.5	5	10	10
3A	Mid-Dose SD-809	5	5	10	10
4A	High-Dose SD-809	15	5	10	10
5A	High-Dose Comparator Tetrabenazine	15	5	10	10

[a] = The doses were administered twice daily approximately 8 hours apart, except on study days 0, 33, 34, 90, and 91 when the doses were administered 12 hours apart ± 1 hour due to blood collection.

[b] = All animals were euthanized following 92 consecutive days of dose administration after the final blood collection.

Eight to 10 animals per group were dose with 2.5mg/kg/dose, 5 mg/kg/dose, 15 mg/kg/dose of SD-809 or 15 mg/kg/dose tetrabenazine, BID for 28 or 91-92 days.

One male animal in the control group of the toxicokinetic group was found dead on day 71 without obvious cause.

Toxicology Groups

Clinical observational that were observed during study week 12 found ear twitching increased in a dose-dependent manner in all males in the SD-809 and tetrabenazine dose groups as well

as in a mid-dose female, high dose female, and tetrabenazine females. Intermittent tremors were increased in a dose-dependent manner in mid-dose male, high dose male and tetrabenazine male. Rotarod performance was markedly decreases in the high dose (2.7 s) SD-809 and in the tetrabenazine (10.8s) animals, relative to controls (18.5 s). Catalepsy was increased in the SD-809 mid-dose (2.5 s), high dose (10.6 s) animals and in the tetrabenazine (21.8 s) animals, relative to controls. Handling-induced convulsions occurred in 1 high dose male and 1 tetrabenazine male.

Interim necropsies performed on10 animals/sex/group during study week 4 included selected organs weights; selected tissues were examined microscopically from the control animals, 15 mg/kg/dose SD-809-treated, and 15 mg/kg/dose comparator tetrabenazine treated groups. Primary necropsies performed on 15 animals/sex/group during study week 13; that included selected organs weights; selected tissues were examined microscopically from the control animals, animals given 15 mg/kg/dose SD-809, and animals given 15 mg/kg/dose of tetrabenazine.

Toxicokinetic Groups
Blood samples for toxicokinetic analysis was collected from Group 1A (vehicle) at approximately 1 hour following first daily dose administration and from Groups 2A-4A (SD-809) and 5A (tetrabenazine 15 mg/kg) at approximately 0.5, 1, 3, 6, and 12 hours following administration of the first daily dose on study days 0, 34 (study week 4), and 91 (study week 13). Gross necropsy was performed on the male animal in the control group was found dead to determine the cause of death. All surviving animals euthanized and discarded (study day 92).

Toxicokinetic Findings
Steady state exposures to the alpha and beta dihydro metabolites of tetrabenazine were similar at the end of the study in rats dosed with the high dose of 15 mg/kg SD-809 or 15 mg/kg. Systemic exposure to the alpha metabolite was markedly higher in males, relative to females in rats dosed with SD-809 or tetrabenazine.

Toxicology Findings
There were no noteworthy SD-809- or tetrabenazine -related findings on necropsies conducted at week 4 or 13.

Mammary gland hyperplasia was observed in females in the SD-809 dose groups at both the 4-week interim and 13-week terminal sacrifices. Estrous cycle arrest occurred in females dosed with SD-809 or tetrabenazine and there were no test article-related findings in males.

Dr. Toscano's Conclusions:

- "The NOAEL was < 2.5 mg/kg BID based on estrus cycle arrest in females and decreased body weights in males."
- "There were no test article-related findings that were unique to SD-809."
- "Exposure to the alpha and beta metabolites of tetrabenazine was similar in rats dosed with SD-809 or tetrabenazine. Exposure to the alpha metabolite was markedly higher in male rats, relative to females."

Conclusions

The "finding allows the sponsor to bridge to the existing nonclinical safety information for the RLD regarding the primary metabolites of tetrabenazine, α- and β-HTBZ. However, it is important to note that there was no quantitation at steady state of other metabolites of SD-809 or tetrabenazine in the 3-month study conducted in rat."

Genetic Toxicology

Table 11: Summary of Genotoxicity Study Results

Test	Study	Compound	Result
In vitro Microsome Reverse Mutation S. typhimurium and E. coli	SD-809-NC-028	SD-946 (α-dihydrotetrabenazine);	negative for mutagenicity
	SD-809-NC-030	SD-947(β-dihydrotetrabenazine)	negative for mutagenicity
	SD-809-NC-032	SD-948(d6-α-dihydrotetrabenazine)	negative for mutagenicity
	SD-809-NC-034	SD-949 (d6-β-dihydrotetrabenazine),	negative for mutagenicity
	SD-809-NC-056	SD-809 spiked with (b) (4) (impurity),	negative for mutagenicity
	SD-809-NC-066	SD-1021(Metabolite M1),	negative for mutagenicity
	SD-809-NC-058	(b) (4) (impurity)	negative for mutagenicity
In vitro Chromosome Aberration Test in Human Peripheral Blood Lymphocytes.	SD-809-NC-029	SD-946 (α-dihydrotetrabenazine)	did not cause chromosomal aberrations
	SD-809-NC-031	SD-947 (β-dihydrotetrabenazine)	did not cause chromosomal aberrations
	SD-809-NC-033	SD-948 (d6-α-dihydrotetrabenazine)	did not cause chromosomal aberrations
	SD-809-NC-035	SD-949 (d6-β-dihydrotetrabenazine)	did not cause chromosomal aberrations
	SD-809-NC-057	SD-809 and (b) (4) (Impurity/Degredant)	did not cause chromosomal aberrations
	SD-809-NC-067	SD-1021 (metabolite M1)	did not cause chromosomal aberrations

	SD-809-NC-059	(b) (4) (impurity)	(b) (4) was negative for clastogenicity in the absence of human liver S9 fraction. When incubated with human liver S9 fraction for 3 hours or at 22 hours in the absence of S9 fraction (b) (4) markedly increased the number of cells with chromosomal aberrations or polyploidy, at a cytotoxic concentration (> 50% suppression of growth
In vivo micronucleus Mouse Bone Marrow	SD-809-NC-044	SD-808 (tetrabenazine) with SD-809 (d6-tetrabenazine)	SD-808 and SD-809 did not increase the number of micronucleated polychromatic erythrocytes in the bone marrow

(SD-809)=d6-TBZ=deuterated tetrabenazine
SD-808 (tetrabenazine)=Non-deuterated tetrabenazine
Source: CDTL information adapted from the Primary Nonclinical Review

The sponsor conducted in vitro bacterial reverse mutation studies and in vitro chromosomal aberration for the primary metabolites of SD-809(d6-α-HTBZ and d6-β-HTBZ) and tetrabenazine, α-HTBZ and β-HTBZ) summarized in Table 11. Dr. Toscano concurred with the sponsor's conclusion that none of the test articles was positive for mutagenicity or clastogenicity.

SD-809 and tetrabenazine were assessed in an in vivo micronucleus assay conducted in mouse, the same species used to conduct the micronucleus assay for the RLD. Dr. Toscano comments that both SD-809 and tetrabenazine were negative in the in vivo micronucleus assay (see table 11).

Dr. Toscano reviewed studies of the M1 metabolite that included an in silico evaluation, an in vitro reverse mutation (Study SD-809-NC-066) and chromosomal aberration (Study SD-809-NC-067) studies for genotoxic potential. Derek Nexus version 4.0.5 and the CASE Ultra system (Version 1.5.0.0) representing an Ames Salmonella dataset. The in silico analyses

predicted that M1 will be negative for mutagenicity and the in vitro studies were negative for mutagenicity or clastogenicity.

The sponsor's genotoxicity studies included two impurities:

- (b) (4)
-

The sponsor conducted in vitro bacterial reverse mutation studies and in vitro chromosomal aberration for (b) (4) and SD-809 spiked with (b) (4) was negative for mutagenicity (Study SD-809-NC-056) and clastogenicity (Study SD-809-NC-057). (b) (4) was (b) (4) was negative for clastogenicity in the absence of human liver S9 fraction. However, there was a marked increase the number of cells with chromosomal aberrations or polyploidy, at a cytotoxic concentration (> 50% suppression of growth), when incubated with human liver S9 fraction for 3 hours or at 22 hours in the absence of S9 fraction. Dr. Toscano explained (in conversation) these results show that (b) (4) was explored adequately to a concentration causing cytotoxicity/growth suppression but the results do not indicate there is a signal for clastogenicity associated with (b) (4).

Embryofetal Development Study

A Twice-Daily Oral (Gavage) Study of the Effects of Deuterated Tetrabenazine on Embryo/Fetal Development in Rats.

SD-809 was studies in doses of 5, 10, 30 mg/kg/day b.i.d. and SD-808 (nondeuterated tetrabenazine) in the same study in a dose of 30 mg/kg/day administered by oral gavage b.i.d. All animals (25 females/group; TK: 6 females/group) survived until planned sacrifice.

Dr. Toscano noted there were no test article-related external or visceral malformations or variations. There were no test article-related skeletal malformations. However, a 7th cervical rib (a variation) occurred in a dose-related manner in SD-809 dose groups (1, 2, 3, 5; control, low dose, mid-dose, high dose groups of SD-809, respectively); two fetuses in the SD-808 group had a 7th cervical rib. A seventh cervical rib was only observed in one animal in each litter where the malformation was present.

SD-809 and Tetrabenazine Metabolites

Exposure to SD-809 and its deuterated primary metabolites, α- and β-dihydrotetrabenazine, was higher (40-70%) in pregnant rats, a similar finding was not observed in pregnant rats at the high dose of 30 mg/kg/day of tetrabenazine. However, this finding was not observed in the 3-month study conducted with non-pregnant female rats, at drug levels that were approximately 6 times the MRHD for SD-809 based on body surface area. The sponsor did not assess the steady state area under the curve (AUC) for M1 or M4 in the pivotal 3-month study or in this embryofetal development study conducted in rat. Dr. Toscano notes that "if

the Clinical Pharmacology review team finds that the currently available human data on SD-809-related metabolites are inadequate, then, due to the lack of nonclinical data on circulating metabolites, it will not be possible to make a determination if the sponsor has successfully bridged to the nonclinical data available for the RLD, or M1 or M4 in the pivotal 3-month study or embryofetal development study conducted in rat."

Dr. Toscano noted, the dose-dependent increase in the incidence of 7th cervical rib at all doses of SD-809 in the pivotal study, also occurred in animals dosed with tetrabenazine but this skeletal variation is not mentioned in the Xenazine label. The lowest dose at which this finding occurred was 5 mg/kg/day (30 mg/m2/day), which is equal to the MRHD based on body surface area. Overall, there were no developmental effects that were unique to SD-809 compared to tetrabenazine.

Estrus cycle disruption occurred in rats dosed with SD-809 in the 3-month repeat dose study; however, a NOEL was not established in this study. The Xenazine label describes this effect occurring in female rats at doses of tetrabenazine greater than 5 mg/kg but the lowest dose of SD-809 tested in the 3-month study was 5 mg/kg/day (30 mg/m2). Dr. Toscano concluded that although, estrus cycle disruption is not unique to SD-809, it appears to occur at lower doses compared to tetrabenazine.

Key Study Findings

- "The maternal NOAEL was 10 mg/kg/day SD-809. BW gain was affected at higher doses."
- "The developmental NOAEL was < 5 mg/kg/day SD-809 based on a dose dependent increase in the incidence of 7th cervical rib. This finding was not unique to SD-809, as it also occurred with tetrabenazine."
- "Exposure to tetrabenazine and its related alpha and beta metabolites was higher in rats dosed with 30 mg/kg/day of SD-809, relative to animals dosed with 30 mg/kg/day of the non-deuterated form (SD-808)."

CDTL Comment:

The submitted nonclinical information does not indicate there is a unique toxicological concern observed with SD-809 compared to tetrabenazine. However, the clinical pharmacology data are inconclusive in determining if M1 and M4 are major human metabolites.

In her Supervisory Memo, Dr. Freed concludes, "Without an adequate understanding of the in vivo metabolic profile in humans, it is not possible to determine if all major circulating metabolites have been adequately evaluated in the appropriate nonclinical studies."

The status of M1 and M4 remain uncertain largely because the levels of M1 and M4 derived from SD-809 have not been adequately assessed in humans, relative to the levels derived from tetrabenazine. M4 was shown to be a major human metabolite in the RLD but M4 was identified after the approval of Xenazine and the information is not yet described in the Xenazine label; therefore Teva cannot reference it in this 505(b)(2) application. Using only semi-quantitative methods, the sponsor describes the amount of M4 derived from SD-809

relative to the amount of M4 derived from tetrabenazine. The levels of M1 and M4 in humans need to be assessed using validated quantitative methods.

If M1 or M4 is subsequently determined to be a major human metabolite for SD-809, the sponsor's nonclinical bridging studies may be inadequate. Dr. Toscano states in his review "an assessment at steady state (AUC) is the appropriate measure and this was not provided for M1 or M4 in the pivotal 3-month study or embryofetal development study conducted in rat."

4. Clinical Pharmacology

The α-HTBZ and β-HTBZ metabolites of SD-809 and tetrabenazine are potent inhibitors of VMAT2 in the central nervous system. They deplete presynaptic monoamines, including dopamine, which reduces chorea in patients with HD. The parent compounds SD-809 and tetrabenazine are rapidly and extensively metabolized to α-HTBZ and β-HTBZ.

Table 12: Summary of SD-809 Clinical Pharmacology Studies

Study Number	Design	Subject Population	Subject Characteristics	Treatment	Number of subjects exposed to SD-809	Study Status
Phase 1 Studies with SD-809 Unformulated Powder-in-Capsule and Tetrabenazine Unformulated Powder-in-Capsule[a]						
AUS-SD-809-CTP-06	Randomized, double-blind, single-dose, 2-way crossover study of the PK, safety, and tolerability of SD-809 and tetrabenazine	Healthy adult volunteers	Age range 18-39 years 48% male	SD-809 25 mg (single dose) Tetrabenazine 25 mg (single dose)	21 subjects	Complete
SD-809-C-12	Open-label, sequential-group study to evaluate mass balance recovery, metabolite profile, and metabolite identification of SD-809 and tetrabenazine	Healthy adult volunteers	Age range 37-62 years 100% male	Cohort 1: [^{14}C]-SD-809 25 mg (single dose) Cohort 2: [^{14}C]-tetrabenazine 25 mg (single dose)	6 subjects (+6 subjects exposed to tetrabenazine only)	Complete
Phase 1 Studies with SD-809 Tablets and Tetrabenazine Commercially Available Tablets						
AUS-SD-809-CTP-07 Part 2	Open-label, sequential-group, single and multiple ascending dose study of the PK, safety, and tolerability of SD-809 and tetrabenazine	Healthy adult volunteers	Age range 18-42 years 71% male	SD-809 7.5 mg, 15 mg, and/or 22.5 mg (single dose; repeated doses) Tetrabenazine[b] 25 mg (single dose; repeated doses)	24 subjects	Complete
SD-809-C-21	Randomized, double-blind, placebo- and positive-controlled, 6-period crossover study to evaluate the effects of SD-809 and tetrabenazine on cardiac repolarization	Healthy adult volunteers	Age range 18-49 years 75% male	SD-809 12 or 24 mg Tetrabenazine[c] 25 mg Moxifloxacin 400 mg Placebo equivalents	46 subjects	Complete

Study Number	Design	Subject Population	Subject Characteristics	Treatment	Number of subjects exposed to SD-809	Study Status
Phase 1 Drug-Drug Interaction Study with SD-809 Tablets and Paroxetine						
SD-809-C-08	Open-label, drug-drug interaction (DDI) study of single doses of SD-809 and repeated doses of paroxetine in CYP2D6 Extensive Metabolizers and Intermediate Metabolizers	Healthy adult volunteers	Age range 19-49 years 67% male	SD-809 22.5 mg (single dose on Day 1 and Day 11) Paroxetine 20 mg on Days 4 through 12	24 subjects	Complete
Phase 3 Studies with SD-809 Tablets						
SD-809-C-15 (First-HD)	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of SD-809 in subjects with chorea associated with HD	Adult subjects with manifest HD and chorea	Age range 23-74 years 56% male	SD-809 or placebo 6 mg/day to 48 mg per day, administered BID, titrated based on chorea control and tolerability	45 subjects	Complete
SD-809-C-16 (ARC-HD), ARC-Rollover	Open-label, single-arm, long-term safety study of SD-809	Adult subjects with HD and chorea who completed First-HD	Age range 23-75 years 57% male	SD-809 6 mg/day to 72 mg/day, administered BID, titrated based on chorea control and tolerability	75 subjects[d]	Ongoing

Study Number	Design	Subject Population	Subject Characteristics	Treatment	Number of subjects exposed to SD-809	Study Status
Phase 3 Study with SD-809 Tablets and Commercially Available Xenazine Tablets						
SD-809-C-16 (ARC-HD), ARC-Switch	Open-label, single-arm, long-term safety study of SD-809	Adult subjects with HD and chorea currently receiving Xenazine	Age range 32-75 years 60% male	SD-809 starting regimen based on algorithm for achieving AUC of total (α+β)-HTBZ comparable to that of Xenazine; titrated after one week based on chorea control and tolerability to maximum of 72 mg/day	37 subjects[e]	Ongoing

Abbreviations: DDI, drug-drug interaction; HD, Huntington's disease; HTBZ, dihydrotetrabenazine; PK, pharmacokinetic.
Notes: Two additional studies, AUS-SD-809-CTP-07 Part 2 and SD-809-C-11, are presented in the Summary of Biopharmaceutic Studies and Associated Analytical Methods (Section 2.7.1).
[a] Tetrabenazine comparator used in studies AUS-SD-809-CTP-06 and SD-809-C-12 was synthesized by Auspex and delivered as unformulated powder-in-capsule.
[b] Commercially available tetrabenazine tablets sourced in Australia.
[c] Commercially available tetrabenazine tablets sourced in Northern Ireland.
[d] A total of 40 subjects who received SD-809 in Study SD-809-C-15 also received SD-809 in Study SD-809-C-16; these subjects are counted only once in the total number of subjects exposed
[e] Subjects in the United States (n=36) received prescribed Xenazine (US-sourced) prior to switch to SD-809. The 1 subject recruited ex-US received Australia-sourced tetrabenazine.

Source :Teva

Absorption

Approximately 80% of SD-809 (75%-87%) is absorbed following oral dosing. SD-809 and tetrabenazine are metabolized so rapidly that SD-809 and tetrabenazine are no longer detectable within 3 hours of oral administration.

Food increases the Cmax of the deuterated α-HTBZ and β-HTBZ metabolites by as much as 50% but the AUC is not effected (Table 13). The sponsor administered SD-809 with food in their clinical studies and they have proposed taking SD-809 with food in the product label.

Table 13: Food Effect on The Single Dose Pharmacokinetic Parameters of α-HTBZ and β-HTBZ Metabolites in Fed and Fasting Conditions

		Total-(α+β)-HTBZ Single-Dose Data					
Study	Dose/Formulation/ Conditions	C_{max} (ng/mL)	t_{max} (h)	T_{lag} (h)	AUC_t (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{½}$ (h)
AUS-SD-809-CTP-06 (N=19)	25mg SD/PIC/Fasted	74.6 (37)	1.50 (0.67-2.00)	na	530 (54)	542 (54)	8.62 (38.2)
AUS-SD-809-CTP-07 Part 1 (N=24)	15mg SD/A/High Fat	33.3 (33)	6.00 (1.50-8.00)	0.50 (0.00-3.00)	296 (48)	305 (46)	6.99 (23)
	15mg SD/A/Fasted	22.5 (36)	2.25 (1.00-8.00)	0.00 (0.00-1.00)	263 (45)	273 (45)	9.35 (25)
	15mg SD/B/High Fat	28.7 (39)	6.00 (2.50-12.00)	0.51 (0.00-3.00)	306 (47)	315 (46)	7.02 (20)
	15mg SD/B/Fasted	14.5 (42)	4.00 (1.00-12.00)	0.00 (0.00-1.00)	243 (49)	259 (47) (N=23)	9.95 (16) (N=23)
AUS-SD-809-CTP-07 Part 2 (N=12)	7.5mg SD/Tablet/Std Meal	21.4 (32)	3.00 (2.50-5.00)	1.00 (0.00-2.50)	167 (41)	176 (39)	7.18 (19)
	15mg SD/Tablet/ Std Meal	45.3 (18)	3.26 (2.50-4.00)	1.00 (0.00-1.05)	396 (35)	408 (36)	7.66 (18)
	22.5mg SD/Tablet/ Std Meal	67.5 (25)	3.75 (3.00-5.02)	0.00 (0.00-1.00)	599 (48)	610 (48)	8.38 (26)

Source:Teva

Distribution

The sponsor references the information for Distribution from the Xenazine label:

"Results of PET-scan studies in humans show that radioactivity is rapidly distributed to the brain following intravenous injection of ^{11}C-labeled tetrabenazine or α-HTBZ, with the highest binding in the striatum and lowest binding in the cortex.

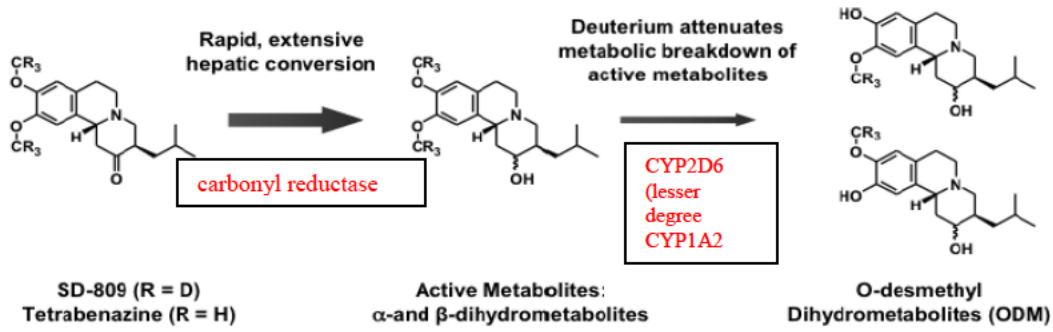
The in vitro protein binding of tetrabenazine, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%, and β-HTBZ binding ranged from 59% to 63%."

Metabolism

Deuteration does not change the metabolic pathway of SD-809, and from the information provided by the sponsor, it appears to be the same tetrabenazine. Parent SD-809 and tetrabenazine are rapidly metabolized by carbonyl reductase (Figure1) to the dihydro metabolites, alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ).

The α-HTBZ and β-HTBZ metabolites are active and both are potent inhibitors of VMAT2, which is believed to be responsible for the anti-choreic effect of tetrabenazine and SD-809. The α-HTBZ and β-HTBZ metabolites are O-dealkylated by CYP450 enzymes, mostly by CYP2D6 (with minor contribution of CYP1A2), to form 9- and 10-desmethyl-α- and β-DHTBZ. 9- and 10-desmethyl-α- and β-DHTBZ are metabolized further to sulfate or glucuronide conjugates.

Figure 1: Summary of Initial Metabolism of SD-809 and Tetrabenazine



Note: The active metabolites (α- and β-dihydrotetrabenazine) are also referred to as α-HTBZ and β-HTBZ in this summary.

Source: modified Teva figure

Systemic exposure (AUC) to total (α+β)-HTBZ following SD-809 administration is approximately 2-fold greater than following tetrabenazine administration (Table 14).

Table 14: Pharmacokinetic Parameters for SD-809, Tetrabenazine, and Their Dihydro Metabolites Following a Single-Dose of SD-809 25 mg or Tetrabenazine 25 mg (Study AUS-SD-809-CTP-06)

Analyte	Parent Drug		Total (α+β)-HTBZ		α-HTBZ		β-HTBZ	
Parameter	SD-809	Tetrabenazine	SD-809	Tetrabenazine	SD-809	Tetrabenazine	SD-809	Tetrabenazine
C_{max} (ng/mL)	0.327 (85.3)	0.314 (111.0)	74.6 (37.1)	61.6 (38.2)	46.1 (30.4)	41.2 (36.0)	29.6 (49.4)	20.5 (51.5)
t_{max} (h)	0.67 (0.33-1.50) n=18	0.67 (0.33-2.00) n=15	1.50 (0.67-2.00)	1.00 (0.67-2.50)	1.5 (0.67-2.52)	1.00 (0.67-2.00)	1.50 (0.67-2.50)	1.00 (0.67-2.50)
AUC_{inf} (ng•h/mL)	0.30 (101.9)[b]	0.26 (168.2)[b]	542 (53.8)	261 (69.6)	373 (39.3)	189 (59.2)	171 (94.0)	74.0 (99.5)
$t_{½}$ (h)	NC	NC	8.62 (38.2)	4.82 (50.8)	8.97 (34.7)	5.47 (51.4)	5.00 (79.7)	2.95 (57.2)

Source: TEVA

The results of Study AUS-SD-809-CTP-07, Part 2 show, the PK parameters of the dihydro metabolites (HTBZ) were linear and dose-proportional over a 3-fold dose range (7.5 mg to 22.5 mg). Following administration of single doses of SD-809, mean AUCinf and mean Cmax for the individual and total (α+β)-HTBZ increased in a dose-proportional manner as well. Dr. Dimova concurred with the sponsor that the pharmacokinetics of total (α+β)-HTBZ are linear and proportional to SD-809 dose following single doses of 6 mg to 24 mg and after repeated doses of 7.5 mg to 22.5 mg twice daily (BID).

The rate at which CYP2D6 forms the O-desmethyl (ODM) metabolites of SD-809 is lower relative to the rate at which the ODM metabolites of tetrabenazine are formed. This change results in longer circulating half-lives for deuterated α-HTBZ and β-HTBZ relative to the nondeuterated metabolites. As Dr. Dimova notes, this also results in higher plasma levels (approximately 2X higher) of α-HTBZ and β-HTBZ with SD-809 compared to non-deuterated tetrabenazine.

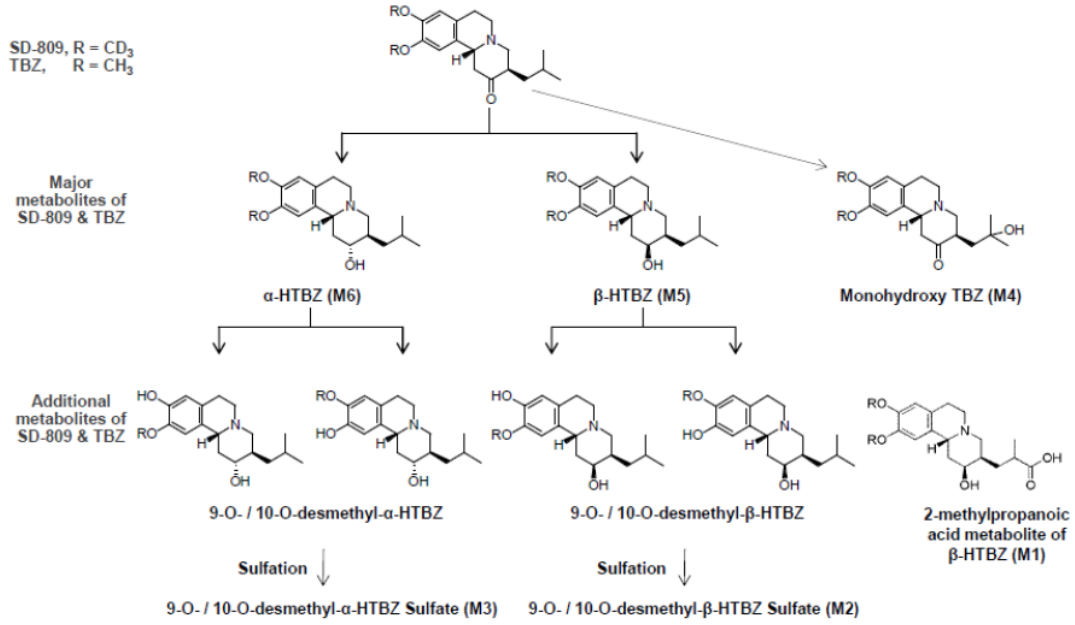
Major Human Metabolites (MHM)

Mass Balance Recovery and Metabolite Profiles for SD-809 and Tetrabenazine (Study SD-809-C-12)

The sponsor conducted a single dose Mass Balance Recovery and Metabolite Profiling and Identification Study (SD-809-C-12). Twelve healthy male subjects (women were excluded) received [^{14}C]-SD-809 25 mg (6 per group or [^{14}C]-tetrabenazine 25 mg. Plasma, stool and urine were collected. Recovery of total radioactivity was similar following administration of [^{14}C]-SD-809 (mean 92.2% of the dose) and [^{14}C]-tetrabenazine (mean 91.4% of the dose).

The study results also confirmed that SD-809 was eliminated mainly by the kidneys with the majority of the radioactivity found in the urine (SD-809 mean 82.9%; tetrabenazine mean 80.4%) recovered within 48 hours following dosing.

Figure 2: Metabolic Pathway of SD-809 and Tetrabenazine in Humans



SD-809: Deutetrabenazine
TBZ: Tetrabenazine
HTBZ: Dihydro metabolite of SD-809 or of tetrabenazine
R = CH_3 for tetrabenazine and metabolites
R = CD_3 for SD-809 and metabolites
M = Metabolite M1 through M6 assigned in clinical Study SD-809-C-12 based on Xenazine label and / or prevalence in Study SD-809-C-12

Twenty-two metabolites of SD-809 were among the 24 metabolites of tetrabenazine. Six metabolites M1-M6 in SD-809 and Tetrabenazine were chosen for evaluation because they "were determined to represent > 10% of radioactivity from either one or both treatments (SD-809 or tetrabenazine)." A metabolite is major if it is at least 10% of the parent molecule. Because SD-809 and tetrabenazine are rapidly metabolized, α-HTBZ plus β-HTBZ is considered to be the parent for the determination of major metabolites. Both M1 and M4 exceed the 10% of the total plasma sample radioactivity in this Mass Balance study. M1 is the

2-methylpropanoic acid metabolite of d6-β-HTBZ and M4 is monohydroxy tetrabenazine also a metabolite of d6-β-HTBZ.

Dr. Dimova noted the sponsor considered M1 and M4 to be major metabolites when they initially presented the results of Mass Balance Study (SD-809-C-12) during the End of Phase 2 (EOP2) meeting.

In EOP2 Meeting Package the sponsor states, "Based on the results of the mass balance study, M1 is a major human metabolite of SD-809 accounting for 12.7% of radioactivity (Table 15) in the pooled plasma samples and is present in similar percentage amounts to the active metabolites α-HTBZ (15.9%) and β-HTBZ (13.3%). For tetrabenazine, M1 accounts for a lower percentage of radioactivity (4.0%) but is still present in the same percentage amounts as the active metabolites α-HTBZ (5.0%) and β-HTBZ (2.2%)."

Table 15: Mass Balance Study (SD-809-C-12) Listing Metabolites of SD-809 Exceeding 10% of Total Plasma Radioactivity After 25 mg 14C Radiolabeled SD-809 or Tetrabenazine

Table 2.7- 24: Comparison of metabolites exceeding 10% of total plasma sample radioactivity following oral administration of either [^{14}C]-SD 809 or [^{14}C]-tetrabenazine

Metabolite Number	Nominal Retention time (min.)		Identification	Percentage of sample radioactivity	
	SD-809	TBZ		SD-809	TBZ
M1	20.7	21.0	Acid Metabolite of HTBZ	12.7	4.0
M2	39.3	38.8	Sulphate of O-desmethyl HTBZ	4.9	18.7
M3	48.6	48.6	Sulphate of O-desmethyl HTBZ	4.5	15.4
M4	59.7	60.2	+ 16 amu Metabolite	19.9	11.7
M5	61.7	62.5	β-HTBZ	13.3	2.2
M6	73.8	74.3	α-HTBZ	15.9	5.0
Reference: SD-809-C-12 TBZ: Tetrabenazine					

Source:Teva

However, during the EOP2 meeting (on 12/5/2012), the sponsor reversed their opinion on M1 being a MHM. "Auspex notes that data provided in the meeting package were preliminary derived from a single pooled sample per cohort. Auspex can now present data from the individual subjects based on time-proportional pooling ('updated results') that are provided (Table 16)." These data demonstrate that M1 is not present as a major metabolite of SD-809. These results show that M1 for SD-809 is approximately 2-fold higher than observed for tetrabenazine. Given this Auspex believes there is no safety risk given that SD-809 is given at approximately half the dose of tetrabenazine. Auspex therefore believes that no further justification for M1 exposure needs to be demonstrated."

In the same EOP2 Meeting Package, the sponsor provided justification for the higher M1 and M4 levels detected in the Mass Balance Study, " the actual exposure to patients will not

significantly increase given that the dose of SD-809 is less than half that of tetrabenazine" (i.e., the maximum dose of SD-809 would be 48 mg daily). However, at the 120-Day Update in the open label clinical trial SD-809-C-16, patients were allowed to increase the total daily dose up to 72 mg/day, as need to treat their chorea. Twenty-eight of 119 patients took more than 48 mg daily of SD-809 to control their chorea, and 12 patients had taken 72 mg/day at some point during the study.

There are a few noteworthy observations in the individual patient results from Study SD-809-C-12 (Table 16). The sample size is small with only six subjects per cohort. There is substantial variability in the percent of total sample radioactivity for M1 derived from SD-809. In three of the six patients, M1 meet or exceed the criteria (10%) for being a MHM.

Although the M4 metabolite was found to be a major metabolite in tetrabenazine and SD-809 in the sponsor's mass balance study, it was not identified in the RLD' s label. The levels of M4 resulting from SD-809 are appear to be similar to slightly lower than the levels resulting from tetrabenazine.

Table 16: Comparison of plasma metabolites following administration of 25 mg of [14C]-SD-809 or [14C]-tetrabenazine to healthy male subjects Study SD-809-C-12

Percentage of total sample radioactivity								Metabolite Number	Percentage of total sample radioactivity							
SD-809									Tetrabenazine							
S001	S002	S003	S004	S005	S006	Mean	SD		S007	S008	S009	S010	S011	S012	Mean	SD
6.1	**13**	8.6	**10**	**13**	4.3	9.2	3.6	**M1**	< 1.0	3.1	3.9	7	5	4.7	4.1	2.0
2.5	2.3	1.6	4.4	2.7	1.4	2.5	1.1	**M2**	< 1.0	6	6	9.2	8.3	7.9	6.4	2.9
4.6	6	2.2	5.1	3.5	2.4	4.0	1.5	**M3**	**16.4**	**11**	**15**	**18.4**	**26.1**	**11.2**	**16.4**	5.6
8.1	**11.7**	**13**	**13.8**	**18.1**	**12.6**	**12.9**	3.2	**M4**	**21.1**	**17.3**	**13**	**16**	7.3	**18.7**	**15.6**	4.9
6.9	4.4	**13.8**	3.1	9.2	**12.1**	8.3	4.2	**M5**	< 1.0	1.1	4.8	< 1.0	1.9	< 1.0	1.8	1.5
9.8	**11.4**	**14.6**	7.4	**14.3**	**20.7**	**13.0**	4.6	**M6**	5.9	2.3	3.9	4.5	2.5	4.7	4.0	1.4

M1 Acid Metabolite of HTBZ (subsequently further identified as 2-methylpropanoic acid metabolite of β-HTBZ)
M2 Sulphate of O-desmethyl β-HTBZ
M3 Sulphate of O-desmethyl α-HTBZ
M4 Mono-hydroxy TBZ
M5 β-HTBZ
M6 α-HTBZ

SD Standard Deviation

Note: values < 1.0 % were taken as 1 for calculation of the mean and SD.

Source: TEVA

In the NDA, the sponsor presented the mean percentage from the SD-809-C-12 Study, which presents M1 as just being under the threshold for reporting as a major metabolite (>10%) at 9.2% Table 17.

Table 17: Exposure to Metabolites Following Administration of a Single 25 mg Dose of [14C]-SD-809a or [^{14}C]-Tetrabenazine (Study SD-809-C-12; PK Population, (N=6/Treatment)

	DPM/g Plasma (mean [SD])[b]			% Total Plasma Radioactivity (mean [SD])	
		Total (α+β)-HTBZ Matched AUC Dose			
Metabolite	SD-809 25 mg	SD-809 12.5 mg[c]	Tetrabenazine 25 mg	SD-809 25 mg	Tetrabenazine 25 mg[d]
M1: 2-methylpropanoic acid-β-HTBZ	54 (19)	27 (9)	25 (14)	9.2 (3.6)	4.1 (2.0)
M2: sulfate of ODM-β-HTBZ	15 (5)	7 (2)	40 (21)	2.5 (1.1)	6.4 (2.9)
M3: sulfate of ODM-α-HTBZ	24 (9)	12 (5)	94 (45)	4.0 (1.5)	16.4 (5.6)
M4: mono-hydroxy SD-809 or tetrabenazine	77 (14)	39 (7)	86 (31)	12.9 (3.2)	15.6 (4.9)
M5: β-HTBZ	52 (31)	26 (16)	10 (9)	8.3 (4.2)	1.8 (1.5)
M6: α-HTBZ	82 (36)	41 (18)	22 (8)	13.0 (4.6)	4.0 (1.4)
Sum of Additional Metabolites[e]	--	--	--	31.9 (7.1)	30.0 (8.7)
Total Metabolites (M1-M6 and additional metabolites)	**--**	**--**	**--**	**81.7 (3.0)**	**78.2 (12.4)**

Reference: SD-809-C-12, Section 16.1.13.4.
Abbreviations: DPM, disintegrations per minute; HTBZ, dihydrotetrabenazine; ODM, O-desmethly; SD, standard deviation; TBZ, tetrabenazine.
[a] [14C]-SD-809 and [14C]-tetrabenazine administered via unformulated powder-in-capsule, following an overnight fast.
[b] The product of % plasma radioactivity for each individual * individual DPM/g plasma. Average DPM/g after 25 mg single dose: SD-809: 614; tetrabenazine: 569.
[c] Estimated values for SD-809 12.5 mg based on (DPM/g in plasma after 25 mg dose * 50% * % plasma radioactivity per metabolite).
[d] Components <1.0% total radioactivity are taken as 1.0% for calculation purposes.
[e] Metabolites between 1 and 10% of total radioactivity measured in aggregate included a sulfate of ODM HTBZ, a glucuronide of HTBZ, mono-hydroxy HTBZ, 9-ODM β-HTBZ and mono-hydroxy ODM TBZ.

Source: Teva

The identification of M1 as a MHM is important because M1 is not described as a circulating MHM in the RLD, and it is not shown to be MHM (<10%) resulting from tetrabenazine in the sponsor's Mass Balance Study. In addition, M1 is only present in low levels following oral administration of SD-809 in rat, and it may not have been covered in the bridging 3-month toxicology study in rat, the pivotal embryofetal toxicology study or in lifetime carcinogenicity studies for Xenazine.

CDTL Comment:
Individuals in the Mass Balance Study had observed levels of M1 that indicate it is a MHM. There was substantial inter-subject variability in the levels of M1 in the study (as much as 3 fold). Women were not included in the study and it may be possible that women may have higher levels of M1 and M4 than the levels reported in male subjects. The small sample size may not accurately represent the full range of inter-subject variability for levels of M1. Some patients could have levels have levels of M1 that are much higher than 13. The percentage of the total plasma sample radioactivity is a semi-quantitative measurement, LC/MS should be used with validated reference standards to quantify the amounts of M1 and M4 in human subjects, which is the method used to assess levels of α-HTBZ and β-HTBZ in the sponsor's PK studies (M1 and M4 were not assessed in these studies).

Bioanalytical Concerns
Dr. Dimova also questioned the reliability of the analytical methods used in the Mass Balance Study because exposure to the known (α+ β)-HTBZ metabolites (aka. M5 + M6) after administration of 25 mg SD-809 was estimated to be 4x higher (instead of the expected 2x higher) following administration of 25 mg tetrabenazine. In addition, 9-O-desmethyl-HTBZ was not identified as a MHM of tetrabenazine in the Mass Balance Study however, 9-O-

desmethyl-HTBZ (Table 17, see M2) is a known MHM of Xenazine and it is described as such in the Xenazine label.

The pooling strategy used in the Mass Balance Study is also a cause for concern. Plasma samples were only selected from four timepoints (2, 2.5, 6, and 12 h) after oral dosing, even though samples from approximately 20 minutes to 48 hours after dosing were available. The selected samples excluded the 3-4 hour timepoint after dosing, which is the time when the concentration of radioactivity in plasma is at its maximum (Table 18). Dr. Dimova opined that the exclusion of samples at 3-4 hour after dosing has the potential to alter the percent of 9-O-desmethyl-β-DHTBZ in the tetrabenazine samples, which may account for the failure to detect levels of β-DHTBZ that would have classified it as a MHM in the sponsor's Mass Balance Study. The pooling technique may also have the potential to alter the reported levels of M1 and M4.

Table 18: Study SD-809-C-12 Plasma Concentrations (ng equiv/mL): Total Radioactivity Clinical Study Report SD-809-C-12 Amendment 01 ((b) (4) 113049) Version 2.0 06 March 2015

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TABLE 14.2.7.2.1
Plasma Concentrations (ng equiv/mL): Total Radioactivity
Summary Statistics: PK Population

Treatment	Time point	Mean	Median	SD	CV (%)	Geo Mean	Geo CV (%)	Geo n	Min	Max	n
SD-809 (N=6)	PREDOSE	NC	NC	NC	NC	NC	NC	NC	0.0	0.0	6
	20 MIN	NC	NC	NC	NC	NC	NC	NC	0.0	0.0	6
	40 MIN	58.88	58.25	41.96	71.3	43.50	118.9	6	12.6	119.8	6
	1 H	97.63	99.00	30.67	31.4	93.47	33.7	6	60.0	136.5	6
	1.5 H	115.23	111.10	24.13	20.9	113.09	21.6	6	82.4	144.7	6
	2 H	115.80	115.65	22.93	19.8	113.80	21.1	6	79.8	148.5	6
	2.5 H	114.93	116.20	22.45	19.5	112.98	20.9	6	80.2	142.9	6
	3 H	117.58	122.00	18.71	15.9	116.25	17.0	6	87.5	138.9	6
	4 H	118.32	122.25	19.79	16.7	116.87	17.6	6	90.7	138.7	6
	6 H	113.38	122.75	18.65	16.4	111.99	17.7	6	85.8	128.3	6
	8 H	101.13	106.45	17.26	17.1	99.82	18.2	6	74.3	121.7	6
	12 H	83.97	81.80	17.25	20.5	82.51	20.7	6	62.4	110.3	6
	18 H	58.55	61.25	16.51	28.2	56.52	30.4	6	36.4	82.6	6
	24 H	47.15	54.80	16.90	35.9	43.98	45.7	6	21.6	61.9	6
	36 H	33.83	34.40	13.71	40.5	31.27	47.4	6	16.1	49.9	6
	48 H	24.83	22.80	6.63	26.7	24.12	26.8	6	17.1	33.4	6
	72 H	10.12	11.55	5.16	51.0	12.06	13.1	5	0.0	14.6	6
	96 H	1.32	0.00	3.23	244.9	7.90	NC	1	0.0	7.9	6
	120 H	3.12	0.00	4.85	155.7	9.32	11.4	2	0.0	10.1	6
	144 H	NC	NC	NC	NC	NC	NC	NC	0.0	0.0	6
	168 H	NC	NC	NC	NC	NC	NC	NC	0.0	0.0	6
	192 H	NC	NC	NC	NC	NC	NC	NC	0.0	0.0	4

Note: The data in this table are presented in listing 16.2.5.2.2
Treatment definition: SD-809 = 25 mg [14C]-SD-809 TETRABENAZINE = 25 mg [14C]-tetrabenazine
Where Geo=Geometric
For all summary statistics concentration values reported as ND (0.008 ng equiv/mL) have been set to zero
Geometric CV(%) = [exp(SD²)-1]½ * 100 where SD = standard deviation of the natural log transformed data
Summary statistics not calculated are reported as NC

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Source:Teva

The levels of M1 found in plasma samples from the Mass Balance Study indicate that it is a potential MHM. This study used a semi-quantitative technique to determine plasma levels of SD-809 metabolites that do not provided an adequate understanding about the levels of M1 resulting from SD-809. M1 was not found to be a MHM during development of Xenazine.

Although M1 is present in tetrabenazine in the sponsor's Mass Balance Study, the levels associated with tetrabenazine do not reach 10% to qualify it as a MHM.

These conflicting results create uncertainty regarding the status of M1 as a unique MHM derived from SD-809. If M1 was a confirmed MHM, the sponsor would need to show that there was adequate representation in the nonclinical studies described in the Xenazine label or in the sponsor's pivotal bridging toxicology studies. This seems to be unlikely based on the information provided in the Nonclinical Review for the sponsor's 3-month toxicology and embryofetal toxicity studies.

Discussions with Auspex/TEVA Regarding The M1 and M4 Metabolites

The Agency first expressed its concerns to about metabolite levels from SD-809 that exceeded the levels in the RLD at the November 11, 2011, pre-IND meeting (IND 112297).

Preliminary FDA Response: to Question (e)
"The results of your in vitro metabolism studies suggest the possibility that the in vivo levels of certain metabolites might be higher with SD-809 compared to tetrabenazine. For example, according to the data provided in Tables 2.6-3 and 2.6-3, deuterated α- and β- HTBZ are metabolized to certain oxidation products (i.e. α-oxidation product 1, α- oxidation product 3, and β-oxidation product 1) to a greater extent than are the nondeuterated forms. If differences in metabolic profile are observed in humans, then you would need to demonstrate that any metabolite of SD-809 that circulates at levels greater than 10% of the total drug-related exposure (and not detected to a similar extent with tetrabenazine) has been adequately tested in the nonclinical studies (cf. Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals January 2010 ICH Revision 1; Guidance for Industry Safety Testing of Drug Metabolites CDER February 2008). If not, additional nonclinical studies may be needed.

You should also characterize the metabolic pathway of SD-809 in humans."

The specific concern about the need for more information about M1 and M4 discussed at the End of Phase 2 Meeting, December 5, 2012.

Meeting Discussion Question 4(c)
"Per your mass balance study results, there is a 3-fold exposure increase of M1 following the administration of SD-809 compared to that of tetrabenazine. The dose of SD-809 is about half of tetrabenazine. Therefore, there is an uncertainty on whether the total amount of M1 at steady state is comparable to that of tetrabenazine. You need to provide evidence to justify your claim that the actual exposures to the SD-809 metabolites (Table 2.7- 24) at steady state will be similar for both tetrabenazine and SD-809 and are not expected to represent an increased safety risk for patients after dose adjustment. If there is a significant increase of M1 exposure observed following SD-809 administration, the DDI potential of the metabolite M1 needs to be assessed. Please refer to the FDA Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf"

Sponsor's Pre-meeting Response:
Auspex notes that data provided in the meeting package were preliminary derived from a single pooled sample per cohort. Auspex can now present data from the individual subjects based on time-proportional pooling ('updated results') that are provided in the attached document (See Attachment 2). These data demonstrate that M1 is not present as a major metabolite of SD-809. These results show that M1 for SD-809 is approximately 2-fold higher than observed for tetrabenazine. Auspex believes there is no safety risk because SD-809 is given at approximately half the dose of tetrabenazine. Auspex therefore believes that no further justification for M1 exposure is needed.

Meeting Discussion:
The Division expressed concern about the variability in the individual results of SD- 809 metabolites (Attachment 2, Table 2). The sponsor clarified that this variability is similar to that observed for tetrabenazine.

The analytical methods and the uncertainty of the M1 1nd M4 as MHM was discussed with the during a September 25, 2015 teleconference, during the Mid-Cycle Meeting (November 3, 2015) and during the Late Cycle Meeting (February 25, 2016).

Dr. Dimova and the Office of Clinical Pharmacology recommended that the sponsor quantitatively assess the concentration of circulating SD-809-related metabolites. The proposed method using retained plasma samples was discussed at the Mid- and Late-Cycle meeting. In addition, the activity of M1 and M4 should be evaluated in in vitro studies (VMAT2 and off-target binding).

The Clinical Pharmacology reviewers also recommended that the sponsor use adequate plasma pooling methods and sampling times to provide a better assessment of the levels of M1 and M4. On March 7, 2016, (in response to the Late Cycle meeting) the sponsor provided a strategy to assay retained clinical samples from StudyAUS-SD-809-CTP-07 Part 2 from subjects who received twice daily SD-809 and tetrabenazine that achieved steady-state exposure to α-HTBZ and β-HTBZ and 9-O-desmethyl β-HTBZ. The Agency found the strategy acceptable however; the sponsor would need to evaluate the stability of the retained samples to determine if the assays would be valid. The sponsor's projected timeline for assessment of the activity (receptor binding profile) of M1 and M4was April 15, 2016. The assays of M1 and M4 would not be completed until June 15, 2015, this is provided the retained samples were stable and valid assays could be performed using these samples.

Following the Late Cycle Meeting (LCM) on February 25, 2016, the sponsor requested another teleconference to obtain the Agency's feedback on a plan to address the M1 and M4 metabolite issues. The teleconference was held on March 16, 2016, with the Clinical Pharmacology, Nonclinical, Clinical review team members, and the Division and ODE-1 leadership in attendance.

The sponsor proposed:

- To characterize deuterated and non-deuterated M1 and M4 metabolites of SD-809 and tetrabenazine in competitive binding pharmacology studies

- To assess the relative abundance of M1 and M4 using LCMS/MS and estimate pharmacokinetic parameters from the [14C]-human ADME study (SD-809-C-12) from retained plasma samples collected over 96 hours upon confirmation that samples are suitable for analysis

- Teva proposes to compare systemic exposure to M1 and M4 from study AUS-SD-809-CTP-07 Part 2 in subjects who received twice daily SD-809 and tetrabenazine that achieved steady-state exposure to α-HTBZ and β-HTBZ and 9-Odesmethyl β-HTBZ. Teva will express M1 and M4 as fractions of total active metabolites (i.e., as a percentage of total-[α+β]-HTBZ).

- To assess the systemic exposure to M1 and M4 will be assessed in rats after twice-daily oral doses of SD-809 for a period sufficient to achieve steady-state exposure in a study in preparation. . A dose of 15 mg/kg/day twice daily will be used, as this dose resulted in exaggerated pharmacological signs and a reduction in body weight gain but no histopathological findings with similar findings from 15 mg/kg/day twice daily tetrabenazine within the same study. The comparison of exposure to M1 and M4 after oral dose SD-809 or tetrabenazine in clinical and nonclinical samples to show rats have been exposed to M1 and M4 during the bridging toxicology studies.

The sponsor was informed that detecting metabolites of concern in the proposed nonclinical study, as proposed on page 3 of the March 7, 2016 submission, would not be adequate to allow bridging to the existing nonclinical information for the RLD. The sponsor was informed that for each major human metabolite, plasma exposure at steady state, which exceeds the levels demonstrated to occur in humans, should be demonstrated in appropriate nonclinical species.

On April 22, 2016, the sponsor proposed a revised timeline to:

- Submit results of the stability of the retained clinical samples on May 20, 2016.
- Submit results of the analysis of M1 and M4 levels in the retained clinical samples on June 15, 2016.
- Submit results of the animal plasma sample to determine the steady state exposure for M1 and M4 in rabbit, rat and mice on June 15, 2016

Limitations in the sponsor's proposal:

- If the retained plasma samples from the completed clinical study AUS-SD-809-CTP-07 Part 2 or study SD-809-C-21 are not stable, the sponsor would need to complete a new clinical PK study to address the uncertainties about M1 and M4. The need for a new PK study would result in a CR action, even after an extension.

- If the clinical samples are stable, and M1 and/or M4 are found to be MHM, there is uncertainty whether rats make M1 (and perhaps M4), in the same or higher proportion

as humans. If the nonclinical samples are stable, the existing nonclinical studies may not provide adequate coverage for M1 and M4. If not, the sponsor may need to conduct new nonclinical studies, which would result in a CR action even with an extended review cycle.

Elimination

SD-809 is primarily renally eliminated in the form of metabolites (83% of the dose recovered in the urine, SD-809-C-12 mass balance study report). The half-life of total (α+β)-HTBZ at steady state from SD-809 is approximately 7 to 10 hours (Table 19).

Table 19: Mean Pharmacokinetic Parameters (%CV) for Total-(α+β)-HTBZ following Single and Multiple Oral Doses of SD-809

		Total-(α+β)-HTBZ Single-Dose Data					
Study	Dose/Formulation/ Conditions	C_{max} (ng/mL)	t_{max} (h)	T_{lag} (h)	AUC_t (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{½}$ (h)
AUS-SD-809-CTP-06 (N=19)	25mg SD/PIC/Fasted	74.6 (37)	1.50 (0.67-2.00)	na	530 (54)	542 (54)	8.62 (38.2)
AUS-SD-809-CTP-07 Part 1 (N=24)	15mg SD/A/High Fat	33.3 (33)	6.00 (1.50-8.00)	0.50 (0.00-3.00)	296 (48)	305 (46)	6.99 (23)
	15mg SD/A/Fasted	22.5 (36)	2.25 (1.00-8.00)	0.00 (0.00-1.00)	263 (45)	273 (45)	9.35 (25)
	15mg SD/B/High Fat	28.7 (39)	6.00 (2.50-12.00)	0.51 (0.00-3.00)	306 (47)	315 (46)	7.02 (20)
	15mg SD/B/Fasted	14.5 (42)	4.00 (1.00-12.00)	0.00 (0.00-1.00)	243 (49)	259 (47) (N=23)	9.95 (16) (N=23)
AUS-SD-809-CTP-07 Part 2 (N=12)	7.5mg SD/Tablet/Std Meal	21.4 (32)	3.00 (2.50-5.00)	1.00 (0.00-2.50)	167 (41)	176 (39)	7.18 (19)
	15mg SD/Tablet/ Std Meal	45.3 (18)	3.26 (2.50-4.00)	1.00 (0.00-1.05)	396 (35)	408 (36)	7.66 (18)
	22.5mg SD/Tablet/ Std Meal	67.5 (25)	3.75 (3.00-5.02)	0.00 (0.00-1.00)	599 (48)	610 (48)	8.38 (26)

		Total-(α+β)-HTBZ Multiple-Dose Data						
Study	Dose/Formulation/ Conditions	C_{max} (ng/mL)	t_{max} (h)	C_{max}/C_{min}	C_{min} (ng/mL)	$AUC_{(0-12)}$ (ng•h/mL)	$t_{½}$ (h)	Rac
AUS-SD-809-CTP-07 Part 2 (N=12)	7.5mg BID/Tablet/ Std Meal	31.5 (26)	3.25 (2.50-4.00)	3.50 (31)	10.1 (48)	203 (34)	8.76 (22)	184 (16)
	15mg BID/Tablet/ Std Meal (N=11)	72.0 (20)	3.00 (2.02-3.50)	3.75 (30)	21.1 (41)	443 (28)	9.06 (28)	178 (11)
	22.5mg BID/Tablet/ Std Meal	111 (43)	4.00 (2.50-5.02)	3.03 (19)	39.5 (59)	769 (46)	9.50 (24)	207 (30)

Abbreviations: CV: coefficient of variation; PIC: powder in capsule; ER: extended release; SD: single dose; BID: twice daily; na: not applicable; Rac, [AUC_{0-12},Steady State]/[AUC_{inf} Single Dose].
Median (range) presented for t_{max} and T_{lag}.

Intrinsic Factors

The impact of intrinsic factors was only studied using population PK analysis. The population was 23 to 74 years old, 47.7% male, and 100% Caucasian. The pharmacokinetics of SD-809 and its primary metabolites were not studied in specific populations, including pediatric, geriatric subjects and patients with renal or hepatic impairment

Renal Impairment

The sponsor did not asses SD-809 in patients with renal impairment. The Xenazine label makes no mention of the effects of renal impairment of dosing in patients with renal impairment.

Hepatic Impairment

Similar to Xenazine, SD-809 is contraindicated for patients with hepatic impairment.

Impaired CYP2D6 Function
The results of an in vivo drug-drug interaction (DDI) study conducted with SD-809, showed a 3-fold increase in total (α+β)-HTBZ exposure when a strong CYP2D6 inhibitor (paroxetine) was co-administered with SD-809. In the sponsor's clinical trials, the maximum daily dose of SD-809 was limited to 36 mg with a maximum single dose of 18 mg in patients taking strong CYP2D6 inhibitors in the efficacy and safety studies. I agree with Dr. Dimova recommendation that the daily dose of SD-809 should not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.

Drug-Drug Interactions (DDI)
In vitro metabolism studies (conducted with tetrabenazine) indicated that there is no meaningful inhibition or induction of CYP-based enzymes by tetrabenazine and its metabolites α-HTBZ and β-HTBZ at concentrations that are relevant for dosing. The sponsor assessed the M1 and M4 metabolites using a panel of in vitro DDI studies. The results of the in vitro studies indicate that M1 and M4 are not expected to cause clinically relevant drug interactions.

Pharmacometrics

Pharmacokinetic (PK) Bridging Strategy

Auspex was unable to obtain approved Xenazine tablets for PK bridging for their Phase 1 studies. The Xenazine NDA holder claimed the Xenazine was only available to individual patients through a "Named Patient Program". The Agency has not imposed any restricted distribution program on the Xenazine NDA. The Xenazine sponsor chooses to use specialty pharmacies for distribution. To establish a bridge between Xenazine and SD-809 exposure over the intended dose range, the sponsor used two approaches.

- Exposure to the active α-HTBZ and β-HTBZ metabolites of SD-809 and tetrabenazine was evaluated in Phase 1 studies in which tetrabenazine was administered as unformulated powder-in-capsule and as commercially available tablets sourced from Australia and Northern Ireland in Study SD-809-C-21. However, the sponsor is unable to provide bioequivalence information bridging the foreig tetrabenazine product and Xenazine.

- Patients in the ARC-Switch subgroup (N=36) of study SD-809-C-16 (ARC-HD, N=75) were converted overnight from their existing stable Xenazine dose to an SD-809 regimen estimated to provide comparable daily exposure (AUC) of total (α+β)-HTBZ to the patient's prior Xenazine dose. Patients took their usual morning dose of commercially obtained Xenazine from their own personal supply. More intensive PK sampling was obtained in a smaller number of patients within the ARC Switch Subgroup, the Rich Sampling Subgroup (n= 12). Patients in Rich Sampling subgroup had 5 samples per patient drawn over 6 hours post-dose compared to a sparse sampling scheme (2 samples/patient) that was performed in the remaining 24 patients in the ARC Switch subgroup.

The initial switch in the Switch Cohort was a simple 2:1 conversion based on the stable daily dose of Xenazine. This dose conversion ratio was derived from Phase 1 PK studies including study SD-809-CTP-07, supported by population PK modeling and simulation analysis in the Phase 1 stage.

To appropriately compare exposure following administration of Xenazine and SD-809 over the intended dose range, concentrations parameters were normalized to the maximum single dose for each treatment, i.e. 37.5 mg for Xenazine and 24 mg for SD-809. Dose normalized plasma concentrations of total (α+β)-HTBZ in the Switch Cohort following administration of Xenazine and SD-809 appears to be in a similar range, as shown in Figure 3. In addition, the observed dose-normalized Cmax values were compared for Xenazine and SD-809 in the Rich Sampling subgroup. The result shows that the Cmax of SD-809 for highest proposed dose appears to be covered by Cmax of Xenazine at highest approved dose, as shown in Table 20. The Pharmacometrics reviewer concluded, the PK bridging between SD-809 and Xenazine is acceptable if the highest recommend daily dose of SD-809 is 48 mg (24 mg BID). However, the majority of patients in the Switch study experienced dose increase after week 1, suggesting that the 2:1 conversion ratio might not be optimal.

Figure 3: Dose-normalized Plasma Concentrations of Total (α+β)-HTBZ in the Switch Cohort of Study SD-809-C-16 (dose normalized to the maximum single dose for each treatment)

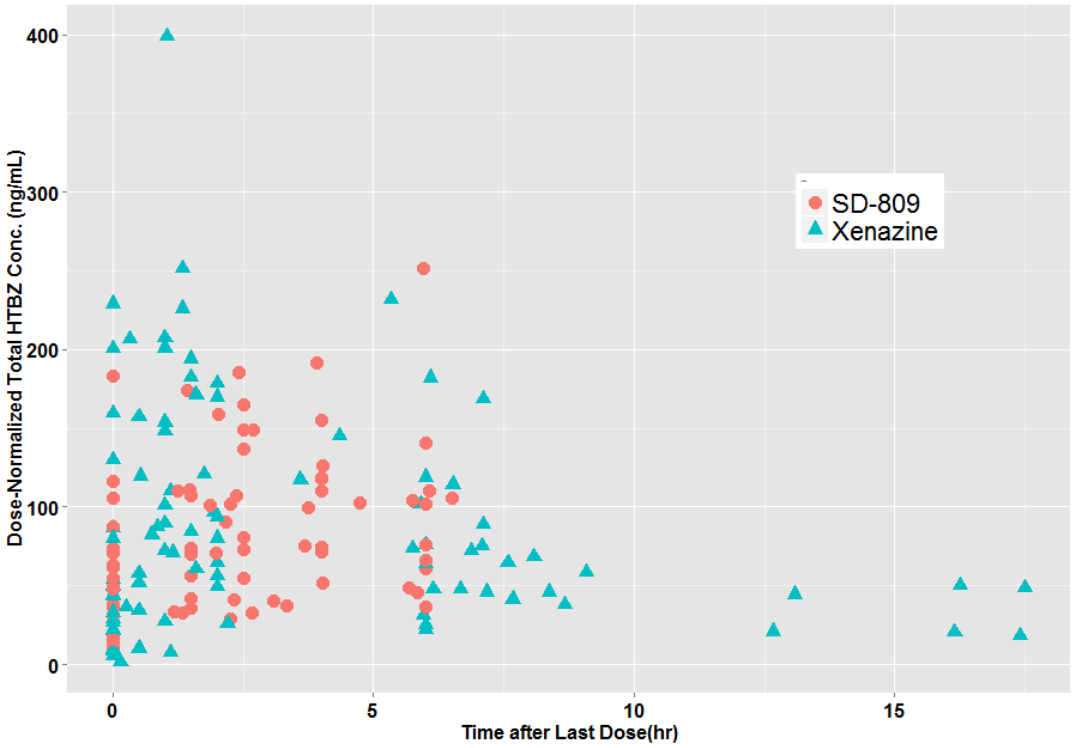


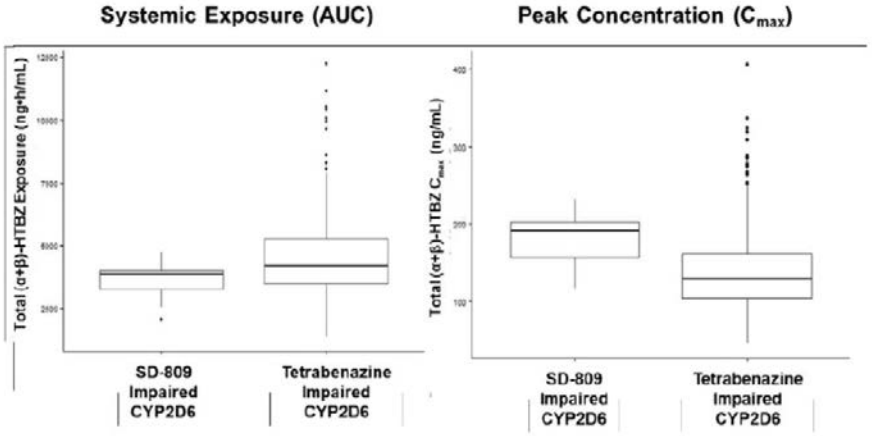
Table 20: Cmax Comparison between Xenazine and SD-809 in SWITCH Cohort (Dose-normalized)

	Xenzaine	SD-809
Cmax Mean (%CV)	120.8 (52.8)	115.5 (51.3)

Note: Data came from the rich sampling subgroup of the Switch Cohort in Study SD-809-C-16; Xenazine dose was normalized to 37.5 mg; SD-809 dose normalized to 24 mg.

In this case, the bridging strategy based on PK samples in patients using their own supply of Xenazine in the ARC-Switch subgroup in Study SD-809-C-16 is acceptable. It is only a portion of a broader strategy that includes reliance on the sponsor's clinical efficacy/safety studies and referencing limited information in the Xenazine label.

Figure 4: Total (α+β)-HTBZ AUC0-24 and Cmax in CYP2D6-Impaired Subjects: Simulations Following 25 mg BID Tetrabenazine and 24 mg BID SD-809 Dosing



Reference: SD-809 data derived from SD-809-CLN-078, Figure 7; Tetrabenazine data replotted from source data in SD-809-CLN-076, Section 9.2.3.
Notes: SD-809 dosing at 24 mg BID; Tetrabenazine dosing at 25 mg BID. CYP2D6-impaired subjects included subjects with a CYP2D6 poor metabolizer phenotype and subjects receiving a concomitant strong CYP2D6 inhibitor. Lower and upper boundaries of the box are the 1st and 3rd quartiles with the whiskers indicating 1.5 times the interquartile range and outliers beyond the whiskers plotted as individual data points. Median is indicated by the horizontal line within the box.

Pharmacometrics Conclusions

The Pharmacometrics review (PM) team concluded the PK bridging between SD-809 and Xenazine is acceptable if the recommend maximum daily dose of SD-809 is 48 mg (24 BID).

However, the PM reviewer disagrees with the sponsor's justification for not requiring a dose adjustment in patients with impaired CYP2D6 function. "Although in subjects with impaired CYP2D6 function, SD-809 at 24 mg BID is predicted to yield median AUC0-24 values that fall within the exposure range of tetrabenazine at 25 mg BID dose in subjects with impaired CYP2D6 function, the predicted median Cmax values at 24 mg BID SD-809 dose in subjects with impaired CYPD2D6 function are higher than the median and even 75% percentile of the predicted Cmax values at 25 mg BID tetrabenazine dose in subjects with impaired CYPD2D6 function (Figure 4), which raises the concern that the higher Cmax values may increase of the

risk of AEs, especially QT prolongation given the positive exposure-QT prolongation relationship."

Moreover, in the pivotal efficacy study SD-809-C-15, the SD-809 dose was adjusted in patients on strong CYP2D6 inhibitors (maximum dose levels for patients on strong CYP2D6 inhibitors were restricted to 18 BID, instead of 24 mg BID for patients with normal CYP2D6 function).

Thorough QTc Study (SD-809-C-21)

The study was a single-site, randomized, double-blind, placebo- and positive-controlled (moxifloxacin), six-period, crossover study to evaluate the effects of SD-809 (12 mg and 24 mg) on cardiac repolarization, as assessed by evaluating the placebo-adjusted, time-matched change from baseline in the QTc interval. The effect of tetrabenazine on cardiac repolarization was also assessed at a dose (50 mg) expected to provide comparable total exposure to active metabolites as SD-809 24 mg.

Forty-eight eligible healthy volunteer subjects were randomized to one of six treatment sequences.

Treatments:

A: 12 mg SD-809 plus moxifloxacin placebo and placebo for tetrabenazine
B: 24 mg SD-809 plus moxifloxacin placebo and placebo for tetrabenazine
C: SD-809 placebo plus moxifloxacin placebo and placebo for tetrabenazine
D: 400 mg moxifloxacin plus SD-809 placebo and placebo for tetrabenazine
E: 50 mg tetrabenazine plus moxifloxacin placebo and SD-809 placebo
F: Placebo for tetrabenazine plus moxifloxacin placebo and SD-809 placebo

Treatments A, B, C, and D were administered in the fed state, following a standard breakfast.

Baseline parameters and at 12 time points following study drug administration (0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 24 hours) to assess the effects of study drug on cardiac conduction and to evaluate the pharmacokinetics of SD-809 and tetrabenazine and their active metabolites α-HTBZ and β-HTBZ.

The IRT-QT Study team concluded the study had adequate assay sensitivity based on the change observed in QTc during treatment with moxifloxacin 400 mg.

The IRT-QT's statistical reviewer used a mixed model to analyze the effect on ΔΔQTcF. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 21. The largest upper bounds of the 2-sided 90% CI for the mean differences between SD-809 12 mg and placebo, and between SD-809 24 mg and placebo are 4.9 ms, 6.9 ms, respectively.

Table 21: Analysis Results of ΔQTcF and ΔΔQTcF for SD-809 12 mg, SD-809 24 mg, and Moxifloxacin 400 mg

		Treatment Group												
	Placebo	Moxifloxacin 400 mg					SD-809 12 mg				SD-809 24 mg			
	ΔQTcF	ΔQTcF		ΔΔQTcF			ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	*Adj 90%CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-2.7	47	-0.1	2.6	(0.2, 5.0)	(-0.7, 5.9)	45	-2.9	-0.1	(-2.6, 2.3)	44	-2.4	0.3	(-2.2, 2.8)
1	-4.7	47	-0.5	4.2	(2.0, 6.3)	(1.2, 7.1)	45	-4.9	-0.3	(-2.4, 1.9)	44	-3.8	0.9	(-1.3, 3.1)
1.5	-5.5	47	3.7	9.2	(7.0, 11.4)	(6.2, 12.2)	45	-6.1	-0.6	(-2.8, 1.6)	44	-4.3	1.2	(-1.0, 3.4)
2	-6.7	47	3.3	10.0	(7.9, 12.2)	(7.1, 13.0)	45	-7.0	-0.2	(-2.4, 1.9)	44	-4.9	1.8	(-0.4, 4.0)
2.5	-3.8	47	7.1	10.9	(8.8, 13.1)	(8.0, 13.8)	45	-3.3	0.5	(-1.6, 2.7)	44	-2.4	1.4	(-0.8, 3.5)
3	-5.9	47	5.3	11.2	(9.2, 13.3)	(8.4, 14.0)	45	-7.0	-1.1	(-3.2, 1.0)	44	-4.6	1.3	(-0.8, 3.4)
4	-4.6	47	8.6	13.2	(10.9, 15.4)	(10.1, 16.2)	45	-5.2	-0.6	(-2.9, 1.6)	44	-1.1	3.5	(1.2, 5.8)
5	-0.0	47	10.4	10.4	(7.9, 13.0)	(7.0, 13.9)	45	0.4	0.4	(-2.1, 3.0)	44	2.6	2.6	(0.0, 5.2)
6	-2.8	47	8.6	11.3	(9.1, 13.5)	(8.3, 14.4)	45	-0.8	2.0	(-0.2, 4.2)	44	0.3	3.1	(0.9, 5.4)
8	-9.6	47	4.5	14.1	(11.8, 16.4)	(11.0, 17.2)	45	-7.0	2.6	(0.3, 4.9)	44	-5.0	4.6	(2.3, 6.9)
10	-5.1	47	6.8	11.9	(9.6, 14.2)	(8.8, 15.0)	45	-5.2	-0.1	(-2.4, 2.2)	44	-4.2	0.9	(-1.4, 3.3)
24	-11.4	47	-5.4	6.0	(3.5, 8.4)	(2.6, 9.3)	45	-13.4	-2.0	(-4.4, 0.5)	44	-10.8	0.6	(-1.9, 3.1)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

Source: IRT-QT Review P-13

No subject in any treatment group had a QTcF greater than or equal to 480ms. Only one subject in the tetrabenazine 50 mg group had a QTcF >450ms but ≤480ms.

However, the IRT-QT review team found a marginal QTc prolongation for tetrabenazine 50 mg. The reviewer used a model that was similar to the one used by the sponsor which included gender, sequence, period, treatment, time as fixed effects, baseline as a covariate subject as a random effect. The analysis results are listed in Table 22. The largest upper bound of the 2-sided 90% CI for the mean difference between tetrabenazine 50 mg and placebo is 10.1 which exceed 10 ms (sponsor's 9.5 ms).

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Table 22: Analysis Results of ΔQTcF and ΔΔQTcF for Tetrabenazine 50 mg

		Treatment Group			
		Tetrabenazine 50 mg			
	ΔQTcF	ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	-3.3	47	-1.8	1.5	(0.1, 2.9)
1	-2.4	47	3.3	5.7	(4.3, 7.1)
1.5	-1.5	47	3.0	4.5	(2.7, 6.3)
2	-1.6	47	4.1	5.7	(3.9, 7.6)
2.5	2.1	47	8.8	6.7	(4.7, 8.7)
3	-0.7	45	7.4	8.1	(6.2, 10.1)
4	-0.3	46	6.9	7.2	(5.2, 9.2)
5	-0.2	45	4.1	4.3	(1.7, 6.8)
6	-3.3	46	1.8	5.1	(3.6, 6.6)
8	-6.2	46	-3.4	2.7	(0.3, 5.1)
10	-2.4	46	-0.9	1.5	(-0.0, 3.1)
24	-11.2	46	-9.7	1.6	(-0.3, 3.4)

Source: IRT-QT Review P-14

The TQT study has several important design limitations. The highest dose studied (single dose of 24 mg) resulted in half of the expected steady state exposure (Cmax) following the highest single therapeutic dose of Xenazine 50 mg. Patients who are CYP2D6 poor metabolizer or taking a strong CYP2D6 inhibitor are estimated to have >3-fold higher exposure to the α- and β-HTBZ metabolites than has been assessed in this TQT study. The study did not evaluate a supermaximal dose of SD-809. The 24 mg dose does not cover the potential exposure to the active metabolites of SD-809 that a patient taking a CYP2D6 inhibitor or patients who are poor CYP2D6 metabolizers could experience after taking a 24 mg tablet of SD-809.

The IRT-QT concluded that the TQT study was not conducted at sufficiently high concentrations to rule out QT prolongation at supratherapeutic or therapeutic concentrations. As with Xenazine, there is a statistic significant exposure response relationship between the sum of the concentration of the two active metabolites (α+β) and QT.

The QT reviewer concluded, "Clinically relevant QT prolongation might be expected in some patients at the highest therapeutic dose of 24 mg b.i.d., especially in CYP2D6 poor metabolizer or patients co-administered a strong CYP2D6 inhibitor."

IRT-QT Recommendation

Because of the clear limitation of this TQT study, consider keeping the same language describing QT-related changes in the Xenazine label, in the SD-809 label. The current Xenazine includes a section describing a small QT change (8msec) associated with Xenazine in the Warnings and Precautions section

CDTL Comment:
The maximum dose permitted in the ongoing, long-term, open label study is 36 mg bid. Patients who are poor CYP2D6 metabolizers could reach exposures by AUC of α- and β-HTBZ that are substantially higher (>3 fold) than the exposure experienced by patients in the TQT study. The Cmax of SD-809 given as a single dose of 36 mg is not predicated to exceed the exposure observed in patients given tetrabenazine at the maximum single dose of 50 mg. Patients on drugs that are strong inhibitors of CYP2D6 or known poor metabolizers would be limited a maximum daily dose of 18 mg bid. Because of this concern, the product label should describe the maximum dose of SD-809 should be 24 mg bid or 18 mg bid in patients with impaired CYP2D6 function (genetic or acquired). The completed TQT study does not evaluate the effect of doses higher than 24 mg on QT. This is a concern because patents may receive treatment with a daily dose of SD-809 that exceeds 48 mg daily. This point was illustrated in the open label study where 28/119 patients were treated with a dose of SD-809 that was higher than 48 mg/day. Patients treated with more than 48 mg of SD-809 are exposed to levels of α- and β-HTBZ (AUC) that exceed the human safety experience of Xenazine.

Bioanalytical Site Inspections

Mass Balance Study SD-809-C-12
((b) (4) study numbers ASX/03 and ASX/04)

Review of EIR of analytical inspection conducted at (b) (4) (b) (4)

Hasan A. Irier, Ph.D. conducted an inspection of the analytical methods and data for the sponsor's Mass Balance Study (b) (4) 113049 (SD-809-C-12) from (b) (4) (b) (4). Based on the inspectional findings and firm's responses, the OSI reviewer concluded, "The data from the audited studies are reliable", and recommended that the analytical portion of the audited studies be accepted for further Agency review.

(b) (4) (b) (4) was the bioanalytical site that conducted the PK analyses for the sponsor's Mass Balance Study (b) (4) 113049 (SD-809-C-12).
The inspection was conducted by ORA Investigator (b) (4) at (b) (4) (b) (4), from (b) (4). The inspection was initiated in support of review of NDA 208082. (b) (4) 113049 (SD-809-C-12)

Xingfang Li, MD submitted the final review recommendation for the bioanalytical site inspection on April 4, 2016. "Following a review of the inspection report, this reviewer recommends that results from the clinical portion of the following study be accepted for further Agency review."

NAI: (b) (4)

Office of Clinical Pharmacology Recommendations:

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the submission (NDA 208082). The OCP conclusions are listed below.

- The proposed dose range of SD-809 (6 mg to 48 mg per day), selected to match the systemic exposure to total (α+β)-HTBZ across the range of approved Xenazine dose, is supported by results of the efficacy trial and is acceptable.
- The sponsor's PK bridging strategy (in ARC-Switch study) to demonstrate comparable bioavailability to justify the reliance on Xenazine for a 505(b)(2) application, for which the primary basis of approval will be a clinical efficacy trial, is acceptable.
- The ability of the sponsor to rely on the Agency's determination that tetrabenazine is safe depends, in part, on how similar SD-809 is to Xenazine with respect to the levels of the active metabolites, and on the condition that there are no new major metabolites unique to SD-809. However, the results of the mass balance study (SD-809-C-12) to compare the metabolism of SD-809 to that of tetrabenazine are inconclusive. OCP recommends the sponsor perform a quantitative assessment of the concentration of circulating SD-809-related metabolites to determine if M1 and M4 are major metabolites in humans dosed with SD-809. The non-clinical and clinical teams will decide whether this could be performed post approval.
- The daily dose of SD-809 should not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.
- The activity (VMAT2 and off-target binding) of the metabolites M1 and M4 should be evaluated. This could be done post approval as a PMR. The off target binding assays were submitted as an amendment to the NDA but will not be reviewed this cycle.

CDTL Comment:

The clinical safety data does not address the effects of M1 and M4 on embryofetal development or carcinogenicity. M4 is a MHM in SD-809 but it is not identified as a MHM in the Xenazine label. However, if M1 and/or M4 were confirmed to be a MHM unique to SD-809, the sponsor may not be able to rely on the Agency's finding of safety for Xenazine.

The unknown potential of M1 to cause fetal malformation would need to be assessed before SD-809 is marketed because of the potential that children may conceived while a parent is taking SD-809. The sponsor proposed submitting data is a piecemeal approach would require an extension of the current review cycle. However, approval would be still be contingent on a favorable outcome at several steps in the process in order to complete the review within an extended review cycle. The sponsor's approach does not provide assurance that the application could be approved, even within an extended first cycle. The available results show that M4 is a MHM, that was not adequately assessed in the sponsor's nonclinical study reports submitted in the NDA. If M1 is confirmed to be a MHM, it is unlikely that the nonclinical bridging studies provide adequate coverage.

5. Clinical Microbiology

Austedo is a solid, oral dose form. The Microbiology assessment was conducted as part of the Drug Substance review fulfilling the requirement. The NDA not include additional Microbiological information.

6. Clinical/Statistical- Efficacy

Xiangmin Zhang, Ph.D. is the statistical reviewer for this application.

Efficacy

Table 23: Studies Conducted by the Sponsor to Support Safety and Effectiveness of SD-809

Table 1: Clinical Studies Conducted with SD-809

Study Number	Design	Subject Population	Subject Character-istics	Treatment	Subjects Exposed to SD-809	Study Status
Phase 3 Study -- Randomized, Double-Blind, Placebo-Controlled, Efficacy and Safety (SD-809 Tablets)						
SD-809-C-15 (First-HD)	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of SD-809	Adult subjects with manifest HD and chorea	Age range 23-74 years 56% male	SD-809 or placebo 6 to 48 mg/day, administered BID, titrated based on chorea control and tolerability	45 subjects	Complete
Phase 3 Study – Open-Label, Long-Term Safety (SD-809 Tablets)						
SD-809-C-16 (ARC-HD)	Open-label, single-arm, long-term safety study of SD-809	Two cohorts of adult subjects with manifest HD and chorea:	Age range 32-75 years 60% male		112 subjects[a] total	Ongoing
		ARC-Rollover: Subjects completed Study SD-809-C-15		SD-809 6 mg/day to 72 mg/day, given in two divided doses, titrated based on chorea control and tolerability	75 subjects	
		ARC-Switch: Subjects on a stable regimen of Xenazine		SD-809 dose comparable to previous Xenazine regimen, titrated based on chorea control and tolerability	37 subjects	

Source: Teva

The sponsor submitted the results of a single controlled efficacy study (SD-809-C-15) as evidence of safety and effectiveness. The sponsor also references Agency's finding of safety and effectiveness for Xenazine as supporting information. On face, the evidence supports the sponsor's effectiveness claim and the application was sufficient to support filing the 505(b)(2) NDA.

At the End of Phase 2 meeting, the sponsor proposed a randomized withdrawal trial design for the pivotal efficacy study. Sometime after the EOP2 meeting, the sponsor changed the design of the pivotal efficacy study to a parallel groups design. The sponsor did not consult with the Division regarding the design of this parallel groups study or request Special Protocol Assessment.

Study SD-809-C-15 -First Time Use of SD-809 ER in HD (First-HD)
Study SD-809-C-15 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of SD-809 in adults with chorea associated with HD. Subjects were randomized 1:1 to receive either SD-809 or placebo. Randomization was stratified by each patient's prior exposure to tetrabenazine.

Patients were titrated to an optimal dose of study drug during an 8-week Titration Phase, followed by a 4-week Maintenance Phase. All patients started on 6 mg of SD-809 or placebo once daily. The dose of study drug was adjusted weekly in increments of 6 mg per day (SD-809 or placebo) during the Titration Phase until there was adequate control of chorea, the subject experienced a protocol defined "clinically significant" adverse event, or the reached maximal allowable dose of 48 mg/day, or 36 mg/day if the patient was receiving a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, and paroxetine). Daily doses of 12 mg or higher were divided b.i.d. given 10 hours apart. The overall treatment period was 12 weeks, including the 8-week Titration Phase and the 4-week Maintenance Phase. The treatment period was followed by a 1-week Washout Period prior to a safety follow-up visit at Week 13. The study sites included 34 sites in the United States and Canada. The first patients enrolled on August 5, 2013, and the last patients completed the study on December 5, 2014.

Protocol Changes
The protocol changes do not meaningfully change the study population or analysis plan (Table 24).

Table 24: Study SD-809-C-15 Protocol Amendments

Table 5. Summary of Protocol Amendments

Amendment	Date	**Major Changes** (Other changes administrative or clarification)
01	09 Apr 2013	• Added additional specifications regarding caregivers • Added that an unscheduled clinic visit should be conducted if a subject requires a dose reduction during the maintenance phase based on a telephone contact • Removed the inclusion criterion requirement for a positive family history of characteristic motor exam features • Added specifications to the inclusion criteria regarding when the Baseline TMC may be <8 • Removed "schizophrenia, or bipolar disorder" from exclusion criterion #1 • Added an appendix with a list of prohibited antipsychotic drugs • Added psychiatric illness to exclusion criterion #5
02	21 Nov 2013	• Revised exclusion criteria to allow subjects on approved doses of citalopram or escitalopram • Increased ECG monitoring for subjects on citalopram or escitalopram • Added an additional safety endpoint, "Number of subjects with on-treatment QTcF values >450ms, >480ms, >500ms" • Added new appendix for citalopram or escitalopram dosing guidance
03	27 Feb 2014	• Revised exclusion criteria to allow subjects with remote tetrabenazine exposure, >6 months prior to Screening • Added stratification by prior exposure to tetrabenazine to subject randomization

Study Populations

Patients in the placebo group had several differences at baseline (Table 25) compared to the group treated with SD-809. The mean age for patients in the placebo group was 52.1 years compared to age 55.4 years for the SD-809 group. Approximately two thirds of the patients in the placebo group were male however; the percentage of men and women in the SD-809 group was nearly equal. The mean baseline total maximal chorea (TMC) score was slightly worse in the placebo group (8.5) compared to the SD-809 group (8.0). Overall, there were few CYP2D6 poor metabolizers in the study population. The number of patients treated with an antidepressant at baseline was slightly higher in the SD-809 group compared to the placebo group.

Table 25: Study SD-809-C-15 Baseline Characteristics

Parameter	SD-809 (N=45)	Placebo (N=45)	Total (N=90)
Mean (SD) Age[a], years	55.4 (10.32)	52.1 (13.36)	53.7 (11.98)
Minimum, Maximum	23, 74	30, 73	23, 74
Gender, n (%)			
Male	22 (48.9)	28 (62.2)	50 (55.6)
Female	23 (51.1)	17 (37.8)	40 (44.4)
Race, n (%)			
Black	0	5 (11.1)	5 (5.6)
White	45 (100)	38 (84.4)	83 (92.2)
Multiple	0	2 (4.4)	2 (2.2)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	45 (100)	45 (100)	90 (100)
Mean (SD) Weight at Screening, kg	74.13 (13.618)	74.11 (15.129)	74.12 (14.312)
Minimum, Maximum	47.2, 99.5	44.9, 100.4	44.9, 100.4
Mean (SD) BMI at Screening, kg/m^2	25.44 (4.282)	25.96 (4.584)	25.70 (4.418)
Minimum, Maximum	17.1, 35.3	15.8, 35.4	15.8, 35.4
Mean (SD) CAG Repeat Length	43.4 (2.69)	44.3 (4.41)	43.9 (3.66)
Minimum, Maximum	40, 53	36, 59	36, 59
CYP2D6 Genotype, n (%)			
Poor Metabolizer	3 (7.1)	2 (4.5)	5 (5.8)
Not Poor Metabolizer[b]	39 (92.9)	42 (95.5)	81 (94.2)
Missing	3	1	4
Mean (SD) Total Maximal Chorea Score at Baseline[c]	12.07 (2.727)	13.24 (3.488)	12.66 (3.169)
Minimum, Maximum	8.0, 19.5	8.5, 21.5	8.0, 21.5
Using Antidepressant at Baseline, n (%)	28 (62.2)	24 (53.3)	52 (57.7)

Source: Tables 14.1.3.1 and 14.3.19.3 and Listings 16.2.4.9.1 and 16.2.4.11
Abbreviations: BMI, body mass index; CAG, cytosine adenine guanine; CYP2D6, cytochrome P450 2D6; SD, standard deviation.
[a] Age = (Date of informed consent - Date of birth)/365.25 rounded down to the nearest integer.
[b] Includes subjects who are intermediate, extensive, and ultra-rapid CYP2D6 metabolizers.
[c] The Total Maximal Chorea score is determined from Item 12 of the Unified Huntington's Disease Rating Scale.

Source: Teva

Key Inclusion Criteria

- A documented expanded cytosine adenine guanine (CAG) repeat (≥37) at or before Screening.
- Total Maximal Chorea Score (TMC) ≥8 at Screening and Baseline.
- Total Functional Capacity (TFC) score ≥5 at Screening
- Patient has a score of ≥11 on the Swallowing Disturbance Questionnaire (SDQ at Screening.
- UPDRS dysarthria score of ≥3 at Screening

Key Exclusion Criteria

- Patient has active suicidal ideation at Screening or Baseline
- Patient has a serious untreated or undertreated psychiatric illness, such as depression, at Screening or Baseline.
- Patient had a score ≥11 on the depression subscale of the Hospital Anxiety and Depression Scale (HADS) at Screening or Baseline
- Patient received tetrabenazine within 6 months prior to Screening
- Patient has history of any of the following suicidal thoughts or behavior at
- Screening or Baseline:
    - Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on the C-SSRS), irrespective of level of ambivalence at the time of suicidal thought
    - Previous preparatory acts or behavior
    - A previous actual, interrupted or aborted suicide attempt
- Patient has evidence of significant renal impairment at Screening, indicated by a creatinine clearance <50 mL/min, as estimated by the Cockroft-Gault formula.
- Patient requires treatment with drugs known to prolong the QT interval (as specified in the protocol).

Analysis Populations

Intent-to-Treat Population

The Intent-to-Treat (ITT) Population was defined as all randomized patients. Patients in the ITT Population were analyzed according to their assigned treatment group (randomized), regardless of the treatment they actually received.

Modified Intent-to-Treat Population

The Modified ITT (mITT) Population was defined as all patients in the ITT Population who received study drug and had at least one post-baseline assessment of the Total Maximal Chorea (TMC) score.

Per-Protocol Population

The Per-Protocol Population was defined as all patients in the mITT Population who were compliant (80% to 105%) with randomized study drug, had an assessment of TMC score at Week 9 or Week 12, and had not taken prohibited concomitant medications.

Safety Population
The Safety Population was defined as all patients who were administered any study drug. Patients in the Safety Population were analyzed according to the treatment they received.

Primary Efficacy Endpoint
The primary efficacy endpoint was the change in TMC score from Baseline (defined for each patient as the mean of values from the Screening and Day 0 visits) to Maintenance therapy (defined for each patient as the mean of values from the Week 9 and Week 12 visits). The TMC is a single item of the Motor subscale from the Unified Huntington's Disease Rating Scale (UHDRS). The TMC scores score can range from 0 to a maximum score of 28.

The primary endpoint was analyzed for the mITT Population using an analysis of covariance (ANCOVA) model with the change from Baseline in TMC as the dependent variable, treatment group as a factor, and the Baseline TMC score as a covariate.

Key Secondary Efficacy Endpoints
The following were the key secondary efficacy endpoints to be analyzed using a hierarchical testing procedure:

1. The proportion of patients who are a treatment success at the end of therapy, based on the Patient Global Impression of Change (PGIC)
2. The proportion of patients who are a treatment success at the end of therapy, based on the Clinical Global Impression of Change (CGIC)
3. Change in the SF-36 physical functioning score (based on items 3a to 3j) from Baseline to Week 12
4. Change in the Berg Balance Test (BBT) score from Baseline to Week 12

The planned analyses of the PGIC and CGIC were based on the mITT population using Pearson's chi-square test. The secondary endpoints of SF-36 Physical Functioning score and BBT score were analyzed on the mITT population using ANCOVA models with treatment as a factor and endpoint specific baseline as the covariate.

Other Secondary Endpoints
The following additional efficacy endpoints were:

- The change in total motor score (TMS) from the UHDRS from Baseline (defined for each patient as the mean of values from the Screening and Day 0 visits) to maintenance therapy (defined for each patient as the mean of values from the Week 9 and Week 12 visits).
- The percent change in TMC from Baseline (defined for each patient as the mean of values from the Screening and Day 0 visits) to maintenance therapy (defined for each patient as the mean of values from the Week 9 and Week 12 visits).
- The change in TMC from Baseline (defined for each patient as the mean of values from the Screening and Day 0 visits) to maintenance therapy (defined for each patient as the mean of values from the Week 9 and Week 12 visits) based upon the video recordings (i.e., independent rating of chorea).

CDTL Comment

Although the TMS is not a key secondary endpoint, and it is not included in the sponsor's hierarchy of endpoints, the sponsor argues that the finding is statistically significant based on a post hoc application of the Bonferroni correction for multiple comparisons. However, the TMS includes the primary endpoint, the TMC in its entirety. Therefore, the TMS is likely to be positive if the TMC is statistically superior to placebo. The TMS has several other limitations. The TMS includes items that rate eye movements, tongue protrusion (motor impersistence/chorea) and the Lauria (palm-fist-side) test. These items in the TMS are not shown to be clinically meaningful. The TMS may only recapitulate the findings of the TMC, or the results may be driven entirely by the TMC (no analysis provided with the TMC removed from the TMS), and the clinical meaning of the items in the TMS minus the TMC is uncertain, as described.

Efficacy Results

Table 26: Study SD-809-C-15 Efficacy Results

Endpoint	SD-809 (N=45)	Placebo (N=45)	Difference (95% CI) (SD-809 – Placebo)	p-value
Primary Endpoint				
Total Maximal Chorea Score[a], LS Mean (SD)	-4.42 (2.953)	-1.93 (2.666)	-2.49 (-3.69, -1.29)	<0.0001
Key Secondary Endpoints				
PGIC Treatment Success[b], n (%)	23 (51.1)	9 (20.0)	31.1[c] (12.4, 49.8)	0.0020
CGIC Treatment Success[b], n (%)	19 (42.2)	6 (13.3)	28.9[c] (11.4, 46.4)	0.0022
SF-36 Physical Functioning[d], LS Mean (SD)	0.74 (9.773)	-3.61 (9.669)	4.34 (0.41, 8.27)	0.0308
Berg Balance Test[d], LS Mean (SD)	2.2 (3.47)	1.3 (4.04)	1.0 (-0.3, 2.3)	0.1415
Additional Prespecified Endpoints				
Change in UHDRS Total Motor Score[a]	-7.35 (6.344)	-3.36 (5.469)	-3.99 (-6.52, -1.46)	0.0023
Percentage Change in Total Maximal Chorea Score[a]	-36.97 (25.704)	-16.17 (19.646)	-20.80 (-30.47, -11.13)	<0.0001
Change in Total Maximal Chorea Score Based on Video Rating[a]	-2.3 (2.55)	-0.4 (2.54)	-1.9 (-3.0, -0.9)	0.0005

Abbreviations: CGIC, Clinical Global Impression of Change; CI, confidence interval; LS, least squares; PGIC, Patient Global Impression of Change; SD, standard deviation; UHDRS, Unified Huntington's Disease Rating Scale.
[a] Change from Baseline to maintenance therapy. Baseline was defined as the mean of values from Screening and Day 0. Maintenance therapy was defined as the mean of values from the Week 9 and Week 12 visits.
[b] Treatment success at Week 12 defined as "much improved" or "very much improved".
[c] Difference in percentages of treatment success.
[d] Change from Baseline to Week 12.

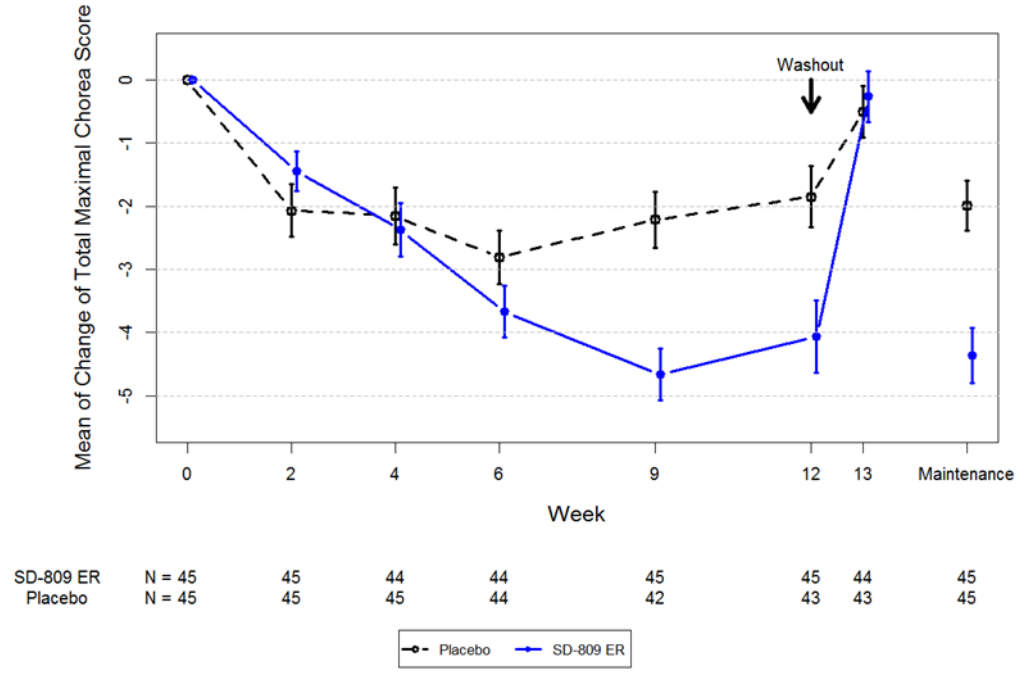
Source: Teva

The result for the primary efficacy outcome is statistically significant in favor of SD-809 over placebo (Table 26). The p-values for the change in TMC score and the patient and investigator global rating are very persuasive. The clinical meaning of changes on the TMC score is not established. The results of the global or functional endpoints are helpful in supporting the clinical meaning of a benefit shown for the TMC score.

Dr. Zhang independently performed ANCOVA analyses on PGIC, CGIC and BBT without using imputation and on SF-36 physical functioning score carrying the last available observations for patients missing Week 12 measurements. These alternate approaches for dealing with missing data did not indicate different statistical conclusions for these secondary endpoints.

The Percent change in the TMC score and the Blinded rating of the TMC are derivatives of the primary endpoint and do not provide additional information about the effectiveness of SD-809.

Figure 5: Study SD-809-C-15 mean (± standard error) of change from Baseline in TMC score by week and treatment



Source: FDA Statistical Reviewer

The effect of SD-809 on the TMC score peaks at week 9, one week after starting maintenance phase of the study (Figure 5). The effect on the TMC score is quickly lost after SD-809 is discontinued at week 12. By week 13, TMC scores are nearly back to baseline values. A similar effect was reported following withdrawal of tetrabenazine in patients with HD (Frank et al., 2008).

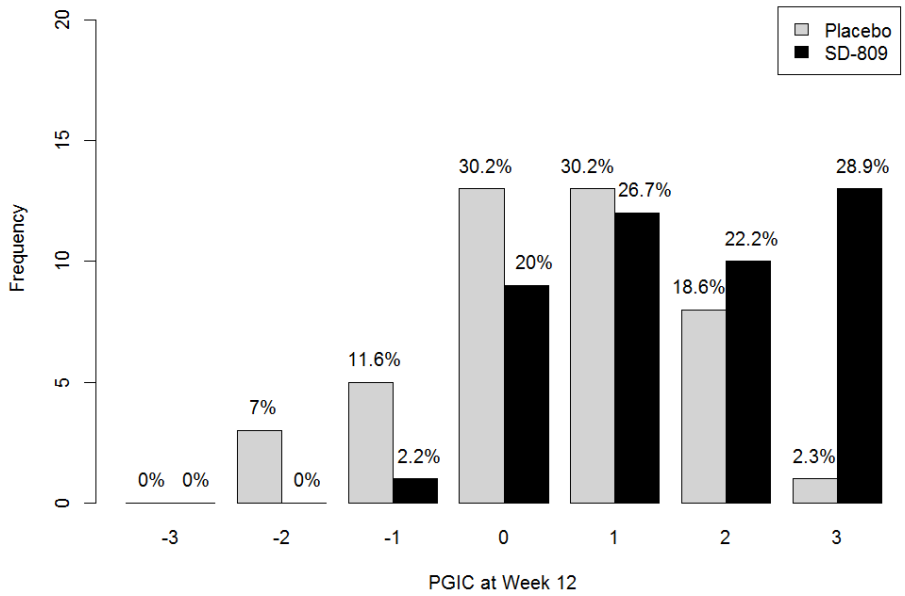
Global Rating Scales (from the sample Case Report Form)

The PGIC used in the study was a single-item questionnaire that asks the patient to assess their overall HD symptoms at specific visits after initiating therapy by using a 7-point Likert Scale, with responses ranging from very much worse (-3) to very much improved (+3) to assess overall response to therapy. Patients were asked to response to the question, "With respect to the patient's overall Huntington's disease symptoms, how would you describe the patient compared to immediately before starting study medication?"

The CGIC was also a 7-point Likert Scale, with responses ranging from very much worse (-3) to very much improved (+3) to assess overall response to therapy. Clinicians were asked to response respond to the question, "With respect to the patient's overall Huntington's disease symptoms, how would you describe the patient compared to immediately before starting study medication?"

The potential limitation of the PGIC and the CGIC are that they ask patients and investigators to rate the patient's HD symptoms in comparison to their baseline (before starting study medication). It asks patients/caregivers and investigators to recall past performance which is susceptible recall bias, and it also may prompt investigators to look at baseline efficacy measures or ratings from previous visits, also potentially introducing bias.

Figure 6: Study SD-809-C-15 Distribution of Patient Global Impression of Change at Week 12



-3: Very Much Worse; -2: Much Worse; -1: Minimally Worse; 0: Not Change;
1: Minimally Improved; 2: Much Improved; 3: Very Much Improved.
Source: FDA Statistical Reviewer

The proportion of patients who responded as "Much Improved" or "Very Much Improved" was considered treatment responders. The proportion of responders on the PGIC and CGIC were statistically significant favoring treatment with SD-809 over placebo (Figures 6, 7, and Table 26).

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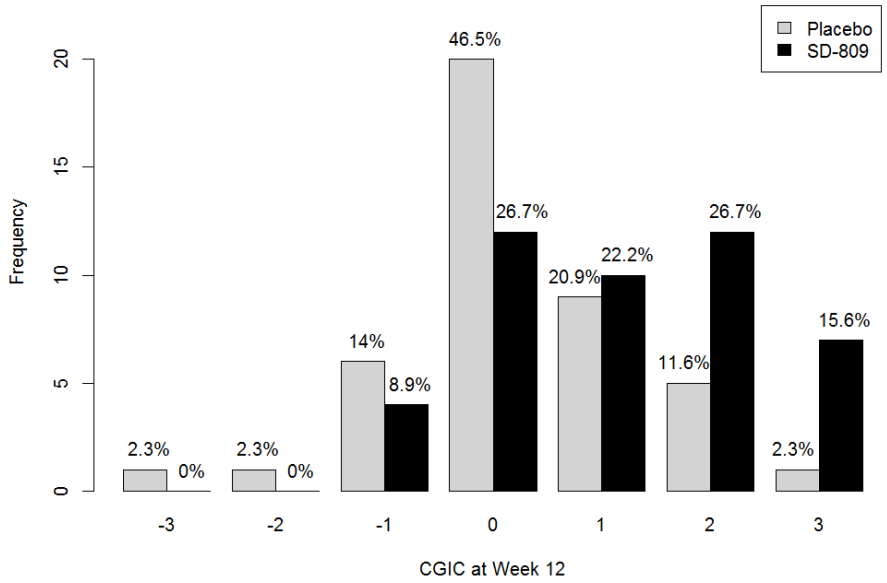
Figure 7: Distribution of Clinical Global Impression of Change at Week 12



-3: Very Much Worse; -2: Much Worse; -1: Minimally Worse; 0: Not Change;
1: Minimally Improved; 2: Much Improved; 3: Very Much Improved.
Source: FDA Statistical Reviewer

Subgroup Analyses

The biometrics reviewer found no substantial differences in the analysis of the TMC, PGIC or CGIC for clinically important subgroups including gender or age. There were too few non-caucasian trial participants to comment on an effect of race. Similarly, the effect on Region on the study results was not assessed because all but 7 patients in the trial came from sites in the US. These 7 patients were enrolled at one of 3 centers in Canada.

Recommendations and Conclusions of Biometrics Reviewer:

Study SD-809-C-15 provided efficacy evidence that Austedo is efficacious as a treatment of chorea associated with Huntington's disease: Austedo tablet is statistically better than placebo in terms of change from Baseline to maintenance in total maximal chorea score.

Based on the statistical evidences from Study SD-809-C-15, the reviewer concluded that Austedo extended release tablet is superior to placebo in treating chorea associated with Huntington's disease.

SF-36

The sponsor only selected a subscale of the SF-36 as a Key secondary endpoint, The Physical Functioning items.

SF-36 Physical Functioning Score Items

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

1 = Yes, limited a lot 2 = Yes, limited a little, 3 = No, not limited at all

3a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
3b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
3c. Lifting or carrying groceries
3d. Climbing several flights of stairs
3e. Climbing one flight of stairs
3f. Bending, kneeling, or stooping
3g. Walking more than a mile
3h. Walking several hundred yards
3i. Walking one hundred yards
3j. Bathing or dressing yourself

Table 27: SF-36 Physical Functioning Score: Change From Baseline to Week 12 (ITT population identical to mITT population)

Table 14. SF-36 Physical Functioning Score: Change from Baseline to Week 12 (Intent-to-Treat Population; N=90)

	Change in SF-36 Physical Functioning Score from Baseline to Week 12		
Statistic	SD-809 (N=45)	Placebo (N=45)	Difference in Means (SD-809 - Placebo) and 95% CI[a]
n	45	43	
Least Squares Mean[b] (SD)	0.74 (9.773)	-3.61 (9.669)	4.34 (0.41, 8.27)
Minimum, Maximum	-29.5, 27.4	-42.1, 12.6	--
95% CI for Mean[a]	(-3.08, 2.80)	(-5.67, 0.28)	--
p-value[b]	--	--	0.0308
p-value[c]	--	--	0.0308

Source: Table 14.2.4.2 and Listing 16.2.6.3.
Abbreviations: CI, confidence interval; SD, standard deviation; SF-36, Short Form 36 Health Survey.
Notes: Increases in SF-36 score indicate reduced disability.
[a] Confidence interval based on the t-distribution.
[b] Least squares means and p-value from a two-sided test of the effect of treatment from an analysis of covariance model with a term for treatment and the Baseline score as a covariate.
[c] p-value from the test of a treatment effect for maintenance therapy relative to Baseline using a linear mixed model repeated measures approach with terms for treatment and week as categorical variables, the treatment by week interaction, and the Baseline value as a covariate, and assuming an unstructured covariance matrix.

Source: Teva

Using the ANCOVA model, the LSmean score different for the change in SF-36 scores from baseline to week 12 is statistically significant in favor of SD-809 in the mITT population (Table 27). However, table 28 shows the actual mean scores at baseline and week 12. The baseline mean Physical Functioning score is higher (better) in the SD-809 group compared to the placebo group. There is only a very small change in the mean Physical Functioning scores in the SD-809 group from baseline to week 12 compared to -3.3 point decline in SF-36 score the placebo group. Given the relative short duration of the study, a marked decline in physical function is not expected to occur over 12 weeks even in untreated patients with HD. Almost all of the difference between the two treatment groups lies in the change from baseline to week 12 in the placebo group, suggesting SD-809 is not associated with improved Physical Functioning. None of the results for remaining SF-36 domains shows that SD-809 is superior to placebo (Table 29). The Aggregate Physical Component score also does not show there is a significant advantage of SD-809 compared to placebo (Table 30).

Table 28: SF-36 Physical Functioning Score: Change from Baseline to Week 12 (ITT population identical to mITT population)

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Protocol Number: SD-809-C-15

Table 14.2.11.1
SF-36 SCORE
mITT POPULATION

			SD-809 (N=45)		Placebo (N=45)			
Subscale	Visit	Statistic	Value	Change from Day 0	Value	Change from Day 0	Difference in Mean Change from Day 0 (SD-809 - Placebo) and 95% CI	p-value(1)
Mental Health	Day 0	n	45		45			
		Mean	53.14		51.01			
		Median	55.64		50.01			
		SD	10.506		9.457			
		Min - Max	19.0 - 64.1		35.9 - 64.1			
	Week 12	n	45	45	43	43		
		Mean	54.58	1.44	52.04	1.64	-0.20 (-4.19, 3.79)	0.9216
		Median	55.64	0.00	52.82	0.00		
		SD	8.991	9.931	8.229	8.825		
		Min - Max	27.5 - 64.1	-19.7 - 39.4	35.9 - 64.1	-11.3 - 22.5		
Physical Functioning	Day 0	n	45		45			
		Mean	47.54		43.24			
		Median	50.72		46.51			
		SD	10.755		10.247			
		Min - Max	17.0 - 57.0		19.2 - 57.0			
	Week 12	n	45	45	43	43		
		Mean	47.40	-0.14	39.90	-2.69	2.55 (-1.57, 6.67)	0.2218
		Median	50.72	0.00	44.41	-2.10		
		SD	10.305	9.773	11.972	9.669		
		Min - Max	21.3 - 57.0	-29.5 - 27.4	14.9 - 57.0	-42.1 - 12.6		

Program Name: t2_sf36.sas Creation date, time: 11MAR2015:11:39
Source: Listing 16.2.6.3
(1) p-value is from the two-sample t-test, testing for a difference in mean change from Day 0 between treatments.

Table 29: SF-36 Score Subscale Scores ITT Population Change from Baseline to Week 12

Subscale	Difference in Least Squares Mean Change from Day 0 SD-809 – Placebo (95% C.I.)	p-value
Bodily Pain	0.30 (-2.88, 3.47)	0.8518
General Health	0.90 (-2.79, 4.59)	0.6297
Mental Health	1.37 (-1.87, 4.60)	0.4035
Physical Functioning	4.34 (0.41, 8.27)	0.0308
Role Emotional	-2.88 (-6.57, 0.80)	0.1238
Role Physical	2.79 (-1.52, 7.10)	0.2017
Social Functioning	2.80 (-0.84, 6.44)	0.1301
Vitality	2.35 (-0.68, 5.37)	0.1268

Confidence interval based on the t-distribution.
Least squares mean and p-value from a two-sided test of the effect of treatment from an analysis of covariance model with a term for treatment and the baseline score as a covariate.
Source : Adapted from Teva's tables

Table 30: The SF-36 Aggregate Physical Component Score: Change from Baseline to Week 12

Table 14.2.11.4
SUMMARY OF SF-36 SCORE USING ANALYSIS OF COVARIANCE (ANCOVA) MODEL
mITT POPULATION

			SD-809 (N=45)		Placebo (N=45)		
Subscale	Visit	Statistic	Value	Change from Day 0	Value	Change from Day 0	Difference in Mean Change from Day 0 (SD-809 - Placebo) and 95% CI
Aggregate Physical Component Score	Day 0	n	45		45		
		Mean	49.12		45.06		
		Median	52.13		46.10		
		SD	9.644		8.203		
		Min - Max	23.9 - 61.5		26.7 - 61.6		
		95% CI for Mean (1)	(46.22, 52.01)		(42.59, 47.52)		
	Week 12	n	45	45	43	43	
		Mean	49.70	0.58	43.56	-0.79	1.37 (-1.72, 4.46)
		Least Squares Mean (2)	47.99	1.20	45.35	-1.44	2.64 (-0.42, 5.69)
		Median	50.98	0.82	44.73	-1.35	
		SD	8.254	7.367	10.512	7.201	
		Min - Max	25.5 - 64.8	-15.9 - 19.8	23.1 - 60.9	-13.6 - 15.6	
		95% CI for Mean (1)	(47.22, 52.18)	(-1.63, 2.79)	(40.32, 46.79)	(-3.01, 1.43)	
		p-value (2)					0.0898

Program Name: t2_sf36_n.sas Creation date, time: 11MAR2015:11:40
Source: Listing 16.2.6.3
(1) Confidence interval based on the t-distribution.
(2) Least squares mean and p-value from a two-sided test of the effect of treatment from an analysis of covariance model with a term for treatment and the baseline score as a covariate.

SF-36 Role Physical Score

The SF-36 has several subscales that make up the larger Aggregate Physical Component Score (Physical Health), which included information from the Role-Health, General Health and Bodily Pain scales (Figure 9).

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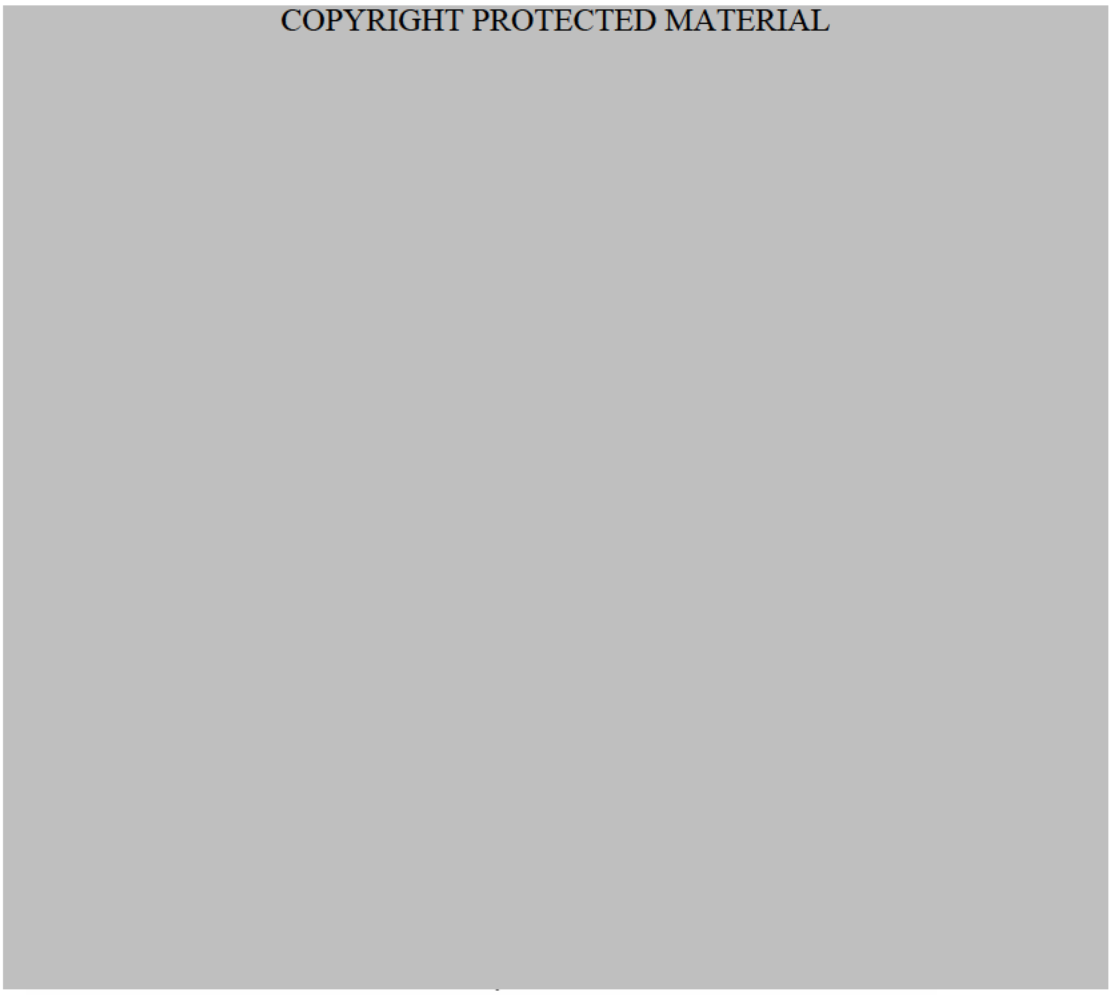
Figure 9: Schematic for Scoring for the SF-36

eight SF-36 scales. Each item is used in scoring only one scale.



Ware JE, SF-36 Health Survey Update http://www.sf-36.org/announcements/SF-36_Pre-Publication_Version.pdf. Accessed 4/25/2016.

Role-Physical Items of the SF-36

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

1 = All of the time
2 = Most of the time
3 = Some of the time
4 = A little of the time
5 = None of the time

4a. Cut down the amount of time you spent on work or other activities
4b. Accomplished less than you would like
4c. Were limited in the kind of work or other activities

4d. Had difficulty performing the work or other activities (for example, it took extra effort)

The results for the Role-Physical Score did not show SD-809 had an advantage over placebo. The results of the Role Physical and General Health scales are not consistent with the positive outcome on the Physical Functioning Scale suggesting this finding cannot be interpreted as showing clear benefit.

CDTL Efficacy Conclusion
I agree with the conclusions of Drs. Bergmann and Zhang, the results of study SD-809-C-015 compared the effect of SD-809 (up to 48 mg) to placebo for reducing the Total Maximal Chorea (TMC) score. The LSmean treatment difference (SD-809 minus placebo) in the pivotal efficacy shows a statically significant reduction in the TMC (primary endpoint) score in HD patients treated with SD-809 of -2.49 ($P<0.0001$) compared to placebo. The benefit to patients is supported by the observed statistically significant improvement of SD-809 compared to placebo and the patient CGI and physician rated CGI. The effect of the total maximal chorea score is similar to the reduction seen with Xenazine (-3.5) (Huntington Study, 2006). An optimal study design would have included a larger sample size and evaluation of multiple doses of SD-809.

The results of SF-36 are not clearly interpretable as a positive outcome. Failure to show superiority on other performance domains of the SF-36 (Role Physical) and the Aggregate Physical Component score indicate that the finding on the Physical Function domain is not clinically meaningful. The sponsor conducted an analysis of the Physical Function domain using a two-sample t-test, testing for a difference in mean change from Day 0 between treatments which failed to show a significant benefit of SD-809 over placebo ($p=0.22$) suggesting the result for Physical Functioning is not robust.

The evidence of effectiveness observed in study SD-809-C-15, and support evidence from the Agency's finding of effectiveness for the reference drug (Xenazine), meets the statutory requirement showing SD-809 is effective for treating chorea associated with HD.

5. Safety

The safety of SD-809 relies in part on the Agency's finding of safety for the RLD (Xenazine), the controlled safety experience from study SD-809-C-15, and the (uncontrolled) long-term, open label study SD-809-C016. The adverse event tables in this review were created from the sponsor's datasets and they are identical to those sponsor's tables adverse events in the study report.

Adequacy of Drug Exposure

During the EOP2 meeting, Auspex projected, the NDA would include at least100 patient exposed to SD-809, and at least 50 patients would have 6 months exposure or more. In the pre-meeting responses, the Division clearly explained that "The adequacy of the safety database and the ability to rely on the Agency's determination that tetrabenazine is safe will depend on how similar SD-809 ER is to Xenazine with respect to the levels of the active metabolites and on the condition that there are no new significant metabolites that are unique to SD-809." The patient exposure experience included in the NDA met the sponsor projection at the EOP2 meeting, which is adequate.

Table 31: Exposure to SD-809 Listed in the 120 Day Safety Update

Study	Any SD-809 Exposure	≥8 Weeks	≥15 Weeks	≥28 Weeks	≥52 Weeks
Phase 3 (Subjects With Chorea Associated With Huntington's Disease)					
First-HD	45	45	--	--	--
ARC-HD (120 day update)[a]					
ARC-Rollover	82	79	71	33	8
ARC-Switch	37	36	32	19	1
Total HD Subjects Exposure[b]	**121**	**119**	**111**	**65**	**16**

Source: Teva

Table 32: Exposure to SD-809 Listed in the 120 Day Safety Update

	<180 days N	≥180 and <365 days N	≥365 days N	Total N
SD-809	34	71	16	121

Source: CDTL

The longest single patient exposure to SD-809 was 557 days.

Disposition Study SD-809-15

There were 33 patients who were listed as Screen Failures. Three randomized patients who did not complete the study are listed in Table 33 with the reasons they discontinued. Ninety patients completed Study SD-809-15, 45 in the SD-809 group and 45 in the placebo group.

Table 33: Study SD-809-15 Non-Completers

USUBJID	AGE	SEX	ARM	Completed	Reason Withdrew	TRT DUR Days
SD809C15-037-3242	56	M	Placebo	N	Adverse event agitation with recent SAEs of chronic cholecystitis and agitated depression	41
SD809C15-040-3262	56	F	Placebo	N	Physician decision lack of efficacy	42

SD809C15-104-3441	61	F	SD-809 ER	N	Adverse event atrial fibrillation	81

Source: CDTL

Deaths

There were no patient deaths in Study SD-809-C-15.

Study SD-809-15 Serious Nonfatal Adverse Events

Two patients reported three serious, nonfatal adverse events (Table 34). Patient SD809-C15-104-3441also withdrew from the study before completion because of an adverse event. Agitated depression was the primary reason patient SD809C15-104-3441withdrew from the study, and it was the only serious adverse event that seemed related to SD-809.

Table 34: Study SD-809-15 Serious Nonfatal Adverse Events

USUBJID	Age	Sex	TRT01A	AEDECOD	ASTDY	AEOUT
SD809C15-104-3441	61	F	SD-809 ER	Cholecystitis chronic Agitated depression	69 74	RECOVERED RECOVERED
SD809C15-119-3462	72	F	Placebo	Chronic obstructive pulmonary disease	57	RECOVERED

Source: CDTL

Study SD-809-C-015 Adverse Reactions

Somnolence was the most common adverse reaction in the SD-809 group compared to placebo (Table 35). Diarrhea was only reported in the SD-809 group and it does not appear in the adverse event tables in the Xenazine label.

Table 35: Study SD-809-15 Treatment-Emergent Adverse Reactions Occurring in ≥4% and Greater in SD-809 (Safety Population)

	SD-809 ER (N = 45)		Placebo (N = 45)	
PT	N	(%)	N	(%)
Somnolence	5	11	2	4
Diarrhoea	4	9	0	0
Fatigue	4	9	2	4
Dry mouth	4	9	3	7
Urinary tract infection	3	7	1	2
Insomnia	3	7	2	4
Alanine aminotransferase increased	2	4	0	0
Aspartate aminotransferase increased	2	4	0	0
Anxiety	2	4	1	2

Back pain	2	4	1	2
Constipation	2	4	1	2
Contusion	2	4	1	2

4% = 2 patients
Source: CDTL

Somnolence and/or fatigue were more likely to be reported as an adverse event during the Titration Phase (Table 36) of the study. No patient in study SD-809-C-015 withdrew because of complaints related to somnolence suggesting somnolence may lessen with continued use.

Table 36: Study SD-809-15 Treatment Emergent Adverse Events ≥ 4% and Greater in SD-809 by Treatment Phase (Epoch)

EPOCH	AEBODSYS	AEDECOD	SD-809 (N=45) %	Placebo (N=45) %
Titration	Nervous system disorders	Somnolence	11	4
Titration	Gastrointestinal disorders	Diarrhoea	9	0
Titration	Gastrointestinal disorders	Dry mouth	9	7
Titration	General disorders and administration site conditions	Fatigue	7	4
Titration	Injury, poisoning and procedural complications	Contusion	4	2
Maintenance	Gastrointestinal disorders	Constipation	4	0
Maintenance	Infections and infestations	Urinary tract infection	4	0
Maintenance	Psychiatric disorders	Insomnia	4	0

4% = 2 patients
Source :CDTL

When the terms related to somnolence are combined (Table 37), somnolence is shown to be substantially more frequent in the SD-809 treated group compared to placebo. Some of the patients may have reported more than one term related to somnolence.

Table 37: Study SD-809-15 Terms Related to Somnolence

	SD-809 ER (N = 45)		*Placebo (N = 45)*	
PT	***Number of patients***	***Proportion (%)***	***Number of patients***	***Proportion (%)***
Somnolence	5	11	2	4
Fatigue	4	9	2	4
Dizziness	3	7	4	9
Hangover	1	2	0	0
Total	13	29	8	18

Source: CDTL

Combining terms related to depression does not change the proportion of patients reporting depression as an adverse event (Table 38).

Table 38: Study SD-809-15 Terms Related to Depression

	SD-809 ER (N = 45)		*Placebo (N = 45)*	
PT	***Number of patients***	***Proportion (%)***	***Number of patients***	***Proportion (%)***
Depression	1	2	3	7
Agitated depression	1	2	0	0

Suicidality Assessment

Table 39: Study SD-809-15 Suicidality Reported as an Adverse Event

USUBJID	**SAFFL**	**TRT**	**AEDECOD**	**EPOCH**	**DOSE mg**
SD809C15-104-3441	Y	SD-809 ER	Suicidal ideation	Maintenance	48

Columbia Suicide Severity Rating Scale (C-SSRS)
One patient in the placebo) answered affirmatively to question 1 of the C-SSRS ("wish to be dead") at the Week 12 visit. This patient was treated for depression (mirtazapine) at Baseline, then experienced AEs during the trial including worsening depression, insomnia, and akathisia. This patient did not report any AEs of suicidal ideation or provide an affirmative response to any question on the C-SSRS at any other visit.

CDTL Comment:
Somnolence is the most common adverse event reported for Xenazine and SD-809. The proportion of patients reporting adverse event terms related to Somnolence in study SD809-C-015 may be counted twice if they reported more than one term.

Depression is frequent in patients with HD with reported estimates as high as 33% to 60% of patients with manifest HD. The risk for suicide is also increased. Multiple studies provided estimates of the risk of suicide in individuals with HD and those at risk. The suicide rate in the US general population is approximately 1.5%. Estimates in patients with HD vary from 5.7% to greater than 20%depending on the stage of illness and country. Suicide is the third most common cause of death in patients with HD after pneumonia and cardiovascular disease (Craufurd, 2014). Study SD-809-C-015 was not designed to look for differences in the incidence of suicide and depression. The small sample size and short duration of observation also limit the ability to draw conclusions about the risk of depression and suicide associated with SD-809.

Open label Study SD-809-C-16

Study SD-809-C-16 was an open label study that included patients who successfully completed participation in Study SD-809-C-15, or were receiving treatment with Xenazine and remained on a stable for ≥8 weeks before Screening.

Study SD-809-C-16
Alternatives for **R**educing **C**horea in **H**untington **D**isease (ARC-HD) was an open-label, long-term safety study of SD-809 in patients with chorea associated with HD. The study is ongoing with 112 patients enrolled by the NDA cutoff in 37 sites in the US, Canada, and Australia.

The study population was divided into two-cohorts:

- Rollover Cohort (N=82) had successfully completed study SD-809- C-15 (First-HD), including a 1-week washout.
- Switch Cohort (N=37) switched overnight from stable dosing (≥8 weeks) with Xenazine to SD-809. The Switch analysis is completed but patients could elect to continue open label treatment.

Study Design of SD-809-C-16
Rollover patients entered the open-label study off of SD-809 or Xenazine. SD-809 was titrated over the initial 8 weeks to a tolerated dose that reduced chorea. Patients in the Switch Cohort were converted overnight from Xenazine to an SD-809 dosing regimen predicted to provide comparable systemic exposure (AUC) to total (α+β)-HTBZ relative to the patient's prior Xenazine dose. The SD-809 dose in the Switch cohort was approximately half of the stable daily Xenazine dose in mg/day, divided b.i.d. The maximum allowed daily dose of SD-809 in study SD-809-C-16 was initially 48 mg, except in patients taking a strong CYP2D6 inhibitor Patients receiving a strong CYP2D6 inhibitor were limited to a maximum daily dose of SD-809 of 36 mg (18 mg bid).

However, in a subsequent protocol amendment (version 2), the maximum allowed daily dose of SD-809 was increased to 72 mg daily (36 mg bid.), only for patients not taking a CYP2D6 inhibitor.

The amendment increasing the maximum daily dose of SD-809 to 72 mg is more than half (50 mg) of the maximum recommended daily dose of Xenazine (100 mg). Exposure to SD-809 metabolites is no longer limited by constraining the dose of SD-809 the half of the maximum dose of Xenazine.

Given the uncertainty of whether M1 and M4 are major human metabolites with levels that exceed those associated with the RLD (Xenazine). A daily dose of 72 mg of SD-809 per day may produce levels of M1 and M4 that significantly exceed the levels observed for patients treated with the maximum recommended daily dose of Xenazine (100 mg/day). In the 120-Day Update Exposure datasets, there were 28 patients treated with a daily dose of SD-809 that was more than 48 mg/day, of these, 17 patients received 60 mg or more daily, and 12 of these patient were treated with 72 mg/day, at some time during the ongoing open label study.

Disposition Study SD-809-C-016

One hundred thirty six patients were screened, 14 were excluded and 122 were enrolled. One hundred nineteen patients were included in the Safety Population but 11 of these patients discontinued prematurely for reasons listed in table 40. The visit cut-off dates were November 7, 2014 for the NDA submission and March 31, 2015 for the Safety Update.

Table 40: Study SD-809-C-016 Discontinuations Including 120 Day Update

Reason	N
Adverse Event	6
Lost To Follow-Up	1
Non-Compliance With Study Drug	1
Physician Decision	1
Protocol Deviation	1
Withdrawal By Patient	1

Four of the six patients who discontinued for an adverse event cited depression as the adverse event leading to withdrawal (Table 41).

Table 41: Study SD-809-C-016 Discontinuations for Adverse Event Including 120 Day Update

STUDYID	USUBJID	AETERM	ASTDY	TRTEMFL	DOSE
SD-809-C-16	SD809C15-007-3043	Suicidal ideation	250	Y	48
SD-809-C-16	SD809C15-027-3161	Major depression	132	Y	36
SD-809-C-16	SD809C15-083-3365	Depression	102	Y	42
SD-809-C-16	SD809C15-083-3369	Anxiety	153	Y	0
SD-809-C-16	SD809C15-333-3561	Depression	256	Y	36
SD-809-C-16	SD809C16-342-7822	Failure to thrive	149	Y	72

Deaths in Study SD-809-C-16

There were no deaths reported during the study

Study 016 Serious Nonfatal Adverse Events (Table 41)

Two patients experienced serious adverse events related to depression. In the remainder of the patients with a nonfatal serious adverse event, the event appeared to be related to medical complications of advanced HD or unrelated illness.

Table 42: Study 016 With 120 day Update Serious Nonfatal Adverse Events

USUBJID	STUDYID	Preferred term	Study Day	Outcome	Dose mg	Age	Sex
SD809C15-027-3161	SD-809-C-16	Major depression	132	Resolved With Sequelae	36	58	M
		Suicidal ideation	132	Resolved	36		
		Anxiety	132	Resolved With Sequelae	36		
SD809C15-028-3582	SD-809-C-16	Dehydration	158	Resolved	42	64	F
		Encephalopathy	158	Resolved	42		
SD809C15-028-3583	SD-809-C-16	Depression suicidal	148	Resolved	48	57	F
SD809C16-083-	SD-809-C-16	Pneumonia	208	Resolved	48	67	M

7323							
SD809C16-093-7841	SD-809-C-16	Dehydration	23	Resolved	24	46	F
SD809C15-007-3047	SD-809-C-16	Penile cancer	100	Resolved	54	60	M
SD809C15-024-3121	SD-809-C-16	Chest discomfort	193	Resolved	36	69	F
SD809C15-031-3627	SD-809-C-16	Hip fracture	106		12	69	F
SD809C15-083-3373	SD-809-C-16	Upper limb fracture MVA	24	Unknown	12	37	F
SD809C16-342-7822	SD-809-C-16	Failure to thrive	149	Not Resolved	72	40	F

Falls were the most frequently reported adverse reaction (Table 43) in the open label study however, in the controlled study (SD-809-C-015) falls were reported in 7% of patients treated with SD-809 compared to 20% of patients in the placebo group.

The proportion of patients reporting somnolence as an adverse event is similar to the proportion observed in the controlled study. Somnolence was more frequent in the Switch cohort (Table 44) suggesting that rapid conversion to SD-809 is associated with a greater risk for somnolence. Diarrhea was frequent in the controlled study and in the open label study, which seems to be unique to SD-809 compared the Xenazine where only one patient reported diarrhea in the pivotal clinical study according to the Xenazine label.

Table 43: Study 016 with 120 Day Update Adverse Reactions Total ≥ 4% SD-809 by Cohort

AEBODSYS	AEDECOD	Rollover N=82	Rollover %	Switch N=37	Switch %	Total N=119	Total %
Injury, poisoning and procedural complications	Fall	15	18	9	24	24	20
Nervous system disorders	Somnolence	10	12	11	30	21	18
Psychiatric disorders	Depression	18	22	2	5	20	17
Psychiatric disorders	Insomnia	12	15	3	8	15	13
Psychiatric disorders	Anxiety	10	12	4	11	14	12
Gastrointestinal disorders	Diarrhoea	6	7	4	11	10	8
General disorders and administration site conditions	Irritability	8	10	2	5	10	8
Gastrointestinal	Constipation	4	5	3	8	7	6

disorders							
Infections and infestations	Nasopharyngitis	4	5	3	8	7	6
Psychiatric disorders	Suicidal ideation	4	5	2	5	6	5
Nervous system disorders	Akathisia	4	5	2	5	6	5
Gastrointestinal disorders	Dry mouth	4	5	2	5	6	5
Gastrointestinal disorders	Nausea	5	6	1	3	6	5
General disorders and administration site conditions	Fatigue	5	6	1	3	6	5
Investigations	Weight decreased	5	6	1	3	6	5
Gastrointestinal disorders	Dysphagia	3	4	2	5	5	4
Gastrointestinal disorders	Vomiting	4	5	1	3	5	4
Injury, poisoning and procedural complications	Laceration	1	1	4	11	5	4
Infections and infestations	Urinary tract infection	4	5	1	3	5	4
Renal and urinary disorders	Pollakiuria	4	5	1	3	5	4

Table 44: Study 016 with 120 Day Update Somnolence Related Terms Adverse Events by Cohort and Total

AEBODSYS	AEDECOD	Rollover N=82	Rollover %	Switch N=37	Switch %	Total N=119	Total %
Nervous system disorders	Somnolence	10	12	11	30	21	18
General disorders and administration site conditions	Fatigue	5	6	1	3	6	5
Nervous system disorders	Lethargy	2	2	0	0	2	2
Nervous system disorders	Hypersomnia	2	2	0	0	2	2
Total	Somnolence Related terms	19	23	12	32	31	26

Table 45; Study 016 Patients with 120 Day Update Adverse Events Related to Depression by Cohort and Total

AEBODSYS	AEDECOD	Rollover N=82	Rollover %	Switch N=37	Switch %	Total N=119	Total %
Psychiatric disorders	Affective disorder	0	0	1	3	1	1
Psychiatric disorders	Depressed mood	0	0	1	3	1	1
Psychiatric disorders	Depression	18	22	2	5	20	17
Psychiatric disorders	Major depression	1	1	0	0	1	1
Total	Depression Related Terms	19	23	4	11	23	19

Suicidality Assessment

Table 46: Study 016 with 120 Day Update Patients with Adverse Events Related to Suicidality by Cohort and Total

AEBODSYS	AEDECOD	Rollover N=82	Rollover %	Switch N=37	Switch %	Total N=119	Total %
Psychiatric disorders	Suicidal ideation	4	5	2	5	6	5
Psychiatric disorders	Depression suicidal	1	1	0	0	1	1
Total	Suicide Related terms	5	6	2	5	7	6

Columbia Suicide Severity Rating Scale (C-SSRS)

Patient SD809C15-100-3422 answered affirmatively to question 1" Wish to be Dead" of the C-SSRS during an unscheduled visit at approximately Week 15. A follow up administration of the C-SSRS all responses on the C-SSRS were negative.

Depression (Table 45) and suicidality (Table 46) were more frequent in the open label study which is likely due to the longer period of observation. The dose of and conversion to SD-809 sudden switch versus titration suggest that rapid conversion may be associated with fewer adverse events related to depression however; the small sample size does not support conclusions.

Clinical Laboratory

I agree with Dr. Bergmann's observations and conclusions there were no clinically significant shifts of WBC or RBC measures of central tendency in controlled study SD-809-C-015 or the open label study. Outlying values were not associated with adverse event related to SD-809.

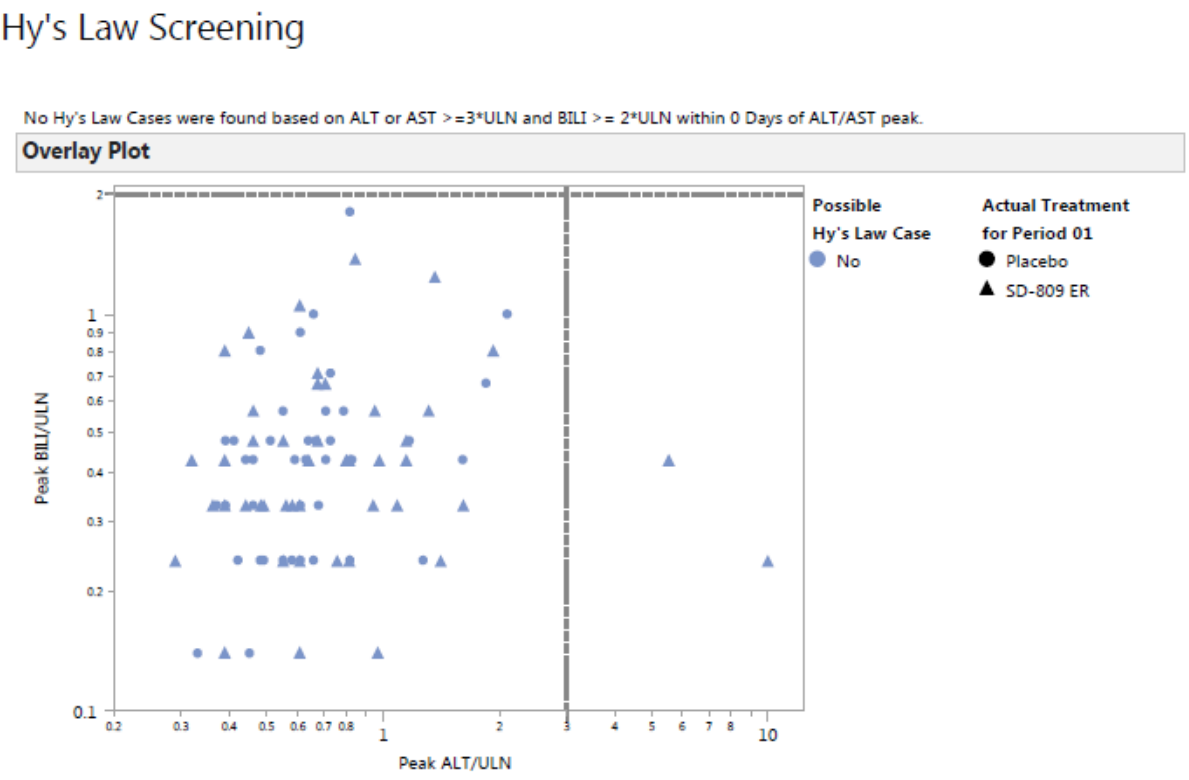
A single patient had elevated serum AST and ALT at Week 12 to 10 times and 4.8 times the ULN for ALT and AST, respectively with normal bilirubin and ALP. A gastroenterologist evaluated the patient and the transaminase levels returned to normal after sertraline was

discontinued. The patients AST and ALT remained within the normal range after rechallenge with SD-809. There were no Hy's Law Cases were found based on ALT or AST >=3XULN and BILI >= 2XULN within 0-7 Days of ALT/AST peak.

Figure 9: Hy's Law Case Analysis

Study: SD-809

Analysis Population: Safety



Vital Signs

There were no clinically meaningful differences in measures of central tendency for pulse and BP between the group treated with SD-809 and the placebo group.

Orthostatic pulse and BP was monitored in both the controlled an open label clinical study. Dr. Bergmann reviewed individual patient orthostatic blood pressure and heart defined as a decrease in systolic blood pressure ≥20 mm Hg, or a decrease in diastolic blood pressure of ≥10 mmHg. Orthostatic changes in vital signs occurred in 5 (11%) patients in the SD-809 group and 10 (22%) patients in the placebo group.

Electrocardiograms (ECGs)

There were no clinically significant differences between the treatment groups in any of the mean ECG parameters. Patients with outlying values were did not reach the threshold of clinical concern. Dr. Bergmann noted that only one patient in the SD-809 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. There were no ECG-related AEs reported for any patient in the SD-809 group. Four AEs identified via ECG were experienced by two patients in the placebo group.

Eighteen patients were taking citalopram or escitalopram in Study SD-809-C-16. No increases of QTc were noted over the course of the study and values remained well within the normal range

CDTL Safety Conclusions:
I agree with Dr. Bergmann conclusion concerning the review of the clinical safety data for SD-809. I do not find reason for new safety concerns or increased risk of adverse reactions in relation to the referenced listed product.

6. Advisory Committee Meeting

The application does not meet conditions for utilization of an advisory committee on the initiative of FDA. Although SD-809 is classified as a NME, it is not a drug with that represents a therapeutic advances over currently marketed products from the standpoint of safety or effectiveness. Xenazine is approved for the identical population and indication.

7. Pediatrics

SD-809 is exempt from PREA requirements because the product received orphan designation from OOPD.

8. Other Relevant Regulatory Issues

Financial disclosures

Dr. Bergmann identified three investigators and two sub-investigators who received compensation for performing additional trial related duties such as, blinded review of TMC video exams or safety monitoring. The TMC video rating was exploratory analysis in study SD-809-C-15. I agree with Dr. Bergmann's assessment that it is unlikely that the individuals could have influenced the efficacy or safety conclusions of the clinical studies included in the NDA. The highest enrolling site was site (b) (6), which enroll (b) (6) (b) (6). The two remaining sites enrolled (b) (6) and (b) (6) patients (one screen failure) respectively.

Good Clinical Practice (GCP)
The sponsor affirmed that the standard procedures for handling and processing eCRF records will follow Good Clinical Practice (GCP) and the Sponsor's (or CRO's) Standard Operating Procedures (SOPs). To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor planned to conduct a quality assurance audit.

The sponsor affirmed that no individual debarred by FDA from conducting clinical investigations participated in any of the studies for SD-809.

Office of Scientific Investigations (OSI) audits

Table 47: Clinical Sites Inspected by OSI

Name of CI, Site #, and Location	Protocol and # of Patients	Inspection Dates	Final Classification
William M. Mallonee, M.D Wichita, KS 67226 Site#83	Protocol SD-809- C-15 13 patients	9/21-25/2015	Pending (preliminary classification VAI)
Daniel Claassen, M.D. Nashville, TN 37232-2551 Site# 31	Protocol SD-809- C-15 7 patients	8/31-9/17/2015	Pending (preliminary classification VAI)

The sites listed above were selected for OSI audits because they were high enrolling sites for study SD-809-C-15.

Although minor regulatory deviations were noted at both sites, the findings were classified as being unlikely to have a significant impact on overall results. The data generated by both site were considered reliable and appear acceptable in support of the pending application.

Controlled Substance Staff Review

Alicja Lerner, MD, PhD, was the Controlled Substance Staff (CSS) reviewer for this application. Dr. Lerner concluded that the sponsor did not adequately assess the potential for withdrawal and abuse during development of SD-809. The conclusions and recommendations from CSS are listed below.

CSS Reviewer's Conclusions

1. Austedo (SD-809, deutetrabenazine) has never been marketed in the U.S. As a New Molecular Entity (NME), its abuse potential is unknown.

2. There are no preclinical and clinical studies designed to evaluate abuse potential and dependence of Austedo.

3. The clinical data which compares adverse events including neuro-psychiatric adverse events following administration of Austedo and tetrabenazine is too small to make any judgments about similarity or lack of abuse potential of these two drugs, although these data seem to show more neuro-psychiatric adverse events for Austedo.

4. Very little data was provided to see a difference in abuse potential for Austedo and tetrabenazine.

CDTL Comment:

Although Austedo is technically a NME, it is highly similar to tetrabenazine with the exception the replacement of two hydrogen atoms with deuterium (OCD_3). There are no differences in the metabolic pathway of Austedo compared to Xenazine. The reference drug in the 505(b)(2) NDA, Xenazine is not labeled as having abuse potential based on observations of withdrawal and rebound in the pivotal clinical trial. (Frank et al., 2008)

CSS Reviewer's Recommendations

1. There is no systematic evaluation of clinical dependence, the data provided by the sponsor is too limited to allow any final conclusions, and therefore, additional evaluation of clinical dependence is needed. In particular, the data submitted so far raises the possibility of the rebound phenomena, which are concerning. Of note, one possibility is to evaluate dependence at the end of the trial ARC-HD (SD-809-C-16) which is still ongoing.

2. Rebound is of particular concern in the study population as it may increase symptoms of Huntington's disease, including chorea, worsen balance problems and increase possibility of falls, injuries and fractures and also psychiatric disorders (depression, psychosis, suicidality).

3. Evaluation of clinical dependence either at the end of the trial lasting at least 4 weeks or an independent clinical dependence study will be necessary as PMR. Dependence evaluation may be performed at the end of the on-going study SD-809-C-16-ARC HD for the duration of 3-4 weeks and include a summary of all adverse events broken down by weeks (1, 2, 3, 4) and a comparison of the scores from the follow-up period. All scales should be administered biweekly with the baseline scores (which were acquired before the start of drug administration) for the following scales:

1. Hospital Anxiety and Depression Scale (HADS),
2. Columbia Suicide Severity Rating Scale (C-SSRS),
3. Epworth Sleepiness Scale (ESS),
4. Montreal Cognitive Assessment (MoCA).
5. Total Maximal Chorea Score (TMC)
6. Unified Huntington Disease Rating Scale, including behavioral and cognitive scores
7. Unified Parkinson's Disease Rating Scale Speech/Dysarthria
8. Barnes Akathisia Rating Scale (BARS)
9. Berg Balance Test Score (BBT)

CDTL Comment:

The repeat administration of SD-809 (fed), the half-life of the active SD-809 metabolites, α-HTBZ and β-HTBZ is 8 to 10 hours. In the placebo controlled efficacy study (SD-809-C-15), all patients discontinued study drug after the Week 12 visit, and returned at Week 13. The week 13 visit followed withdrawal from SD-809 or placebo. Observations in the washout

period included evaluations of safety, chorea and motor function. The one week washout period allowed for passage of 16 half-lives of deuterated α-HTBZ and β-HTBZ, which is sufficient time for clearance of both active metabolites, and the emergence of rebound or withdrawal symptoms.

Frank, et al, (Frank et al., 2008) reported on 30 HD patients who received long-term treatment with tetrabenazine. These patients were randomized in a double blind fashion to one of three treatments: 1) complete withdrawal (without taper), 2) partial withdrawal or 3) no withdrawal from their stable dose of tetrabenazine. "Participants were examined before withdrawal of tetrabenazine. Chorea re-emerged between days 1 to 3 but chorea was not significantly worse on day 3 or 5 compared to day 1 suggesting there was no rebound effect on chorea following abrupt withdrawal of tetrabenazine."

The CSS reviewer also expressed concern for rebound phenomenon causing increased fall, psychiatric events including suicidality. Review of fall or injury related adverse event terms from the controlled study SD-809-C-15 suggest fall and injury were consistently more frequent in the placebo group (Table 48). Nine patients (5 Placebo and 4 SD-809) reported 22 adverse events in the Follow Up phase (at week 13) for study SD-809-C-15. The results show that fall and injury were reported as adverse events more frequently in the placebo group (Table 49). There were no new psychiatric adverse events reported for either treatment group in the Follow Up period.

Table 48: Study SD-809-C-15 Adverse Events Suggesting Fall or Injury

	SD-809 ER (N = 45)			***Placebo (N = 45)***		
PT	***Events***	***Number of patients***	***Proportion (%)***	***Events***	***Number of patients***	***Proportion (%)***
Fall	5	3	6.67	16	9	20
Face injury	0	0	0	1	1	2.22
Jaw disorder	1	1	2.22	0	0	0
Joint injury	0	0	0	1	1	2.22
Laceration	1	1	2.22	1	1	2.22
Limb injury	0	0	0	1	1	2.22
Lip injury	0	0	0	1	1	2.22

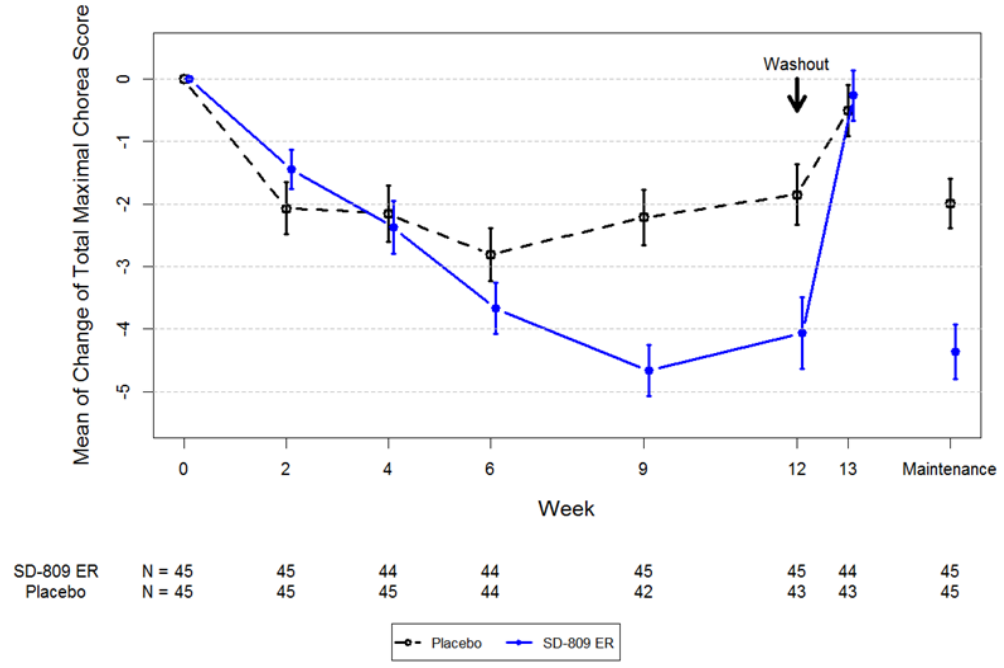
Table 49: Study SD-809-C-15 All Adverse Events Reported in the Follow Up Period

AEBODSYS	**AEDECOD**	**Placebo**	**SD-809**
Gastrointestinal disorders	Abdominal pain	0	1
Gastrointestinal disorders	Nausea	0	1
Gastrointestinal disorders	Toothache	1	0
General disorders and administration site conditions	Fatigue	0	1
Infections and infestations	Sinusitis	0	1
Infections and infestations	Urinary tract infection	0	1
Injury, poisoning and procedural complications	**Contusion**	1	0
Injury, poisoning and procedural complications	**Face injury**	1	0

Injury, poisoning and procedural complications	**Fall**	3	0
Injury, poisoning and procedural complications	**Laceration**	1	0
Injury, poisoning and procedural complications	**Lip injury**	1	0
Injury, poisoning and procedural complications	**Rib fracture**	1	0
Metabolism and nutrition disorders	Decreased appetite	0	1
Musculoskeletal and connective tissue disorders	Back pain	0	1
Musculoskeletal and connective tissue disorders	Jaw disorder	0	1
Nervous system disorders	Dizziness	0	1
Nervous system disorders	Dyskinesia	0	1
Psychiatric disorders	Anxiety	0	1
Renal and urinary disorders	Pollakiuria	0	1
Renal and urinary disorders	Urinary hesitation	0	1

TMC scores worsened in both groups at from weeks 12 to 13 in both the placebo and SD-809 groups to just below their scores at baseline. The observed worsening of chorea after SD-809 was discontinued was expected in patients treated with SD-809 which reduces chorea. The observed worsening of chorea in the placebo group during the washout period is not explained by any effect of medication. TMC scores did not worsen beyond baseline levels in either group after 16 half-lives had passed, making it less likely that a dramatic rise in TMC scores would be observed in another 1 to 2 weeks.

Total Maximal Chorea Score Over Time (Intent-to-Treat Population; N=90)



Source: FDA Statistical Reviewer

CDTL Comment:
Given the small sample size and uncontrolled design of Study SD-809-C-016, it seems unlikely to provide an interpretable assessment of abuse potential. In addition, over longer periods of observation (1 year or longer), patients are expected to experience worsening chorea, cognitive, behavioral, and psychiatric symptoms caused by progression of HD. Patients would be expected to show worsening beyond their baseline severity for any of these symptoms due to progression of their HD following withdrawal of SD-809 based on the elapsed time and disease progression.

The concern for abuse of Xenazine should be focused on the general population instead of the HD patient population. Patients are likely to have limited access to SD-809 due to the progressive disability caused by HD. Explorations of web forums on abuse (e.g., Bluelight) and FAERS may be better suited to address this question. A PubMed search for "tetrabenazine abuse, over-use, addiction" failed to find any reports of tetrabenazine abuse.

5. Labeling

The proprietary name, Austedo, was granted by DMEPA on March 17, 2015.

Labeling Discussions

Labeling was not discussed with the sponsor because of the deficiencies described in this review.

Prescribing Information
Deborah Myers, RPh, MBA was the primary DMEPA reviewer for this application.

RECOMMENDATIONS

A. Highlights of Prescribing Information, *Dosage and Administration Section*
   1. Consider adding the statement, "Austedo should be swallowed whole. Do not chew, crush, or break tablets" to the *Dosage and Administration Section.* Inclusion in this section will increase the prominence of this information and helpto minimize the potential for wrong technique medication errors.
   2. Consider adding the statement "Austedo should be administered with food *[see Clinical Pharmacology (12.3)]*" to the *Dosage and Administration Section*. Inclusion in this section may help providers to more easily access this important information regarding appropriate dose administration.
   3. To minimize the risk for misinterpretation and wrong frequency errors, please consider replacing (b) (4) with (b) (4) "once daily" in the starting dose statement. To provide clarity regarding the route of administration, also consider adding the word "orally" so that this statement reads "6 mg orally once daily".

B. Full Prescribing Information, Section 2.1 *Basic Dosing Information*

1. Consider revising the statement [redacted] to read "Austedo should be swallowed whole. Do not chew, crush, or break tablets" to improve readability.

C. Full Prescribing Information, Section 2.2 *Individualization of Dose*

1. Consider adding "administered orally" in the dosing statement so that it reads, "The starting dose should be 6 mg administered orally once daily" to prevent this information from being overlooked and minimize the risk for wrong route errors.
2. Consider replacing [redacted] in the Table with [redacted] "once daily" and "twice daily" to prevent misinterpretation and confusion. Mistakes can result [redacted] and should be avoided when communicating dosing information.
3. Consider adding the word "maximum" in the first line of the last paragraph preceding "single dose of [redacted] mg [redacted] to reinforce that this is the maximum single dose.

D. Full Prescribing Information, Section 16.2 *Storage*

1. Consider adding the degree symbol (°) following the 15 and 59 within the storage statement for clarity.

Recommendation From DMEPA to the sponsor:

Container Labels

1. Our post-marketing experience indicates that similarity of the product code numbers of the NDC (middle 3 digits) has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 170, 171, and 172). If these numbers cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits or putting them in bold type. As an example:

XXXX-**XXXX**-XX.

See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013.*

6. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Jasminder Kumar, Pharm.D., Risk Management Analyst, Division of Risk Management (DRISK). DRISK submitted their updated review of this NDA on May 2, 2016.

DRISK decided to defer their review of the need for a risk evaluation and mitigation strategy (REMS) for Austedo (deutetrabenazine), NDA 208082.

The Clinical Review team does not recommend a REMS for Austedo based on the labeling history for Xenazine, which included removing a Communication Plan only REMS after 7 years.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
PMRs and PMCs were not discussed with the sponsor. The review team will discuss the need for PMRs and PMCs after the deficiencies in the NDA have been adequately addressed.

Several PMRs have been suggested by review team members including:

- A PMR to repeat a TQT study that evaluates a supramaximal dose of SD-809
- Evaluation of the abuse potential of SD-809

Depending on the outcome of studies that evaluate the status of the M1 and M4 metabolites as major metabolites, the nonclinical team may recommend additional nonclinical PMRs.

7. Recommended Comments to the Applicant

Comments will be provided in the Complete Response Letter.

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/s/

GERALD D PODSKALNY
05/24/2016

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	208082
Priority or Standard	Standard
Submit Date(s)	2015 May 29
Received Date(s)	2015 May 29
PDUFA Goal Date	2016 May 29
Division/Office	Division of Neurology Products, ODE I, OND, CDER
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	2016 April 25
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 chorea in patients with Huntington's disease.
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Treatment of chorea in patients with Huntington's disease.

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Glossary

AC	advisory committee
ADaM	Analysis Data Model data standard
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAG	cytosine adenine guanine
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of 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
CYP2D6	cytochrome P450 2D6 human enzyme
DMC	data monitoring committee
DNP	Division of Neurology Products
DPP	Division of Psychiatry Products
ECG	electrocardiogram
eCRF	electronic case report form

eCTD	electronic common technical document
ESS	Epworth Sleepiness Scale
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
GABA	gamma-aminobutyric acid
GCP	good clinical practice
GRMP	good review management practice
HADS	Hospital Anxiety and Depression Scale
HD	Huntington's disease
ICH	International Conference on Harmonization
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LOCF	last observation carried forward
MAED	MedDRA Adverse Event Diagnosis Service
MedDRA	Medical Dictionary for Regulatory Activities
MHM	major human metabolite
mITT	modified intent to treat
MMRM	mixed effect model repeat measurement
MOCA	Montreal Cognitive Assessment
ms	millisecond
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
PDUFA	Prescription Drug User Fee Act
PeRC	Pediatric Review Committee

PGIC	Patient Global Impression of Change
PI	prescribing information
PI	principal investigator
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PPP	per protocol population
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update report
PT	preferred term
QTcF	Fridericia's corrected QT interval
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
SAE	serious adverse event
SAP	statistical analysis plan
SDQ	Swallowing Disturbance Questionnaire
SDTM	Study Data Tabulation Model data standard
SF-36	Short Form 36 Health Survey
SNRI	serotonin and noradrenaline reuptake inhibitor
SOC	standard of care
SOP	standard operating procedure
SP	safety population
SSRI	selective serotonin reuptake inhibitor
TBZ	tetrabenazine
TD	tardive dyskinesia
TEAE	treatment emergent adverse event
TFC	Total Functional Capacity
TMC	Total Maximal Chorea
TMS	Total Motor Score
UHDRS	Unified Huntington Disease Rating Scale
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
VMAT2	vesicular monoamine transporter, type 2

1 Executive Summary

1.1. Product Introduction

SD-809 (deutetrabenazine) is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Under the proposed proprietary name Austedo, approval is being sought for the treatment of chorea associated with Huntington's disease (HD).

The drug product is a tablet with 6, 9, or 12 mg of deutetrabenazine. The maximum proposed dose is 48 mg /d given orally in two divided doses with food. In persons who are poor metabolizers of CYP 2D6 or persons receiving concomitant medication that strongly inhibits CYP 2D6, the maximum proposed dose is 36 mg/d in two divided doses.

The drug has been deemed a new molecular entity (NME) and has been granted orphan status. This is a 505(b)(2) application with Xenazine (tetrabenazine, NDA 21894) as the reference listed drug (RLD). The granting of orphan exclusivity for Austedo has not yet been determined.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The First-HD trial (n=90) evaluated SD-809 (deutetrabenazine) compared to placebo in a 12 week blinded, randomized trial in which treatment was titrated to best clinical effect in reducing chorea as measured by the Total Maximal Chorea (TMC) Score, the relevant portion of the Unified Huntington's Disease Rating Scale (UHDRS). Patient and clinician rated assessments of global improvement were key secondary outcome measures.

Using the baseline TMC score as covariate in the analysis, SD-809 was superior to placebo in reducing chorea. The mean difference in reduction of TMC between the treatment arms was 2.5 points ($p < 0.0001$). Patients rated their condition as Much Improved or Very Much Improved more often in the active treatment arm over placebo (23/45 vs. 9/45, $p<0.002$) as did clinicians (19/45 vs. 6/45, $p<0.0022$).

The study was judged by the reviewer to be of sufficient robustness and quality to support a claim of effectiveness for the treatment of chorea in HD.

While approvable on the basis of clinical efficacy, the full risk of SD-809 cannot be assessed. There are three major outstanding issues, each of which would render the application non-approvable.

- The Sponsor must quantify two of SD-809 active circulating metabolites, M1 and M4, in order to determine if they are major or minor compared to the RLD using a validated assay. If the active metabolites are greater than 10% based upon plasma concentration

measurement, the safety experience of the RLD may not be complete and new non-clinical studies would be needed to qualify the metabolites. This has been part of the dialog with the Sponsor throughout the review period, as well as, prior to NDA submission. They have submitted a time line to provide answers on this question. According to their timeline, the necessary data to resolve this question will not be submitted by the PDUFA goal date.

- In discussion held during the developmental program for SD-809, the Sponsor indicated that they would control levels of [redacted] (b) (4) for SD-809. (Limits above [redacted] (b) (4) for either in the final drug product would raise toxicological concerns.) The Sponsor has been requested to provide information concerning the specifications for the drug substance and finished dosage form and submit the validation of the method(s) used to measure contaminants from the production process. This request has not been fulfilled.

- The results of a drug substance-related manufacturing facility have not yet been reported.

With the satisfactory resolution of all three issues, the ratio of risk to benefit for SD-809 is acceptable. Unfortunately, this determination cannot be made by the PDUFA goal date.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

SD-809 (deutetrabenazine) is a drug developed to treat chorea, the involuntary movement disorder that is one of the clinical hallmarks of Huntington's disease. This reviewer recommends non-approval on the basis of the efficacy and safety information available. While the drug appears efficacious, there are unanswered pharmacological questions about the metabolites of SD-809. As a result, the full risk of SD-809 is unknown and the application is not approvable.

Huntington's disease (HD) is a rare genetically inherited degenerative disorder of the brain. About 30,000 people in the US are affected and HD is considered an "orphan disease". It is inherited by receiving an abnormal gene that can come from either parent. The child of an affected parent has a 50-50 chance of inheriting the disease. While the classic sign of the disorder is chorea, involuntary and uncontrollable dance-like movements of the face and limbs, the illness is characterized by progressive motor, behavioral and psychiatric disturbances, and dementia. The onset of the illness is generally between the ages of 30 and 50, progressing to death within 15 to 20 years. Definitive genetic testing is now available to diagnose the disorder in persons at risk before they become symptomatic, making possible an informed decision about having children.

Tetrabenazine (under the trade name Xenazine) is the only approved drug for the treatment of chorea in HD. At higher therapeutic doses, it must be taken orally two to three times a day. SD-809 is deuterated tetrabenazine; deuteration creates a new molecule with improved pharmacological properties so that it may be taken orally just twice a day. Being able to administer a drug just twice a day can be a significant aid to caregivers of HD patients. Because SD-809 is chemically close to tetrabenazine, this application may rely upon safety information contained in Xenazine's FDA approved label. No other approved treatments exist for the other symptoms of HD. As a result, many other psychiatric drugs (antidepressants, anxiolytics, and major tranquilizers) with unproven efficacy or safety in this disorder are used in the treatment of HD.

The efficacy of SD-809 was demonstrated in the First-HD study, a randomized trial in which SD-809 was compared to placebo. Over an 8 week period, HD patients were given increasing doses of medication based upon control of their involuntary movement, up to a maximum of 48 mg/d given in two split doses. They were then observed on this stable dose for 4 weeks. Throughout this period, the severity of the movement

disorder was blindly rated using the Total Maximal Chorea Score, a part of a standardized rating scale for HD. In addition, participants and their physicians were independently asked to rate how they felt they were doing overall. Over half the patients reached 48 mg/d. At the end of the study, the SD-809 group had reduced their chorea on average 2.5 points more than the placebo treated group, a statistically significant difference. In addition, 51% of the SD-809 group felt they were either "Much Improved" or "Very Much Improved" compared with only 20% of the placebo group. The patients' investigators thought 42 % of SD-809 patients and 13% of the placebo patients were so improved. These results were also statistically significant.

The deuterated active metabolites of SD-809 are metabolized in the liver by CYP2D6 which can be inhibited by other drugs, especially some common anti-depressants. In addition, some people do not metabolize SD-809 well through this liver system. Those circumstances will result in limiting the maximum daily dose to 36 mg. Patients requiring more than 36 mg/d of SD-809 should have a blood test to determine their CYP2D6 capability.

The clinical safety profile of SD-809 is reasonably well characterized by First-HD and an additional long-term unblinded treatment study in which First–HD patients could opt to continue to receive the drug (most did). Additional safety information comes from experience with its close relative, tetrabenazine. Compared to tetrabenazine, no new or unusual side effects were seen with SD-809 treatment. The most common drug reactions were sedation, dry mouth, fatigue, and diarrhea. The most common reasons for dose reduction of SD-809 or withdrawing from the SD-809 studies were akathisia (an uncomfortable feeling of motor restlessness) and worsening depression, with or without suicidal thoughts. Because depression and suicide are so prevalent in the HD population, it is impossible to know whether SD-809 (or tetrabenazine, in whose studies this was also observed) increases the frequency or severity of this unfortunate event over its naturally occurring background. SD-809 will be subject to continuing pharmacovigilance on the part of the drug's sponsor and regular analysis of post-marketing safety reports.

However, the metabolites of this drug may circulate at higher blood levels than the reference listed drug upon whose safety information it must depend. If that is the case, the extent of risk of SD-809 is not fully known and the drug is not approvable. Despite notification of this concern prior to NDA submission and during the review period, the Sponsor will not be able to provide the necessary information to answer this question before the legally mandated PDUFA goal date. In addition, a question remains about the residual amount of an impurity

introduced during the manufacturing process of SD-809, and a manufacturing facility inspection report is pending. Making a final assessment of the risk profile of SD-809 depends upon the answers to these unknowns.

If these remaining open issues can be satisfactorily resolved before the PDUFA goal date, SD-809 represents an additional oral therapeutic option for treating the chorea of HD patients. The clinical safety profile of SD-809 is acceptable given the severity of this disorder and the demonstrated benefit. The identified clinical safety concerns can be adequately addressed through appropriate product labeling (including a boxed warning about depression and suicidality) and the Medication Guide. SD-809 appears to provide benefits similar to the other available therapy for chorea, tetrabenazine, and represents a worthy additional oral treatment option for persons with Huntington's disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Huntington's disease (HD) is rare degenerative disorder of the central nervous system. The estimated prevalence in the US is approximately 30, 000 persons. • Genetically inherited in an autosomal dominant pattern, it is caused by an abnormally elongated polyglutamine repeat on the short arm of chromosome 4p16.3 in the HTT gene. Quantifying the number of CAG repeats is the confirmatory test for clinical diagnosis. • While the classic sign of the disorder is chorea, the illness is characterized by progressive motor, behavioral and psychiatric disturbances, and dementia. • Onset of the illness is generally between the ages of 30 and 50, progressing to death within 15 to 20 years. The most common cause of death is aspiration pneumonia. The illness is socially devastating to the individual and their social network; as a result suicide occurs at a	HD is a devastating autosomal dominant neurological disorder with a uniformly fatal outcome after a progressive loss of motor, cognitive and behavioral function over 1 to 2 decades.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	rate 4 to 8 times that of the general population.	
Current Treatment Options	• No treatment is available that affects the basic molecular mechanism of disease or alters the natural history of HD. • Xenazine (tetrabenazine, a vesicular monoamine transporter 2 [VMAT2] inhibitor) is approved for the treatment of chorea of HD. It does not benefit other symptoms or signs of the disorder. • A variety of other medications are used outside of their labeled indications to treat the symptoms of HD. These include anxiolytics, antidepressants, and antipsychotic neuroleptics. They offer only a small degree of palliative benefit and are associated with considerable side-effects.	No effective treatments exist for this orphan disorder beyond Xenazine (tetrabenazine) for the treatment of the chorea of HD. Xenazine is the RLD for this 505(b)(2) application. Many psychotropic agents of unproven safety and efficacy in this population are used for the treatment of HD.
Benefit	• The First-HD trial (n=90) evaluated SD-809 (deutetrabenazine) compared to placebo in a 12 week blinded, randomized trial in which treatment was titrated to best clinical effect in reducing chorea as measured by the Total Maximal Chorea (TMC) Score, the relevant portion of the Unified Huntington's Disease Rating Scale. Patient and clinician rated assessments of global improvement were key secondary outcome measures. • Most patients in the trial were titrated to the maximum administered dose of SD-809, 24 mg tablet twice daily by mouth. • Using the baseline TMC score as covariate in the analysis, SD-809 was superior to placebo in reducing chorea. The mean difference in reduction of TMC between the treatment arms was 2.5 points (p	The degree of reduction of chorea was modest, but judged to be of clinical value by both the patient and investigator. It is a smaller effect size than that seen in the RLD pivotal trial where average improvement was a 3.5 point difference over placebo in the TMC score. This may reflect the possibility that 48 mg/d of SD-809 does not provide the same total serum concentration of active drug metabolites as the "equivalent" dose of the RLD, 100 mg/d in three divided doses (or that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<0.0001). Patients rated their condition as Much Improved or Very Much Improved more often in the active treatment arm over placebo (23/45 vs. 9/45, p<0.002) as did clinicians (19/45 vs. 6/45, p<0.0022). • The study was judged by the reviewer to be of sufficient robustness and quality to support a claim of effectiveness for the treatment of chorea in HD.	SD-809 produces different proportions of active metabolites). This is also borne out in a small crossover study performed within the open label extension study, where the target SD-809 dose was estimated from Xenazine plasma pK measurements. The selected SD-809 dose was too low in most cases and then titrated upwards to achieve better clinical effect. Nevertheless, the reduction of TID to BID dosing for this effective drug could materially improve the social aspect of caring for the HD patient, allowing the caregiver for example to be off at work and not worry about a midday dose administration.
Risk	• The most important common side effects of SD-809 include somnolence and fatigue, both of which prompted dose reductions and discontinuations in First-HD. • Depression and suicidal ideation were common adverse events, given the small size of the development program. These events occurred as SAEs, as reasons for dose reduction, and as a cause of discontinuation. The long-term open label follow-up trial to First-HD had more of these events than First-HD.	The main safety concerns for SD-809 are sedation and somnolence, akathisia, depression and suicidality, potential for toxicity due to the CYP2D6 metabolic pathway, and theoretical risk of QTc prolongation. As described in the label and the scientific publication of the RLD's pivotal trial, these

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Akathisia and motor restlessness was also a reason for dose reduction and a cause for withdrawal from the study. • The active metabolites of SD-809 are metabolized via the CYP2D6 pathway. As a result, patients who are poor CYP2D6 metabolizers and patients taking drugs that inhibit this pathway have higher concentrations of active metabolites and run the risk of increased side effects. • While of theoretical risk, no cases of QTc prolongation occurred in the SD-809 development program. A full risk assessment may not be performed because of certain unknowns that remain unanswered: • SD-809 may be metabolized differently than Xenazine, an approved drug upon whose safety information this approval depends. If that is the case, then a full understanding of the risk profile of SD-809 cannot be known at this time. • The final specification for (b) (4), an impurity potentially introduced via manufacture of the SD-809 drug substance and the methods for its quantification have not yet been submitted by the Sponsor. • The final inspection report of a manufacturing facility has not yet been submitted.	adverse events all occurred to a greater extent with Xenazine. It is very likely however that these adverse events are all dose- related phenomena and could be explained by SD-809 achieving a lower pharmacodynamic level of drug. The background rate of depression and suicide in HD is so large that it would be impossible to perform a meaningful study to assess whether SD-809 adds to that risk. The metabolites of SD-809 may occur in different quantities than the RLD. If that is so and a metabolite requires qualification, new non-clinical studies may be required to fully assess the risk profile of SD-809.
Risk Management	• If metabolites occur in higher concentrations than the RLD and require qualification, new non-clinical studies will allow the risk profile to be more fully understood. • No novel, previously undescribed, or events with increased frequency occurred in the SD-809 safety population when compared to that of	The RLD was subject to a successfully completed REMS that investigated strategies to minimize the occurrence of serious side effects of drug use, including drug interactions. No additional safety precautions were deemed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Xenazine, the RLD for this 505(b)(2) development program. • The RLD label has a boxed warning concerning depression and suicidality and this is also discussed in the Medication Guide. • The RLD label describes all of the adverse events that were considered SAEs, reasons for dose reduction or withdrawal from studies. • The Sponsor has a pharmacovigilance plan that includes enhanced vigilance for expedited AE reports related to depression and suicidality, regular safety review meetings and planned updates to their drug safety database.	helpful. Labeling (including a Medication Guide), and routine pharmacovigilance are adequate to address the safety issues associated with SD-809. The safety section of the label will be similar to that of the RLD, Xenazine.

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2 Therapeutic Context

2.1. Analysis of Condition

Huntington's disease (HD) is rare degenerative disorder of the central nervous system. While the classic sign of the disorder is chorea, involuntary and uncontrollable dance-like movements of the face and limbs, the illness is characterized by progressive behavioral and psychiatric disturbances and dementia (Roos, 2010).

HD is genetically inherited in an autosomal dominant pattern and is caused by an abnormally elongated cytosine–adenine-guanine (CAG) polyglutamine repeat in the HTT gene located on the short arm of chromosome 4p16.3 (Bobori, 2015). Having 36 CAG repeats or more is associated with eventual onset of the disorder, generally between the ages of 30 and 50 (range 2 to 85). In general, the greater the numbers of repeats present, the earlier the onset of overt symptoms. Juvenile-onset cases are less prevalent (about 10% of cases) and generally have at least 55 CAG repeats. Juvenile HD is also characterized by dystonic movements, and chorea occurs less often. The gene defect, which may be detected and quantified (even *in utero*), is rare with a prevalence of 5 to 10 per 100,000 population in the US. The Huntington's Disease Society of America (www.hdsa.org) estimates the prevalence to be about 30,000 individuals. While the illness in the US is found predominantly in whites of European origin, it has been described in Native and African Americans, African blacks, Semitic populations and the Japanese. Genetic testing is now the gold standard for diagnosis. Before 1993, a family history with clinical and postmortem verification in at least one of the parents or grandparents was obligatory.

The illness may present with neurological or psychiatric symptoms but chorea is the most recognized symptom. Other motor symptoms appearing over time include dysarthria, dysphagia, dystonia, incoordination and imbalance with falls. The chorea, while noticeable and disturbing to the patient and family, by itself accounts for little of the illnesses' disability. Behavioral, cognitive and psychiatric disturbances become the more difficult to manage and disruptive aspects of the disease. The illness is inexorably progressive and usually fatal by the end of two decades after the phenotypic motor behavior is noted. The most common cause of death is aspiration pneumonia in association with dysphagia (Heemskerk & Roos, 2012; Lanska, Lavine, Lanska, & Schoenberg, 1988; Sorensen & Fenger, 1992). Suicide is prevalent in this population, estimated at a rate 4 to 8 times that of the general population (Hubers et al., 2012; Schoenfeld et al., 1984).

There are few illnesses of such small prevalence as HD that have as great (and devastating) an impact on the affected person and their social network. As a result, patient-centered groups in

the US are active in their advocacy. As part of the FDA's patient-focused drug development initiative, a public meeting with all interested parties was held on September 22, 2015, culminating in a report entitled *The Voice of the Patient: Huntington's Disease*[1]. Key themes emerged from the meeting:

- HD is a devastating disease with huge impact on the patient and their family, often across multiple generations.
- Current treatments do not adequately manage their most disabling symptoms.
- HD impacts all aspects of the patient's life with limitations on physical activity and loss of independence.
- Medications that are effective in delaying the onset of symptoms or slowing the progression of symptoms are desperately needed.

2.2. Analysis of Current Treatment Option

The need for better treatments for HD is made plain when current treatments are reviewed. Only one drug is currently approved for treating any symptoms resulting from Huntington's disease, the Reference Listed Drug for this 505(b)(2) application, tetrabenazine, indicated for the treatment of chorea associated with HD (Xenazine, NDA 21894, 2008)(Armstrong & Miyasaki, 2012). Its labeled risks and benefits are described in the safety and efficacy portions of this review. There is no evidence to suggest that the subject of this review, deuterated tetrabenazine, offers an advantage in this regard beyond more convenient dosing.

Most HD patients are administered a variety of other drugs used in off label fashion directed towards relieving individual symptoms of HD. Cognitive deficits, while disabling, have no known effective treatment. Drugs that have been used in Alzheimer's disease have typically not been used in HD (drugs that increase cholinergic tone have been reported to worsen chorea). Drugs used to treat the psychotic and affective symptoms of HD mirror the use of these drugs in non-HD psychiatric disturbances. The table below is a partial list of drugs that have been described as being used in HD (Mason & Barker, 2016). Most have been supported by small studies that have not been replicated in adequate or well-controlled trials.

Table 1 Drug treatment of Huntington's Disease (modified from Mason & Barker, 2016)

Symptom	Treatment
Depression	SSRI, SNRI antidepressants including mirtazipine, fluoxetine, citalopram and venlafaxine
	Monoamine oxidase inhibitors
Anxiety	Citalopram
	Lorazepam

[1] http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM491603.pdf

Irritability	Olanzapine, risperidone
	Quetiapine
	Sodium valproate
	Carbamazepine
	Lamotrigine
	Lithium
Impulsivity	Atomoxetine
Apathy	Modafinil
	Amantadine
	Standard antidepressants including mirtazipine, fluoxetine, citalopram and venlafaxine
Psychosis	Neuroleptics: olanzapine, haloperidol, risperidone
Dystonia	GABAergic medication: benzodiazepines, clonazepam, diazepam
Bradykinesia	Dopamine agonists: levodopa, apomorphine
Myoclonus	GABAergic medication: benzodiazepines
Gait disorder	Presumed glutamatergic medications: amantadine

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

SD-809 or deutetrabenazine is the deuterated form of tetrabenazine, an orphan status designated drug approved for the treatment of Huntington's disease chorea. While SD-809 has been designated a new molecular entity (NME), it is also a 505(b)(2) application using tetrabenazine as the Reference Listed Drug (RLD).

Approved in 2008, tetrabenazine 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. The REMS assessment included the following

a. An evaluation of patients' understanding of the serious risks of tetrabenazine, the importance of titration, and monitoring for targeted adverse events
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
d. Surveys designed to monitor the effectiveness of the interventions in educating prescribers on the proper use of tetrabenazine therapy, compliance with the titration and dosing guidelines contained in the labeling, and occurrence of targeted adverse

events and their management by the prescriber

The details of the REMS were later modified to include a pharmacist evaluation. The REMS communication plan met its goals, FDA determined that the approved REMS had ensured that the benefits of the drug outweigh the risks, and was deemed to have been completed August 25, 2015.

Xenazine also has a medication guide (last updated 6/2015 version) that warns about the serious side effects of depression, suicidal thought and suicidal actions. It also includes a warning 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

SD-809 development has been conducted under IND 112975, opened in June, 2012. Highlights of the interactions with the Sponsor about the clinical development plan follow below. (Verbatim communications found in the DNP meeting minutes are *italicized*). The original Sponsor, Auspex Pharmaceuticals, has since transferred rights and responsibilities to Teva Pharma.

Pre-IND Type C Meeting, (November 11, 2011)

> *A single, double blind, randomized withdrawal study may be adequate to support efficacy pending the results of the trial and the Division's review.*
>
> *Additional nonclinical and/or clinical safety information may be needed depending on the level of the known metabolites and the presence of unique metabolites or impurities associated with SD-809 compared to the RLD.*
>
> *The sponsor will need to define specific levels of worsening on the … patient global scale that constitute patient failure in the Phase 3 protocol.*

Considerable discussion was held about the need for the Sponsor to perform non-clinical studies to support SD-809 safety and the safety of its metabolites should the plasma levels of any of these exceed those of the RLD.

End of Phase 2 Type B Meeting (December 5, 2012)

> *On face, the completed and planned nonclinical studies are adequate to support the NDA for SD-809, provided that clinical exposures to the parent compound and any major circulating metabolites fall within the range of those for the RLD, as previously discussed.*
>
> *The Division expressed concern about the variability in the individual results of SD-809 metabolites.*

The randomized withdrawal study design and the target population is an acceptable design for demonstrating efficacy. However, despite the controlled nature of the randomized withdrawal phase, that phase does not provide controlled safety data, due to the fact that treated patients have been shown to be tolerant of the drug. Your clinical trials program must provide adequate safety information for SD-809 (b) (4) (b) (4) because, by design, the PK profile of the active metabolites of SD-809 (b) (4) will differ from Xenazine.

The Division clarified that patients with hepatic impairment defined as Child-Pugh score of 5 points or higher must be excluded from the pivotal trials.

You must use a validated clinical questionnaire to screen for dysphagia prior to study entry. The UPDRS dysphagia and dysarthria scores do not adequately evaluate dysphagia in patients with Huntington's disease. The ability to swallow an intact tablet is important for your (b) (4) formulation because patients cannot crush, split, or dissolve the tablets. [You] should include a justification for the questionnaire they select for use in the trial.

Yes, the primary endpoint of an increase in the Total Maximum Chorea Score following randomized withdrawal is acceptable.

Please explicitly state the definition of a "treatment failure" and clearly distinguish it from the definition of a "treatment success". If you intend to describe the results of the key secondary endpoint in labeling, the results must not provide information that is similar to the information captured by the primary efficacy endpoint. We typically require replication (in a second independent trial) of the results supporting a new or comparative claim in order to describe it in labeling. The analysis of multiple secondary endpoints must include a plan to control for inflation of the type 1 error rate.

Disability caused by drug induced Parkinsonism due to SD-809 (b) (4) may diminish a potential benefit associated with reduced chorea. You should provide an analysis of motor function that includes at least postural stability, gait, and voluntary motor performance. In addition, you must monitor patients for orthostatic changes in vital signs (pulse and BP) in the supine and standing position at baseline and during all face-to-face visits.

A single trial may be adequate to support the efficacy portion of an application; however, it is a matter for review.

> *The adequacy of the safety database and the ability to rely on the Agency's determination that tetrabenazine is safe will depend on how similar SD-809 (b) (4) is to Xenazine with respect to the levels of the active metabolites and on the condition that there are no new significant metabolites that are unique to SD-809.*

Additional discussion was held concerning CYP 2D6 profiling and dosing safety. The informed consent procedure and the protection of HD participants as an especially vulnerable population due to cognitive impairment, including the need for a live-in caregiver, were agreed upon. The Phase 3 study submitted in this application accurately reflects those agreements.

Reviewer Comment: The randomized withdrawal study was later abandoned by the Sponsor in favor of the trial design of Study C-15 (see below). This trial did have a 1 week washout for all participants at the end of 12 weeks.

Pediatric Study Plan (July 9, 2013)

The PeRC meeting of June 26, 2013 agreed with the PSP (that it would not be submitted) and the plan for a full waiver. The Division expressed its agreement to the Sponsor by letter.

Additional Type C Meeting denied (March 25, 2014)

> *We are denying the meeting because we have provided recommendations to the questions posed in your current meeting request during our End-of-Phase 2 meeting held on December 5, 2012.We are unable to formally agree to changes made to the protocol or statistical analysis plan for study SD-809-C-15 because it is ongoing. Please include your rationale for changes made to the protocol and analysis plan for study SD-809-C-15 in your pre-NDA meeting package. Justification for your approach to addressing the non-clinical and clinical pharmacology issues discussed at the End-of-Phase 2 meeting and any supporting information should be included in your pre-NDA meeting package for discussion.*

Pre-NDA Type B Meeting (March 19, 2015)

The Sponsor's proposed bridging strategy to the RLD was thought to be reasonable, subject to review of the data.

Based upon a description and top-line results and adequate bridging to the RLD, the Phase 3 randomized controlled trial [Study C-15] was sufficient for review of a 505(b)(2) application with tetrabenazine (Xenazine, NDA 21894) as the RLD.

The approach to overnight switching from Xenazine to SD-809 was found to be acceptable.

> *As noted in your briefing packet, 117 subjects with HD have been exposed to SD-809; however, only 18 subjects have been exposed for at least 6 months and 3 subjects for at*

least one year. In order to have sufficient exposure data, you plan to rely on the safety database for tetrabenazine. This plan is reasonable as long as you are able to adequately bridge to the data for the RLD (Xenazine).

To add clarity to our preliminary response, you cannot rely on proprietary datasets (or information) contained in the Xenazine NDA. This includes FDA reviews of proprietary information submitted to the NDA or IND for Xenazine.

Details concerning the structure and content of the ISS, ISE, and datasets were agreed upon.

Other regulatory interactions

- Breakthrough and Fast Track designations were requested for this submission and not granted.
- Orphan drug designation was granted December 5, 2012.
- The proprietary name, Austedo, was granted conditional acceptance, March 17, 2015.
- Development of SD-809 for the indication of the treatment of tardive dyskinesia is proceeding (b) (4) (b) (4)

3.3. Foreign Regulatory Actions and Marketing History

SD-809 is not currently marketed or commercially available in any country.

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

4.1. Office of Scientific Investigations (OSI)

Quality assessments of data from the pivotal efficacy trial during the filing evaluation period for this application did not identify any sites for inspection on the basis of data discrepancy. While most sites enrolled small numbers of participants and contributed evenly to the efficacy and safety data pool, two clinical trial sites contributed more. The Office of Scientific Investigations (OSI) of the Division of Clinical Compliance Evaluation was asked to assess the two highest enrolling clinical trial centers that accounted for 19% of the safety population (Study C-15, Sites 83 and 31 with 10 and 7 randomized participants, respectively).

OSI considered both sites to have generated reliable data, albeit with a few deviations from GCP that were considered minor by the inspector.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) has two questions that remain unanswered at this time:

- The Sponsor has agreed to, but has yet to submit, a suitable test method and limit for (b) (4) which is used in the manufacture of the drug substance. (b) (4) is a potential genotoxic impurity and the testing and limits need to be below the threshold for toxicological concern (1.5 µg/person/day) based upon the maximum recommended daily dose of SD-809.

Reviewer comment: It is possible that clinical use will be above the to-be-labeled maximum recommended dose of 48 mg/d as the drug is likely to be used clinically by titration to best clinical response. This occurred in the open-label extension study of SD-809.

- The manufacturing facilities inspection recommendation for a drug substance testing site not previously inspected by FDA needs to be received before OPQ can make their final recommendation regarding this NDA.

It should be noted that (b) (4) the sponsor did not request designation as an extended release tablet in this NDA submission. The biopharmaceutics reviewer asked the sponsor for explanation to support a standard release designation because the final drug product contains some "release controlling excipients". The sponsor explained (b) (4)

The drug product used in the pivotal trial in support of efficacy and safety and the open label extension safety study is the drug product intended for market.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

Based upon the unknown plasma concentrations of metabolites resulting from the likely-to-be-labeled dose range of SD-809, questions remain as to whether the metabolites are qualified and whether a lack of qualification leads to non-approvability. The non-clinical reviewer summarizes the issue in Section 1.3.1 of their review:

> "It is not possible to determine if the nonclinical studies submitted in the application support bridging to the available nonclinical information for the RLD without a determination of the status of SD-809 metabolites as major or minor, as defined by ICH M3(R2), by the Clinical Pharmacology review team. If it is determined that the metabolite profile for SD-809 is similar to the RLD and that there are no new MHMs [major human metabolites] of SD-809, then the current nonclinical package would support the approval of the NDA. However, if the available information on human metabolism of SD-809 is not adequate to determine the status of the metabolites in humans or if it is determined that there are MHMs of SD-809 that are not MHMs of TBZ, then the sponsor would need to demonstrate that the level of each MHM was qualified in nonclinical studies in order to support the level of exposure in humans."

4.5. Clinical Pharmacology

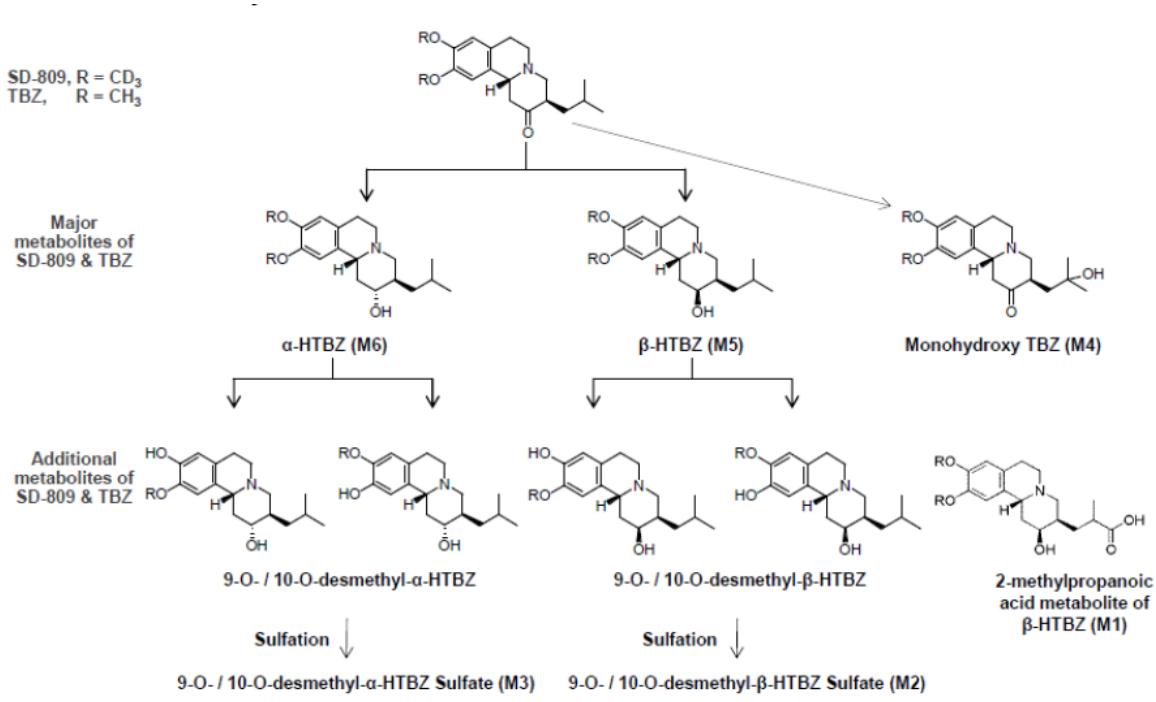
SD-809 is structurally related to tetrabenazine, the RLD for this 505(b)(2) application. Two trideuteromethoxy groups (-OCD3) are placed at the 9- and 10-positions (b) (4) of SD-809 to replace two trihydromethoxy groups (-OCH3) at the corresponding positions in tetrabenazine. The Sponsor posits that deuterium placement at these positions confers metabolic advantages relative to tetrabenazine by attenuating CYP2D6 mediated metabolism without changing the drug's target pharmacology.

SD-809 undergoes rapid and extensive hepatic metabolism by carbonyl reductase, yielding the dihydro metabolites, alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ). Both α-HTBZ and β-HTBZ are pharmacologically active as potent inhibitors of VMAT2, the drug's intended target. Both -OCD3 groups in SD-809 are conserved in the HTBZ metabolites. According to the Sponsor, deuteration does not change the metabolic pathway of SD-809 relative to that of tetrabenazine and all 22 metabolites of SD-809 are among the 24 metabolites of tetrabenazine. As a consequence of deuterium placement in SD-809, the rate at which CYP2D6 forms the O-desmethyl (ODM) metabolites of SD-809 is reduced relative to the rate at which ODM metabolites of tetrabenazine are formed. This difference results in longer circulating half-lives for deuterated α-HTBZ and β-HTBZ relative to the nondeuterated metabolites, thereby extending the kinetics responsible for its pharmacodynamic effect.

The metabolites of SD-809 have been the subject of extensive discussion with the Sponsor who claims that there is no quantitative difference in the major and minor metabolites in reference to the RLD, tetrabenazine. M1 and M4 are the metabolites in question and the Sponsor has been asked to quantify them using methods agreed upon through discussion with the Clinical Pharmacology reviewer. However, it appears to not be possible for the Sponsor to complete this study before the PDUFA goal date for this application. Should a minor metabolite of tetrabenazine turn out to be a major metabolite of SD-809, qualification will likely require additional non-clinical study. This also cannot be done by the PDUFA goal date and so this

application will be non-approvable.

Figure 1 Metabolites of SD-809 (Summary of Clinical Pharmacology Studies, p 60)



SD-809: Deutetrabenazine
TBZ: Tetrabenazine
HTBZ: Dihydro metabolite of SD-809 or of tetrabenazine
R = CH_3 for tetrabenazine and metabolites
R = CD_3 for SD-809 and metabolites
M = Metabolite M1 through M6 assigned in clinical Study SD-809-C-12 based on Xenazine label and / or prevalence in Study SD-809-C-12

4.5.1. Mechanism of Action

SD-809 is a vesicular monoamine transporter 2 (VMAT2) inhibitor. Neurotransmitter release at the synaptic cleft is effected by vesicles merging with neuron terminal membranes and releasing their contents. They are then recycled and become vesicles once again within the cytosol of the presynaptic terminal. The transporter protein is a part of the vesicle wall and brings the designated substrate into the vesicle against a concentration gradient. In the case of VMAT2, the substrates are dopamine, norepinephrine and serotonin among others. Specific VMAT2 function is likely determined by the neuroanatomical circuit in which it is found. By inhibiting VMAT2, the end result is that the quantum of neurotransmitter is reduced within the vesicle itself (Eiden & Weihe, 2011).

4.5.2. Pharmacodynamics

It is difficult to establish clear dose –related pharmacodynamics (i.e.: relationship of

improvement in chorea to the administered dose. There is no animal model corresponding to HD chorea that could inform this topic. The many inter-individual differences that govern brain disease make this a common problem with CNS drugs.

Dose relationship to adverse events is discussed below in the review of safety. The Sponsor did calculate that "the median peak concentration in CYP2D6-impaired subjects receiving 48 mg SD-809 per day is estimated to yield an effect on QTc that is below the threshold of regulatory concern (10 msec)".

4.5.3. **Pharmacokinetics**

The sponsor reports that plasma concentrations of total (α+β)-HTBZ were less variable between subjects in the fed state compared with the fasted state. SD-809 was given with food in all of the clinical studies.

About 80 % of an oral dose of SD-809 is absorbed from the gastrointestinal tract. The Cmax of α-HTBZ and β-HTBZ is 3 to 4 hours after dosing and they have a half-life of about 11 hours. These metabolites are approximately 60% protein bound. PET scans have shown that they are rapidly distributed in the brain (cortex and basal ganglia).

The pharmacokinetics of the active metabolites are altered when administered concomitantly with a strong inhibitor of CYP 2D6 (paroxetine 20 mg daily for a week)

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Table 2 SD-809 pK parameters with and without CYP2D6 inhibition (Summary of Clinical Pharmacology Studies, p 66)

Table 12. Single Dose Pharmacokinetic Parameters for SD-809 and Its Dihydro Metabolites Following Administration of SD-809 Alone or with Paroxetine (Study SD-809-C-08; Per-Protocol PK Analysis Set, N=23)

Parameter	SD-809 22.5 mg[a] Day 1	SD-809 22.5 mg with Paroxetine 20 mg[b] Day 11
	SD-809	
C_{max} (ng/mL)	0.360 (60)	0.377 (53)
t_{max} (h)	3.50 (1.00-6.01)	3.00 (2.00-4.50)
t_{lag} (h)	2.00 (0.00-4.50)	2.00 (0.00-3.50)
AUC_{last} (ng•h/mL)	0.768 (53)	0.815 (60)
	α-HTBZ	
C_{max} (ng/mL)	37.4 (22)	45.4 (25)
t_{max} (h)	4.00 (2.00-7.00)	3.50 (2.00-5.00)
t_{lag} (h)	1.00 (0.00-4.05)	1.00 (0.00-2.50)
AUC_{inf} (ng•h/mL)	427 (34)	780 (28)
$t_{½}$ (h)	10.5 (28)	15.5 (18)
	β-HTBZ	
C_{max} (ng/mL)	24.6 (36)	51.5 (25)
t_{max} (h)	4.00 (2.00-8.01)	3.58 (2.00-6.00)
t_{lag} (h)	1.00 (0.00-4.05)	1.00 (0.00-2.50)
AUC_{inf} (ng•h/mL)	199 (90)	1121 (40)
$t_{½}$ (h)	5.91 (48)	16.2 (28)

Reviewer Comment: Based upon these results the Sponsor reduced the maximum recommended dose of SD-809 from 48 mg/d to 36 mg/d in any situation where CYP2D6 may be impaired in function. The Sponsor's algorithm that predicted using a 2:1 tetrabenazine to SD-809 dose ratio was based on [α-HTBZ + β-HTBZ] plasma concentrations. However it appears that deuterating tetrabenazine does not affect both active metabolites equally in the face of CYP2D6 inhibition The Cmax and half-life of β-HTBZ is affected to a greater extent than that of α-HTBZ. The results of the C-16 Switch substudy would suggest that a halving of the tetrabenazine dose for SD-809 does not produce a similar pharmacodynamic effect and most participants in the Switch study needed increases in dose to satisfactorily control their chorea.

This point is also relevant to the status of this 505(b)(2) application in that the pK-based bridge the RLD, Xenazine, depends upon the active metabolites being proportional to those found in tetrabenazine.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

This NDA application consists of six Phase 1 studies (one of which is a Thorough QT study) and a single Phase 3 double blind efficacy trial with a separate unblinded long term extension study. The open long term extension also contained a cohort of patients who were switched to SD-809 overnight from maintenance tetrabenazine treatment for comparison. The Phase 3 studies are reviewed to evaluate the safety and efficacy of SD-809. The TQT study is listed for reference but was reviewed by the Interdisciplinary Review Team (IRT) for QT studies.

Table 3 Studies considered in this review of efficacy and safety for SD-809.

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							
SD-809-C-15 (First-HD)	Randomized, Double-blind, Placebo controlled, Parallel group, Multi-center	SD-809 6 mg, 9 mg, or 12 mg 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	Change in Total Maximal Chorea 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.	8-week titration to optimal dose, 4-week maintenance (12-week total treatment duration)	90 enrolled and in ITT, mITT, and Safety Population 45 SD-809 45 placebo 81 in Per-Protocol Population 41 SD-809 40 placebo	Adult patients with chorea of Huntington's disease (CAG repeats ≥ 37) with a Total Maximal Chorea score ≥8	34 sites in US and Canada
Studies to Support Safety							
SD-809-C-16 (ARC-HD)	Open-label, 2-cohort, multi-center, Long-term	ARC-Rollover cohort: SD-809 6 mg, 9 mg, or 12 mg QD to BID dosing	Safety; Comparison to tetrabenazine in switch study	After titration period, patients receive long	Rollover: 75 Switch: 37 Total: 112	Rollover: Patients who completed Study	37 sites in US, Canada and Australia

	safety	with meals, about 10 hours apart (BID) ARC-Switch cohort: subjects started on a regimen of SD-809 providing comparable AUC to incoming Xenazine regimen		term maintenance therapy		SD-809-C-15 Switch: HD patients on stable doses of Xenazine	
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
SD-809-C-21	Randomized, double-blind, placebo- and positive controlled, 6-period crossover	SD-809 tablets: 12 mg and 24 mg Tetrabenazine: 50 mg Moxifloxacin: 400 mg Matched placebo for Tetrabenazine, SD-809, and moxifloxacin	Effect upon QTc interval	2 single doses of SD-809 1 single dose tetrabenazine 1 single dose moxifloxacin 2 single doses placebo	48 enrolled and in Safety Population 48 in Per-Protocol Analysis Set 41 in Per-Protocol PK Analysis Set	Heathy volunteers	1 site

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5.2. Review Strategy

The two clinical studies used in the efficacy and safety review of SD-809 are as follows:

SD-809-C-15 (First-HD): "A Randomized, Double Blind, Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated with Huntington Disease"

SD-809-C-16 (ARC-HD): "An Open-Label, Long-Term Safety Study of SD-809 ER in Subjects with Chorea Associated with Huntington Disease"

In this review, these trials will be labeled as C-15 and C-16, respectively. Note that C-16 has two cohorts. One group (Rollover) simply continued from C-15 for long-term open label treatment. A smaller group (Switch) did not come from C-15 but instead underwent an overnight conversion from stable maintenance tetrabenazine treatment to SD-809. A subset of this latter group also had pharmacokinetic sampling performed.

The approach to this review of efficacy and safety is straight forward. In addition to presenting and confirming the efficacy and reviewing the safety findings of the double blind trial (C-15), the Rollover cohort of the open study (C-16) also provides support for safe longer term use of SD-809. The Switch cohort will inform the process of converting patients being treated with tetrabenazine to SD-809. 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.

The tabulations and calculations in this review are performed by the reviewer using JMP 11.1 and JMP Clinical 11.2 software on the Sponsor supplied datasets conforming to CDISC SDTM and ADaM standards. Adverse event analysis used MAED software in addition. Any table or figure taken from the Sponsor's reports is referenced as such in the table or figure caption; the rest are created by me**.**

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. SD-809-C-15 ("First-HD") A Randomized Double Blind Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated with Huntington's Disease

6.1.1. Study Design

Overview and Objective

Study SD-809-C-15, "First-HD, A Randomized Double Blind Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated with Huntington's Disease" is the evidentiary trial for evaluating the effectiveness and safety of SD-809 (deuterated tetrabenazine) in treating the chorea of Huntington's disease.

Trial Design

This is a randomized, double blind, placebo controlled parallel group study in HD patients who have never been exposed to tetrabenazine. The overall treatment was 12 weeks in duration with an 8 week titration period followed by a 4 week maintenance period. The rating of chorea and an evaluation of clinical benefit was performed at Screening, Baseline, Week 9, and Week 12. The design is an accepted one, closely following the design that supported the RLD's approval.

Reviewer Comment: The rating of chorea, performed as part of the Total Motor Score (TMS) evaluation, was in fact done at every patient visit.

The trial was performed in the patient population intended for marketing deutetrabenazine. This population was defined by having manifest HD and genetic testing that confirmed the abnormal number of CAG repeats on chromosome 4 (≥ 37). The inclusion and exclusion criteria were usual and appropriate. Because this is a population with special vulnerabilities (cognitive and behavioral impairment), attention was paid to the ability of the patient to give informed consent.

To participate, the patient had to be an adult, have a Total Maximal Chorea (TMC) score ≥ 8 at Screening and Baseline visits and a Total Functional Capacity (TFC) Score ≥ 5 at Screening. The TMC and TFC are subscales of the Unified Huntington Disease Rating Scale (UHDRS). The patient needed to be able to walk for 20 yards without the help of another and to be able to swallow the study medication whole. A reliable caregiver was required to administer medication and come to all visits.

Previous exposure to tetrabenazine was not allowed in the original protocol. By amendment it was later allowed if the exposure had been more than six months earlier. If the patient lacked the capacity to provide informed consent (as determined by an independent assessment by a qualified healthcare provider not directly involved in other study activities), a legally authorized representative was required to provided written informed consent with the patient providing agreement.

Because sexual activity associated with cognitive impairment and impulse dyscontrol occurs in HD, special attention was also given to methods of contraception.

Inclusion and Exclusion criteria that are unique to this trial and patient population included the

following:

- HD was diagnosed clinically and by genotyping. The participant must have at least 37 polyglutamine CAG repeats on Chromosome 4 to be eligible.
- The participant's motor function has to have a severity of at least 8 points on the Total Maximal Chorea Scale and 5 points on the Total Functional Capacity Scale of the Unified Huntington's Disease Rating Scale (see below).
- The participant must have a reliable caregiver that interacts with the patient on a daily basis, oversees study drug administration, assures attendance at study visits and participates in evaluations, as required.

Patients were excluded if they had history of any of the following suicidal thoughts or behavior at Screening or Baseline:

- Previous intent to act on suicidal ideation with a specific plan (positive answer to question 5 on the Columbia-Suicide Severity Rating Scale), irrespective of level of ambivalence at the time of suicidal thought
- Previous preparatory acts or behavior
- A previous actual, interrupted or aborted suicide attempt
- Has a score ≥ 11 on the Depression Subscale of the Hospital Anxiety and Depression Scale (HADS) at Screening or Baseline.
- Has excessive dysphagia or dysarthria.
- Is taking drugs that prolonged QT intervals or has a QTcF > 450 msec in men or > 460 msec in women.
- The participant may not have received the following within 30 days of entry into the study: antipsychotics, metoclopramide, monoamine oxidase inhibitors, levodopa or dopamine agonists, reserpine, amantadine or memantine.

The dose range of the investigational product, (SD-809, 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.

Three dose strengths of SD-809 were used: 6, 9, and 12 mg tablets. All tablets (SD-809 or placebo) are identical in size and color (white).

The study treatments dose levels for titration were as follows:

Table 4 Study C-15 dose titration steps

Dose Level	Total Daily Dose	Morning Dose	Evening Dose
1	6 mg	6 mg	Placebo
	Tablets	1 x 6 mg	1 x placebo tablet
2	12 mg	6 mg	6 mg
	Tablets	1 x 6 mg	1 x 6 mg
3	18 mg	9 mg	9 mg
	Tablets	1 x 9 mg	1 x 9 mg
4	24 mg	12 mg	12 mg
	Tablets	1 x 12 mg	1 x 12 mg
5	30 mg	15 mg	15 mg
	Tablets	1 x 9 mg and 1 x 6 mg	1 x 9 mg and 1 x 6 mg
6	36 mg	18 mg	18 mg
	Tablets	2 x 9 mg	2 x 9 mg
7	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
8	48 mg	24 mg	24 mg
	Tablets	2 x 12 mg	2 x 12 mg

Assignment to treatment was based upon 1:1 randomization ratio through a web-based automated system. Patients were initially dosed at Visit 2 (Baseline). No stratification procedure was employed.

During the treatment period the sponsor, 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.

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 reach a level at which adequate chorea control had been achieved at a tolerable dose or until the maximum permitted dose was reached. Dose increase was permitted weekly and was limited to an increase of 6 mg/day each week. Doses were taken approximately 10 h apart during the day with meals.

If the patient experienced a protocol-defined “clinically significant” adverse event (defined as related to study medication, moderate or severe in intensity, or an SAE, dose reduction or suspension was allowed. Reductions were performed at the rate of 6mg/d at weekly intervals. Discontinuations were reviewed by the study’s medical monitor.

The trial was administered by a Steering Committee and adhered to GCP and appropriate ethical standards. The committee consisted of a sponsor representative, biostatistician, the study principal and co-principal investigators, a study coordinator, a psychiatrist, and an HD patient advocate. The Sponsor's medical monitor was tasked to review blinded safety data on a monthly basis during the conduct of the trial, including aggregate laboratory and adverse event data, and laboratory alert values. The medical monitor also reviewed all SAEs as they were reported.

A Safety Monitoring Committee was established and chartered to make recommendations to the Steering Committee and medical monitor.

The study used an electronic data capture system. Source data was transcribed onto source document worksheets and then entered into an electronic case report form.

Table 5 Study C-15 Schedule of events (modified from the Study C-15 protocol, p 10)

	Screening		Titration								Maintenance			Follow Up		Uns
Week	Up to -4	BL	1	2	3	4	5	6	7	8	9	10	12/ ET	13	16	
Visit Windows (in days)		0	± 1	± 3												n/a
Visit / Activity	V1	V2	T1	V3	T2	V4	T3	V5	T4	T5	V6	T6	V7	V8	T7	U
Clinic Visit	X	X		X		X		X			X		X	X		X
Telephone Contact			X		X		X		X	X		X			X	
Evaluate/Adjust Dose of study medication			X	X	X	X	X	X	X							
Evaluate Capacity for informed consent	X															
Informed Consent/Assent	X															
Selection Criteria	X	X														
Medical History/Demographics	X															
Vital Signs/Weight	X	X		X		X		X			X		X	X		X
Physical Examination	X	X											X			X
Complete Neurological Exam	X												X			X
Height	X															
12-lead ECG	X												X			
Chemistry/Hematology/UA	X	X				X							X			
CAG Repeat	X															
Randomization via IWRS		X														
Blinded CYP2D6 Genotype		X														
Pregnancy Test/FSH	S	U														
Blood Sampling for Pharmacokinetics											X		X			
HADS	X	X		X		X		X			X		X	X		X
C-SSRS	X	X		X		X		X			X		X	X		X
MoCA		X				X					X		X			
Video recording of TMC	X	X									X		X			
UHDRS - Motor	X	X		X		X		X			X		X	X		X
UHDRS - Cognition		X				X					X		X			
UHDRS - Behavior		X		X		X					X		X			
UHDRS - Functional Assessment		X											X			
UHDRS - Independence		X											X			
UHDRS - TFC	X	X											X			
UHDRS - Summary		X											X			
UPDRS - Dysarthria	X	X		X		X		X			X		X	X		X
Berg Balance Test (BBT)		X		X		X		X			X		X			X
Swallowing Disturbance Questionnaire (SDQ)	X	X		X		X		X			X		X	X		X
Barnes Akathisia Rating Scale (BARS)		X		X		X		X			X		X	X		X
Epworth Sleepiness Scale (ESS)		X		X		X		X			X		X	X		X
Patient Global Impression of Change						X					X		X			
Clinical Global Impression of Change						X					X		X			
SF-36		X											X			

Dispense Study Drug via IWRS		X	X	X	X	X	X	X	X		X					
Assess Drug Accountability/Compliance				X		X		X			X		X			
Assess Adverse Events	X	X	X	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		X

[Uns] Unscheduled Visit
[V#] Clinic visit number
[T#] Telephone visit number
[S] Serum pregnancy test for women of childbearing potential only
[U] Urine pregnancy test for women of childbearing potential only

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% of the expected doses of study drug.

Blinded CYP2D6 genotyping was done at the baseline visit. Patients receiving strong CYP2D6 inhibitors (bupropion, fluoxetine, paroxetine, or quinidine) were limited to a maximum of 36 mg/d of SD-809. A list of prohibited antipsychotic drugs was provided in the protocol, as was a list of prohibited QTc prolonging drugs.

Study Endpoints

Primary efficacy endpoint

The primary efficacy endpoint for this study is the change in Total Maximal Chorea Score (TMC) from Baseline (defined for each patient as the average of values from the Screening and Baseline [randomization] visits) to the end of the maintenance period (defined for each subject as the average of values from the Week 9 and Week 12 visits).

The Total Maximal Chorea (TMC) Score is determined from Item 12 of Part 1 of the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and quantifies chorea based on assessments of the face, mouth and tongue, trunk, and the four extremities. The Total Maximal Chorea score is a sum of chorea scores in the seven body regions. The range of possible scores is 0 to 28; lower TMC scores indicate less chorea.

Figure 2 Total Maximal Chorea Score - UHDRS (from the Study C-15 case report form)

The Total Motor Score of the UHDRS assesses all of the motor features of HD and including maximal chorea, maximal dystonia, ocular pursuit, saccade initiation and velocity, dysarthria, tongue protrusion, finger tapping, hand pronation and supination of hands, rigidity, bradykinesia, gait, tandem walking, and retropulsion. Lower TMS scores indicate better motor function.

The UHDRS is a research tool developed by the Huntington Study Group to provide a uniform assessment of the clinical features and the course of HD (HuntingtonStudyGroup, 1996). The UHDRS has been assessed for repeated administration during clinical studies; it has demonstrated reasonable inter-rater reliability for the motor scores. It is evaluates four symptomatic areas in HD: motor, cognition, behavior and function with ten subscales creating the measurements. The UHDRS scales their possible range of scores is summarized in the sponsor's table below:

Table 6 UHDRS score and subscale components (120 Day Safety Update, p 93)

Symptom/ Disease Area	Scale	Range	Direction of Improvement
UHDRS Components			
Motor	Total Motor Score	0-124	↓
	Total Maximal Chorea Score	0-28	↓
	Parkinsonism Subscale	0-40	↓
Cognition	Symbol Digit Modalities	0-120	↑
	Verbal Fluency	--	↑
	Stroop Interference Score	--	↑
Behavior	Behavioral Assessment	0-176	↓
Function	Functional Assessment	0-25	↑
	Independence Scale	10-100	↑
	Total Functional Capacity	0-13	↑

Key Secondary Endpoints

The following key secondary efficacy endpoints were to be analyzed using a hierarchical testing procedure:

Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) are single-item questionnaires that ask the patient participant (PGIC) and Investigator (CGIC) to assess their HD symptoms. Both assessments use a7-point Likert Scale, ranging from "*Very Much Worse"* (-3) to "*Very Much Improved*" (+3) to assess overall response to therapy. Patients and clinicians were asked, "With respect to your (or the patient's) overall Huntington's disease symptoms, how would you describe yourself (or the patient's condition) compared to immediately before starting study medication." Participants who did not provide a response at Week 12 were assumed to be treatment failures. The PGIC is in the hierarchy of statistical analysis above the CGIC. A treatment success is defined as *Much Improved* or *Very Much Improved* on the PGIC and CGIC at the Week 12 visit.

Change in the Short Form 36 Health Survey (SF-36) physical component summary score from Baseline to Week 12. The SF-36 is a short-form health survey with 36 questions used to evaluate health-related quality of life. While the entire SF-36 was administered in this study, the physical functioning scale (also known as the PF-10) was analyzed as a key secondary endpoint. The physical functioning scale is a 10-item subset of the SF-36 which examines the patient's self-perceived health-related limitations with physical activities.

Change in the Berg Balance Test (BBT) score from Baseline to Week 12. The BBT is a 14-item assessment of sitting, standing, transferring, and turning with higher scores representing better balance. The BBT was used to evaluate if a change in balance was associated with a reduction in chorea, since many medications currently used to treat chorea may worsen balance.

Reviewer Comment: it should be noted that HD patients have difficulties in balance as a feature of their disease independent of the severity of their chorea.

Other measures

A variety of other secondary measures (some used as safety assessments) were included in the study. Except for 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.

- Independent Video Rating of Chorea using the TMC, (range 0-124): Blinded expert raters evaluate randomized video tapes of patients in the trial. All videos for each subject were rated by the same reviewer in a randomized order in a single session and data were collected electronically.

Additional safety parameters include Adverse Events (AE), physical examination, vital signs,

clinical laboratory tests and electrocardiography (ECG).

Statistical Analysis Plan

The Statistical Analysis Plan for Study C-15 was finalized in its second version on November 3, 2014 (the trial's last patient completed December 5, 2014). It was not subject to Special Protocol Assessment or other agreement.

The cohort assessed for efficacy was the modified Intent-To-Treat Population (mITT). The mITT included all randomized patients that received study drug and had at least one post-baseline assessment of the Total Maximal Chorea Score (TMC).

The Per-Protocol Population (PPP) included all persons in the mITT that were at least 80% compliant with randomized study drug, had an assessment of TMC at Week 9 or Week 12, and had not taken prohibited concomitant medications.

The Safety Population (SP) included all participants who were administered any study drug.

Methodological considerations concerning the primary and secondary outcomes are as follows: Primary Endpoint is the change in TMC from Baseline (the mean of values from the Screening and Day 0 visits) to maintenance therapy (the mean of values from the Week 9 and Week 12 visits). If a participant is missing the TMC score at either the Screening or Day 0 visit, the Baseline TMC score is defined as the available score. If a participant is missing the TMC score at either the Week 9 or Week 12 visit, the maintenance therapy TMC score is defined as the available score. For patients with neither a Week 9 nor Week 12 TMC score, the last available assessment will be used in place of the value during the maintenance phase, i.e.: last observation carried forward (LOCF).

The primary analysis of this endpoint was performed on the mITT Population using an analysis of covariance (ANCOVA) model with the change from baseline in TMC as the dependent variable, treatment group as a factor, and the baseline TMC score as a covariate. The SD-809 and placebo treatments will be compared using a two-sided test at the 5% level of significance.

For both the PGIC and CGIC, treatment success is defined as Much Improved or Very Much Improved at the Week 12 visit. Participants whose status at Week 12 is not known as well as patients who are not Much Improved or Very Much Improved at the Week 12 visit will be considered treatment failures.

The global impression measures were analyzed in hierarchical fashion with analysis ending should significance be lacking. For the PGIC and CGIC endpoints, the proportions of participants who are a treatment success will be compared between treatments using Pearson's chi-square

test. The SF-36 and Berg Balance Test round out the pre-planned hierarchy of analysis.

A variety of secondary exploratory analyses were planned.

A supporting analysis of the primary endpoint was carried out using a linear mixed model repeated measures (MMRM) approach based on the mITT Population. For this and all exploratory analyses, including the linear mixed model repeated measures (MMRM) analyses of continuous endpoints, missing data was not imputed and only observed data was summarized.

Subgroup analyses were planned for the mITT Population on the primary and secondary efficacy outcome by CAG repeat value (CAG repeat value < median value, CAG repeat value ≥ median value) and by TMC at baseline (TMC < median value, TMC ≥ median value).

Additional analyses by dose level were planned to look at the effect of receiving a strong CYP2D6 inhibitor (bupropion, fluoxetine, paroxetine) at Baseline or being a poor CYP2D6 metabolizer.

No interim analysis of the trial was planned or performed.

A protocol amendment had allowed for enrollees to have been exposed to tetrabenazine in the past and it was intended to stratify efficacy analysis by this factor. Because in the end only five patients had previous tetrabenazine exposure, this stratification was dropped from the final analysis.

The reader is directed to the Biostatistics review for an in-depth discussion of the technical considerations and full review of the statistical methods.

Protocol Amendments

The first patient enrolled in this study on August 5, 2013 and the last patient completed the study on December 5, 2014. The first version of the protocol was dated February 25, 2013. There were 3 protocol amendments dated April 9, 2013, November 21, 2013 and February 27, 2014. Changes were of no consequence to the outcome of the efficacy of the trial and were designed to enhance patient safety, broaden potential enrollment, or clarify protocol details. The following changes were the most important ones noted:

- Patients receiving allowable doses of citalopram or escitalopram were to have additional electrocardiograms during titration.
- Subjects having an SAE were to have a blood sample drawn for pK measurement, if at all possible.
- Dose reductions during the maintenance period are allowed for the reason of adverse events only.

- SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be followed until resolution or for 28 days after the subject's last follow up visit.
- Exclusion criteria were loosened to allow study entry to patients who had been exposed to tetrabenazine but who had been off for more than 6 months.
- The primary statistical analysis was changed to include stratification for prior exposure to tetrabenazine in the ANCOVA model.

Data Quality and Integrity: Sponsor's Assurance

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 Sponsor.

The data was to be entered into a validated 21 CFR part 11 compliant database. The data management group was to be responsible for data processing and the Principal Investigator electronically signed and dated the appropriate electronic case report form (eCRF) page when instructed to do so by the study CRA. The Principal Investigator reviewed the data in the database, the data queries, and the site notifications.

The Sponsor affirmed that the standard procedures for handling and processing eCRF records followed Good Clinical Practice (GCP) and the Sponsor's (or CRO's) Standard Operating Procedures (SOPs). To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor conducted a quality assurance audit.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Sponsor 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 Sponsor's IND.

Financial Disclosure

The financial disclosures by clinical investigators (Form 3455) were reviewed for all 38 investigators in this covered clinical study. (N.B.: these disclosures also apply to Study C-16). Three principal site investigators and two sub-investigators were additionally compensated for tasks related to the trial. (b) (6) (PI, Site (b) (6)) conducted blinded ratings of the blinded video recordings of patients' movements. (b) (6) (PI, Site

(b) (6) and (b) (6) (PI, Site (b) (6)) provided consultation in the therapeutic area. (b) (6) (sub-investigators, (b) (6)) also conducted blinded ratings of the blinded video recordings of patients' movements.

The Sponsor placed into effect controls in the trial that appropriately mitigated any potential conflict of interest bias. In addition, video ratings were not a primary outcome measure in the trial. These clinical sites at (b) (6) enrolled (b) (6) patients, respectively, out of 123 patients in the trial.

Patient Disposition

A total of 123 patients were screened and gave informed consent to enter the study. Of these, 33 were ineligible or declined study participation. The remaining 90 patients were randomized to either SD-809 (N=45) or placebo (N=45) treatment. Almost all participants completed the trial: SD-809, N=44 (98 %); placebo, N=43 (96 %). One patient in the SD-809 group withdrew from the trial due to an adverse event. In the placebo group one patient withdrew from the study due to an adverse event and one patient was withdrawn by the site investigator (lack of efficacy).

The ITT, mITT and the safety populations are identical and consist of all 90 participants.

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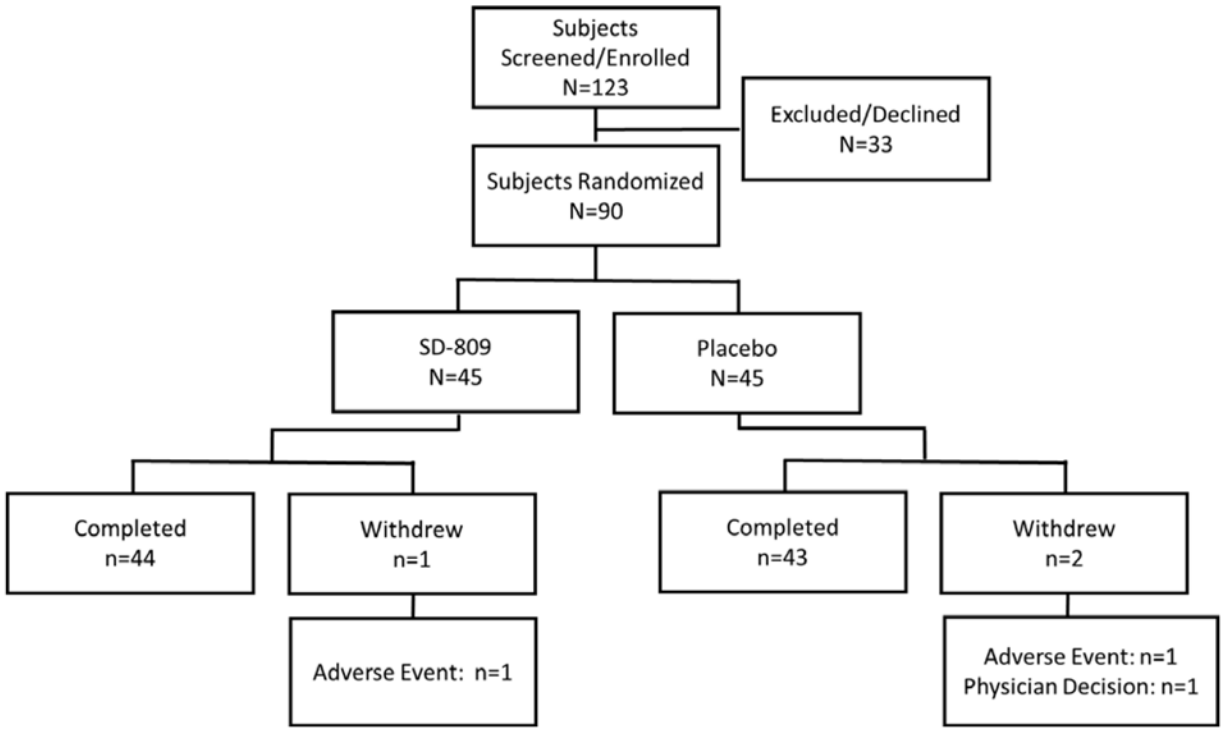
Table 7 Study C-15 Disposition of participants (CSR, p 56)



Protocol Violations/Deviations

There were 6 major protocol violations; all were related to either non-compliance or taking a prohibited medication. None resulted in the exclusion of a participant from the mITT population. It is unlikely that these protocol deviations impacted safety or efficacy conclusions.

Table of Demographic Characteristics

Demographic and baseline characteristics of the ITT study population (n=90) are summarized in the sponsors table below.

The population of this study is representative of the HD population in which this drug will be used. It should be noted that the HD gene found in North America can be traced back to an ancestral source in Suffolk, England from which a small group of individuals migrated to this continent in 1620 (Bruyn, 1968). As a result, the disorder is found predominantly, though not exclusively, in the white population in North America.

Reviewer's comment: The population in this study mirrors very closely all of the demographic features of the participants in the pivotal efficacy trial for the RLD.

Table 8 Study C-15 Demographics characteristics (CSR, p 60)

Parameter	SD-809 (N=45)	Placebo (N=45)	Total (N=90)
Mean (SD) Age[a], years	55.4 (10.32)	52.1 (13.36)	53.7 (11.98)
Minimum, Maximum	23, 74	30, 73	23, 74
Gender, n (%)			
Male	22 (48.9)	28 (62.2)	50 (55.6)
Female	23 (51.1)	17 (37.8)	40 (44.4)
Race, n (%)			
Black	0	5 (11.1)	5 (5.6)
White	45 (100)	38 (84.4)	83 (92.2)
Multiple	0	2 (4.4)	2 (2.2)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	45 (100)	45 (100)	90 (100)
Mean (SD) Weight at Screening, kg	74.13 (13.618)	74.11 (15.129)	74.12 (14.312)
Minimum, Maximum	47.2, 99.5	44.9, 100.4	44.9, 100.4
Mean (SD) BMI at Screening, kg/m^2	25.44 (4.282)	25.96 (4.584)	25.70 (4.418)
Minimum, Maximum	17.1, 35.3	15.8, 35.4	15.8, 35.4
Mean (SD) CAG Repeat Length	43.4 (2.69)	44.3 (4.41)	43.9 (3.66)
Minimum, Maximum	40, 53	36, 59	36, 59
CYP2D6 Genotype, n (%)			
Poor Metabolizer	3 (7.1)	2 (4.5)	5 (5.8)
Not Poor Metabolizer[b]	39 (92.9)	42 (95.5)	81 (94.2)
Missing	3	1	4
Mean (SD) Total Maximal Chorea Score at Baseline[c]	12.07 (2.727)	13.24 (3.488)	12.66 (3.169)
Minimum, Maximum	8.0, 19.5	8.5, 21.5	8.0, 21.5
Using Antidepressant at Baseline, n (%)	28 (62.2)	24 (53.3)	52 (57.7)

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

As noted above, most participants were normal metabolizers of CYP 2D6. They also

represented a usual number of CAG polyglutamine repeats in their gene sequencing. With an autosomal dominant pattern of inheritance, either sex is equally susceptible to inheriting the disorder from either parent. However, there is an imbalance in the placebo group, with male predominance. The baseline severity of chorea as rated by the TMC score is not different between the groups. Most patients were between the ages of 40 and 64 at the time of entry, but 19% of participants were 65 or older. Canadian trial sites accounted for 8% of patients entered.

Table 9 Study C-15 Age distribution of participants

	Actual Treatment Arm					
	Placebo		SD-809 ER			
Age Group	Count	Column %	Count	Column %	Count	% of Total
Age 39 or younger	10	22.2%	4	8.9%	14	15.6%
Age 65 and older	10	22.2%	7	15.6%	17	18.9%
Age between 40 and 64	25	55.6%	34	75.6%	59	65.6%
All	45	100.0%	45	100.0%	90	100.00%

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
Compliance with treatment was high overall (95%) with no difference between the treatment arms. This was likely due to the requirement for a responsible caretaker to oversee the patient at home.

Concomitant Medication
Almost everyone (84 of 90 participants) in the trial was taking at least one other concomitant medication at baseline. The most common medications at baseline were antidepressants (SD-809: 28 [62%] versus placebo: 24 [53%]), anti-epileptics (SD-809: 10 [22%] versus placebo: 5 [11%]), and anxiolytics (SD-809: 6 [13%] versus placebo: 1 [2%]). As excluded by the protocol, no participants were using antipsychotic medications at baseline.

During the trial, the use of concomitant medication did not change substantively with the exception of anti-epileptic drugs, where this class was added to six patients receiving SD-809 and three in the placebo arm were treated. (This appears to be off label use, for behavioral not seizure control). One patient was treated with antipsychotic medication during the trial. There was no planned use of "rescue medication" during the trial.

Following antidepressants, the most common concomitant medications at baseline by class were lipid-modifying agents (n=28, 31%) and anti-inflammatory/anti-rheumatic products (n=17, 19%). Between the treatment arms, there were no differences of note in the use of these classes of drugs.

Efficacy Results – Primary Endpoint

Reviewer Comment: In this section I rely heavily upon the expertise and findings presented in the Statistical Review and Evaluation, Office of Biostatistics to corroborate the Sponsor's analyses of efficacy presented below. While the Sponsor's graphs used below illustrate results using the ITT population, the ITT, mITT, and safety populations are identical in Study C-15.

Primary Endpoint

The Sponsor summary of the statistical results of the primary outcome in Study C-15 is taken from this table of the change of the TMC score from baseline to maintenance therapy (the mean of Week 9 and 12 ratings). The result was highly significant by both the analysis of covariance and a mixed model repeated measures approach.

Table 10 Study C-15 Primary endpoint change from baseline (CSR, p 65)

	Change in Total Maximal Chorea Score		
Statistic	**SD-809 (N=45)**	**Placebo (N=45)**	**Difference in Means (SD-809 - Placebo) and 95% CI[a]**
Least Squares Mean[b] (SD)	-4.42 (2.953)	-1.93 (2.666)	-2.49 (-3.69, -1.29)
Minimum, Maximum	-10.5, 3.0	-8.0, 7.0	--
95% CI for Mean[a]	(-5.25, -3.48)	(-2.79, -1.19)	--
p-value[b]	--	--	<0.0001

This graph from illustrates the Total Maximal Chorea score in the ITT population over the course of the trial.

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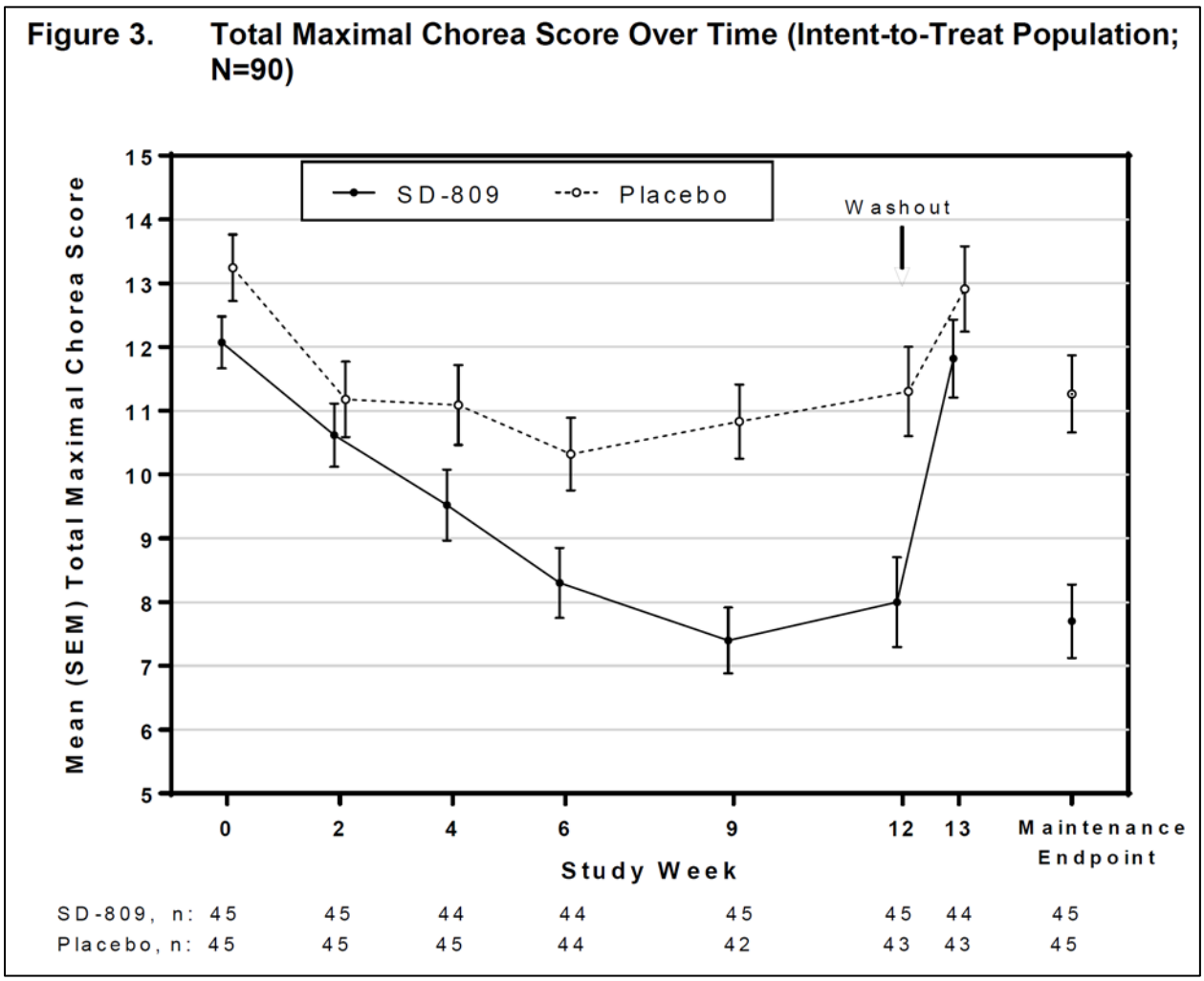
Figure 3 Study C-15 TMC score over time (CSR, p 75)



It is noted that there is a placebo effect especially in the initial weeks of medication titration in the trial but the improvement in TMC separates the two groups as the trial progresses from Week 4 through to the end at Week 12.

Reviewer Comment: It is usual for neurological drugs to take a few weeks to demonstrate their full pharmacodynamic effect. Beginning at a lower dose and titrating for clinical effect also affected the onset of treatment effect.

Week 13 reflects the TMC following 1 week's washout at study's end. No rebound of the severity of chorea beyond baseline levels in noted. The test- retest reliability of the TMC as a metric is also evident in how closely the range of scores and the standard errors of the means

at Week 13 (study's end) mirror the baseline values. This is quantified in the Sponsor's summary of scores by visit.

Table 11 Study C-15 TMC score by visit (CSR, p 76)

Table 19. Change in Total Maximal Chorea Over Time (Intent-to-Treat Population; N=90)

	SD-809 (N=45)			Placebo (N=45)		
	n	Mean (SD) TMC	Mean Change from Baseline[a]	n	Mean (SD) TMC	Mean Change from Baseline[a]
Screening	45	11.91 (2.695)	--	45	12.96 (3.655)	--
Day 0	45	12.22 (3.089)	--	45	13.53 (3.811)	--
Baseline[a]	45	12.07 (2.727)	--	45	13.24 (3.488)	--
Week 2	45	10.62 (3.359)	-1.44 (2.108)	45	11.18 (3.956)	-2.07 (2.807)
Week 4	44	9.52 (3.682)	-2.38 (2.820)	45	11.09 (4.188)	-2.16 (3.041)
Week 6	44	8.30 (3.664)	-3.67 (2.726)	44	10.32 (3.796)	-2.81 (2.800)
Week 9	45	7.40 (3.480)	-4.67 (2.757)	42	10.83 (3.774)	-2.21 (2.899)
Week 12	45	8.00 (4.748)	-4.07 (3.818)	43	11.30 (4.591)	-1.85 (3.188)
Maintenance Therapy[a]	45	7.70 (3.868)	-4.37 (2.953)	45	11.26 (4.075)	-1.99 (2.666)
Week 13	44	11.82 (4.065)	-0.26 (2.656)	43	12.91 (4.380)	-0.50 (2.708)

Key Secondary Endpoints

The Patient Global Impression of Change corroborates the primary outcome. Using a Pearson's chi-square test, the Sponsor compared the proportion of those patients who perceived themselves as *Much Improved* or *Very Much Improved*.

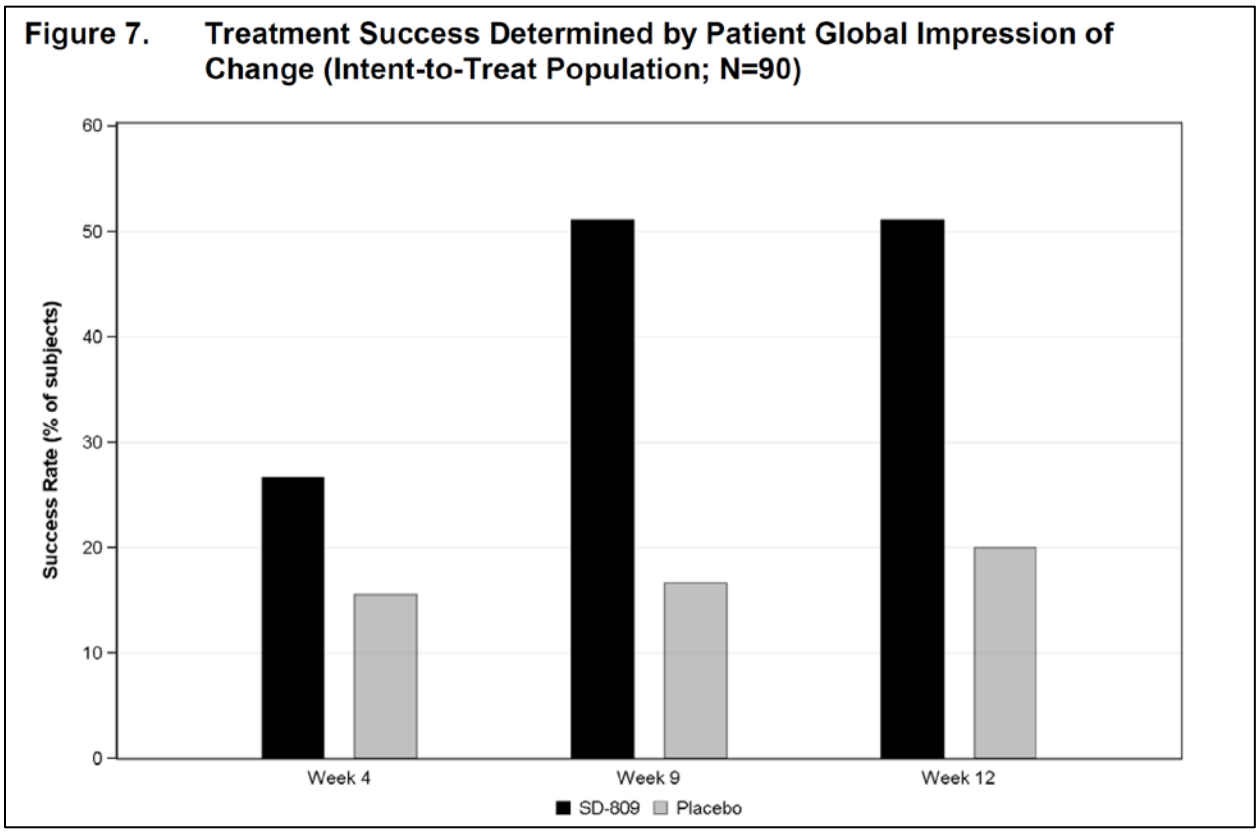
Table 12 Study C-15 Patient global impression of change (CSR, p 67)

Table 12. Treatment Success at End of Therapy Determined by the Patient Global Impression of Change (Intent-to-Treat Population; N=90)

	SD-809 (N=45) n (%)	Placebo (N= 45) n (%)	Difference in Percentages for Treatment Success (SD-809 - Placebo) and 95% CI[a]
Treatment Success at the End of Therapy[b]	23 (51.1)	9 (20.0)	31.1 (12.4, 49.8)
p-value[c]	--	--	0.0020

The patient's self-perceived improvement reflects the improvement in TMC scores as they begin to separate between arms at Week 4:

Figure 4 Study C-15 Patient global impression of change - responders by week (CSR, p 80)



Next in the hierarchy of statistical analysis, the Clinical Global Impression of Change also demonstrates a greater proportion of improved patients in the active treatment arm as judged by site investigators.

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Table 13 Study C-15 Clinical global impression of change (CSR, p 68)

Table 13. Treatment Success at End of Therapy Determined by the Clinical Global Impression of Change (Intent-to-Treat Population; N=90)

	SD-809 (N=45) n (%)	Placebo (N= 45) n (%)	Difference in Percentages for Treatment Success (SD-809 - Placebo) and 95% CI[a]
Treatment Success at the End of Therapy[b]	19 (42.2)	6 (13.3)	28.9 (11.4, 46.4)
p-value[c]	--	--	0.0022

The SF-36 demonstrated a difference in the mean scores using the baseline score as a covariate for the ANCOVA. While there is a statistically significant divergence between the study's arms, it is based more on the numerical worsening of the placebo group rather than an improvement in the treatment group (of less than one point). The clinical significance, if any, is unclear. There are ten different domain scores in this rating scale. By the Sponsor's own analysis of these subscales, there were no statistically significant differences between SD-809 and placebo after adjustment for baseline with the exception of a single domain, the physical functioning subscale.

Table 14 Study C-15 SF-36 Physical Functioning Score (CSR, p 69)

Table 14. SF-36 Physical Functioning Score: Change from Baseline to Week 12 (Intent-to-Treat Population; N=90)

	Change in SF-36 Physical Functioning Score from Baseline to Week 12		
Statistic	SD-809 (N=45)	Placebo (N=45)	Difference in Means (SD-809 - Placebo) and 95% CI[a]
n	45	43	
Least Squares Mean[b] (SD)	0.74 (9.773)	-3.61 (9.669)	4.34 (0.41, 8.27)
Minimum, Maximum	-29.5, 27.4	-42.1, 12.6	--
95% CI for Mean[a]	(-3.08, 2.80)	(-5.67, 0.28)	--
p-value[b]	--	--	0.0308

The last key secondary outcome as specified by the Sponsor is the Berg Balance Test. BBT was improved with SD-809 compared with placebo, although the difference was not statistically significant; the difference in means was less than one point, SD-809 = 2.2 (SD 3.5) vs Placebo =1.3 (SD 4.0); p=0.1415.

Other secondary outcome analyses performed by the sponsor held less value due to the unknown metric qualities of the outcome measures used and because of statistical vulnerability due to the multiplicity of analyses performed. Scales that quantify potentially drug related side

effects are reviewed in the discussion of safety, below.

Subgroup and Subpopulation Analyses

The Sponsor performed a number of subgroup analyses by parsing the various measures used in evaluation and looking for correlations of efficacy. For example, the TMC score was parsed into groups above and below median baseline values. Both subgroups appear to have improved with active drug treatment. The subgroup with higher than median TMC scores at baseline did not perceive their improvement to be clinically significant (PGIC) when compared to the subgroup with lower TMC scores. The site investigators (CGIC) had a similar assessment of these two groups. Otherwise, these analyses did not shed more understanding into the relative efficacy of SD-809 in reducing chorea in any particular subgroup.

Subpopulation analysis by race (83/90 white) or geographic region (US=83; Canada=7) was not possible. The Statistical Reviewer was able to look at gender and age. There was a baseline imbalance between the arms in gender but this was not statistically significant. For both sexes, SD-809 was statistically superior to placebo for the primary (TMC) and secondary (PGIC and CGIC) outcome measures at Week 12. Similarly, for patients aged above and below 65, SD-809 was statistically superior to placebo for the primary (TMC) and secondary (PGIC and CGIC) outcome measures at Week 12.

Data Quality and Integrity – Reviewers' Assessment

This reviewer had no concerns or questions about the quality and veracity of the data. OSI findings are summarized in Section 4.6

6.2. SD-809-C-16 ("ARC-HD") An Open-Label, Long Term Safety Study of SD-809 ER in Subjects With Chorea Associated With Huntington Disease

6.2.1. Study Design

Overview and Objective

This is a long-term unblinded open label safety study of SD-809 in patients with Huntington's disease. The objectives of this study were to

- Evaluate the safety and tolerability of titration and maintenance therapy with SD-809 ER
- Evaluate the safety and tolerability of switching patients from tetrabenazine to SD-809 ER
- Evaluate the pharmacokinetics of tetrabenazine, SD-809 and their respective α- and β-HTBZ metabolites in subjects switching from tetrabenazine to SD-809 ER

Trial Design

This open label study is divided into a screening period, a dose adjustment/titration period, a long term treatment period, and a post-treatment safety follow up period for those participants leaving the study. Evaluations of participants include efficacy, safety and pharmacokinetic measures.

Diagnostic criteria for HD, inclusion and exclusion criteria for entry into the study, and the list of prohibited concomitant medications mirror those of Study C-15. This is also true of study administration, accountability of drug, measures of compliance, and the identification and management of adverse events. The Sponsor intends to continue this study until SD-809 becomes commercially available in the U.S.

Two groups of patients are entered into this study:
Rollover patients are those who successfully completed Study C-15 and continued on long-term SD-809 after a 1-week wash out period. Study C-15 ends with a one week washout followed by a clinical evaluation at the Week 13 visit. This clinical evaluation also serves as the evaluation for the Baseline visit of this study. The Sponsor's expectation was that all participants of C-15 would roll over into C-16.

As Rollover patients had discontinued study drug (SD-809 or placebo) for 1 week at the completion of Study C-15, they undergo titration on SD-809 when initiating Study C-16. During titration, the investigator, in consultation with the participant and their caregiver, determines when an adequate level of chorea control has been achieved. The dose of SD-809 may be adjusted weekly (upward or downward) in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48mg is reached) to identify any of the following:

- a dose that adequately controls chorea,
- the patient experiences a protocol-defined "clinically significant" adverse event (related to study medication and moderate or severe in intensity)
- the patient has an Serious Adverse Event
- the maximal allowable dose is reached.

Participants will have a clinic visit at Week 1 and a telephone contact at Week 2, in order to evaluate safety and establish an optimal dose. Although rollover patients will enter the long term treatment period after Week 2, dose adjustment (upward or downward) may continue through Week 8 to optimize chorea control. Additional dose adjustments may be made after Week 8 if thought to be clinically indicated.

Switch patients are those who were currently receiving stable doses of tetrabenazine for the treatment of chorea associated with HD and then converted overnight to SD-809 based on an algorithm designed to achieve comparable exposure to total (α+β)-dihydrotetrabenazine (HTBZ)

metabolites. Patients in this cohort were given a full screening evaluation within 30 days of the Baseline assessment prior to switching to SD-809. The study's schedule of events follows below.

Participants continue taking their TBZ regimen through midnight of Day 0 and are then switched directly to their assigned SD-809 regimen the next morning. The dose of SD-809 may be adjusted weekly (upward or downward) in increments of 6 mg per day (6 mg/day or 12 mg/day after a total daily dose of 48mg is reached) until one of the following occurs:

- a dose level is reached that adequately controls chorea,
- the patient experiences a protocol-defined "clinically significant" adverse event (related to study medication and moderate or severe in intensity)
- the patient has an Serious Adverse Event
- the maximal allowable dose is reached.

Participants will have a clinic visit at Week 1 and a telephone contact at Week 2, in order to evaluate safety and establish an optimal dose. Although switch patients will enter the long term treatment period after Week 2, dose adjustment (upward or downward) may continue through Week 4 to optimize dose level. Additional dose adjustments may be made after Week 4 if thought to be clinically indicated.

Initial pharmacokinetic data obtained by the Sponsor resulted in the following table for guiding the choice of initial SD-8089 dose:

Table 15 Study C-16 Overnight switch dose selection table (Study C-16 protocol, p 37)

If a Switch Subject's Incoming Total Daily TBZ Dose is:	Then, the Initial Total Daily SD-809 ER Dose Should Be:		Taken As:	
			Morning Dose	Evening Dose
12.5 mg	→	6 mg	6 mg	–
25 mg	→	12 mg	6 mg	6 mg
37.5 mg	→	18 mg	9 mg	9 mg
50 mg	→	24 mg	12 mg	12 mg
62.5 mg	→	30 mg	15 mg	15 mg
75 mg	→	36 mg	18 mg	18 mg
87.5 mg	→	42 mg	21 mg	21 mg
100 mg	→	48 mg	24 mg	24 mg

A **Pharmacokinetics Sub-Study** was conducted to evaluate the pharmacokinetics (pK) of tetrabenazine and SD-809 in the Switch patients. It was planned for approximately 12 participants to have rich pK sampling and approximately 24 participants will have sparse pK

sampling. The pK of tetrabenazine and metabolites were to be assessed at the Baseline visit and the pK of SD-809 and metabolites were to be assessed at the Week 8 visit. If a patient requires a dose change at Week 8, the Week 8 visit assessments were to be conducted except for pK sampling which was to be postponed until Week 15.

Long-term Treatment Period
After the initial titration periods in both the Rollover and Switch studies, all participants merge into the same long-term treatment period. During long term treatment, all patients are contacted by telephone at Week 3 (the first week of long-term treatment period) and return to the clinic on Weeks 4, 8, 15, 28 and every 13 weeks thereafter for evaluation of safety and control of chorea.

Switch patients have an additional telephone contact at Week 7. Rollover patients have an additional telephone contact at Week 5. Patients who have not achieved a stable dose by the Week 4 visit (Switch cohort) or Week 5 telephone contact (Rollover cohort) may have unscheduled visits or telephone contacts in order to further adjust their dose upward or downward. Interactions with patients for dose adjustment alternate between telephone contacts and clinic visits. During long-term treatment, further dose adjustments of SD-809 can be made, if necessary, but not more often than weekly. Dose adjustments were to be based on all available clinical information including any reports of adverse events, degree of chorea control, and safety evaluations. Dose suspensions of up to a week are allowed if clinically warranted.

Pending regulatory decision, no date for study termination has been given by the sponsor. Patients ending participation have a visit at the discontinuation of treatment as well as one week later after washout. A final follow-up telephone contact occurs at 4 weeks after discontinuation of study drug.

Schedule of Events
The data collection for study endpoints and all clinical evaluations enumerated below take place at the following intervals:

Baseline - Day 0
Visit 2 – Week 1 for Switch Cohort and Week 2 for Rollover Cohort
Visit 3 – Week 4
Visit 4 – Week 8
Visit 5 – Week 15
Visit 6 – Week 28
Visit X -- Every 13 weeks after Visit 6 until the study ends
End of Treatment Visit takes place 1 week after Visit 6 or 1 week after any subsequent 13 week visit.

For the Switch cohort, blood sampling for pK takes place at Baseline (Day 0), Visit 4 (Week 8), at the End of Treatment Visit (Week 28) and at unscheduled visits for AEs.

Study Endpoints

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. Because of the design of the study and the small N at later time points, no efficacy analysis was performed.

Efficacy: The changes in Total Maximal Chorea (TMC) score and Total Motor Score from the UHDRS motor assessment are the efficacy endpoints for this study.

Safety: The safety endpoints for this study are the incidence of adverse events; observed values and changes from baseline in clinical laboratory parameters, vital signs, electrocardiogram and QTc; results from a variety of rating scales:

Columbia Suicide Severity Rating Scale (C-SSRS)
Unified Huntington Disease Rating Scale (UHDRS)
Unified Parkinson's Disease Rating Scale (UPDRS) (dysarthria item only)
Barnes Akathisia Rating Scale (BARS)
Hospital Anxiety and Depression Scale (HADS)
Epworth Sleepiness Scale (ESS)
Montreal Cognitive Assessment (MoCA)

The clinical laboratory tests performed during the study are as follows:

Table 16 Study C-16 Clinical laboratory tests (SAP, p 31)

Serum Chemistry		
• Sodium	• Creatinine	• Albumin
• Potassium	• Total calcium	• Total bilirubin
• Chloride	• Phosphate	• Direct bilirubin
• Bicarbonate	• Uric Acid	• Alkaline phosphatase (ALP)
• Magnesium	• Cholesterol	• Alanine aminotransferase (ALT)
• Glucose	• Triglycerides	• Aspartate transaminase (AST)
• Blood urea nitrogen (BUN)	• Total Protein	• Lactate dehydrogenase (LDH)

Hematology	*Urinalysis*
• Hemoglobin • Hematocrit • Red blood cell count (RBC) • Mean cell volume (MCV) • Platelets • White cell count • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	• Leucocytes • Nitrites • Urobilinogen • Protein • pH • Blood • Specific gravity • Ketone • Bilirubin • Glucose • Microscopic exam (if indicated)

Pharmacokinetics: Sampling of plasma concentration of SD-809 were planned for the end of treatment in the study and at unscheduled visits related to adverse events. These plasma concentrations were also to be used in a separate population PK analysis by the sponsor.

Statistical Analysis Plan

Because this is an open label single arm safety study, no formal analysis was planned by the sponsor. The SAP lists simple descriptive analyses for the outcomes listed above.

For TMC, TMS, ESS, SDQ, UPDRS (dysarthria item) and BARS, paired t-tests were used to descriptively analyze changes from Baseline.

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 planned for the Switch study to look at the results of the crossover from TBZ to SD-809 before the end of the open long term extension period. No compensation for multiplicity of analyses was planned.

Protocol Amendments

The study enrolled its first participant on November 11, 2013. There were amendments to the protocol on January 10, 2014 and July 22, 2014. These amendments were generally clarifications of procedures in the initial protocol. They mirrored the procedural amendments to Study C-15. The second amendment allowed for additional dose adjustments and increased the

maximum allowed SD-809 dose in the open trial to be 72 mg daily (36 mg BID). Individuals with CYP2D6 inhibition were restricted to 36 mg daily.

Data Quality and Integrity: Sponsor's Assurance

The Sponsor took steps to assure the accuracy and reliability of data with review of protocol procedures with the clinical investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor.

The Sponsor re-affirmed that the standard procedures for handling and processing eCRF records followed Good Clinical Practice (GCP) and the Sponsor's (or CRO's) Standard Operating Procedures (SOPs). To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor planned to conduct a quality assurance audit.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Sponsor 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). This study was performed under the Sponsor's IND.

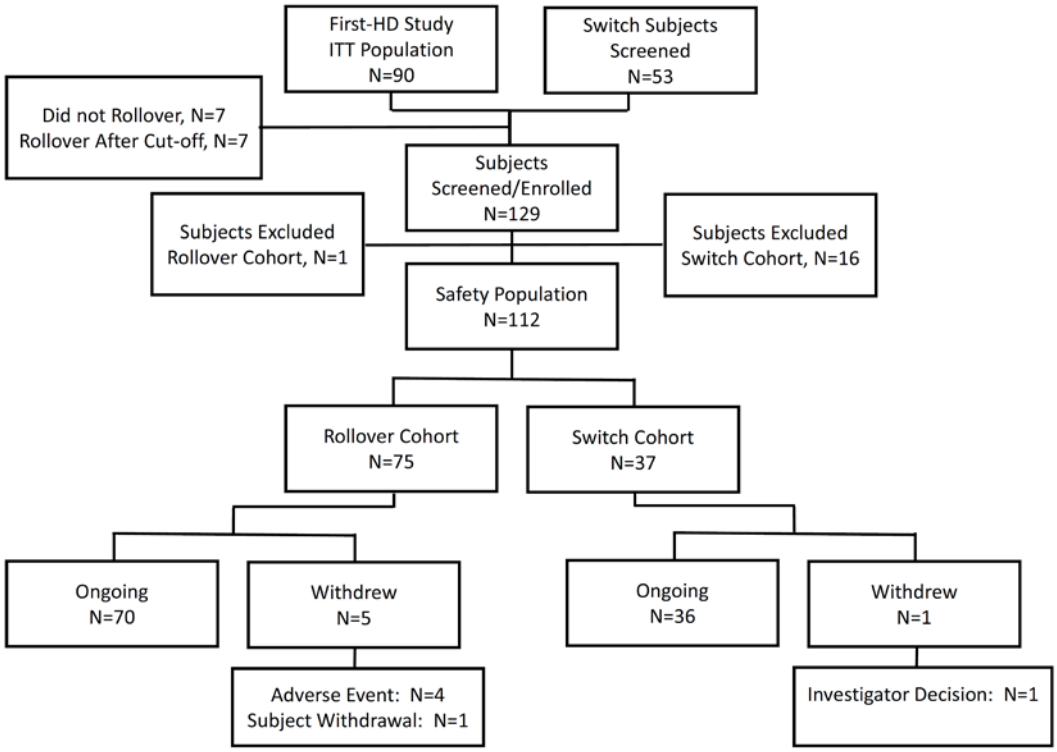
Financial Disclosure

The investigators in Study C-16 were also investigators in Study C-15. The financial disclosure information was reviewed and discussed in the latter trial's Financial Disclosure section above.

Patient Disposition

This section of the review of Trial C-16 incorporates the additional information that was submitted in the 120 Day Safety Update with the cutoff date March 31, 2015.
Patient disposition from the original cutoff date (November 11, 2014) is illustrated in the Sponsor's flow chart below.

Figure 5 Study C-16 Disposition of participants (CSR, p 59)



By the time of the 120 Day Safety Update, the number of patients in the safety population increased to 119, with 7 additional patients in the Rollover cohort. The Sponsor's updated tally of withdrawals from the study is as follows:

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Table 17 Study C-16 Withdrawals (120 Day Safety Update, p 26)

	Rollover Cohort (N=82) n (%)	Switch Cohort (N=37) n (%)	Total (N=119) n (%)
Number of Subjects in Safety Population	82 (100.0)	37 (100.0)	119 (100.0)
Number of Subjects who Withdrew from Study Early[a]	9 (11.0)	3 (8.1)	12 (10.1)
Primary Reason for Withdrawal			
Adverse Event[a]	6 (7.3)	1 (2.7)	7 (5.9)
Lost to Follow-up	1 (1.2)	0 (0.0)	1 (0.8)
Non-Compliance With Study Drug Dosing	1 (1.2)	0 (0.0)	1 (0.8)
Subject Withdrawal	1 (1.2)	0 (0.0)	1 (0.8)
Major Violation or Deviation of Study Protocol	0 (0.0)	1 (2.7)	1 (0.8)
Investigator Judgment	0 (0.0)	1 (2.7)	1 (0.8)

Protocol Violations/Deviations

There were 48 major protocol deviations. These consisted of 34 cases of non-compliance caused by patients thought to have taken more medication than prescribed ("possible overdoses" in the DV dataset). Review of this deviation revealed that these categorizations were given to instances where the patient returned fewer pills than they should have for pill count at the next study visit. The default conclusion was that the patient had taken the missing pills. However, instances of withdrawal from the study do not corroborate this default conclusion. Improperly obtained informed consent involved 14 patients.

Two patients in the Switch study incorrectly overlapped their tetrabenazine treatment with SD-809 for the first day (patients 031-7605 and 083-7327).

It is unlikely that these violations affected the integrity or outcome of the study.

Demographic Characteristics

The characteristics of the Rollover cohort in this study are identical to that of Study C-15. Of the 87 completers of that study, 75 entered this open-label continuation. The demographic characteristics of the Switch cohort (age, gender, ethnicity, concomitant medication, years of

overt disease, number of CAG repeats, and so forth) are also virtually identical to that of the Rollover cohort.

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

Two patients in the Switch cohort were poor CYP 2D6 metabolizers, bringing the total of such patients in C-16 to 6.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Rollover cohort had good compliance (> 96%) in taking SD-809 including during the initial 8 week titration phase. The Switch cohort average compliance was only 80%, while the median compliance was 94%. A few individuals reflected most of the non-compliance in this cohort.

The concomitant medication use was identical to that in Study C-15. There was no plan for rescue medication.

Efficacy Results - Primary Endpoint

Because this was an open trial with a single treatment arm, no primary efficacy endpoint was chosen.

Data Quality and Integrity - Reviewers' Assessment

This reviewer had no concerns over the quality and integrity of the data. The accuracy of coding verbatim descriptions of AEs into Preferred Terms was checked and in some cases, adjusted to reduce any splitting of events across similar terms in a given SOC (e.g. terms related to mood; please see Section 8).

Efficacy Results - Secondary and other relevant endpoints

Because this was an open trial with a single treatment arm, no efficacy analysis was planned.

Durability of Response

The duration of response to SD 809 is difficult to assess given the limitations of the amount of data available for long term use. The Sponsor presented the TMC scores in the Rollover cohort but the numbers in each analysis set decrease rapidly over time, censored by duration of the trial itself. By week 15, only half of the original patients in the Rollover cohort are evaluable (34 of 71).

Additional Analyses Conducted on the Individual Trial

The Sponsor evaluated the safety and tolerability of switching subjects from Xenazine to SD-809 from one day to the next using a 2:1 dose conversion ratio. At entry, 37 patients taking a mean dose of 42 mg Xenazine daily (range 12.5 – 100 mg) were converted to SD-809, mean dose of 20.3 mg daily (range 6 – 48 mg). Over subsequent weeks doses were increased based upon clinical control of chorea.

The quantity of the data in Switch cohort was limited by the data cutoff date created by the Sponsor (November 7, 2014). The sponsor performed an interim analysis of their effort to determine the accuracy of conversion dose choice based upon the first 12 participants. A final analysis of the conversion algorithm was not submitted in the 120 Day Safety, but updated datasets submitted with the safety update did document dose changes that took place in the ensuing weeks after the overnight conversion. The dose taken at Week 1 is the dose based on the stable Xenazine dose at entry. In order to be consistent with the length of the titration period in Study C-15, for comparison I looked at the SD-809 daily dose each patient was taking at Week 8. The graph below represents their Week 1 SD-809 dose compared to the Week 8 dose clinically needed for the 35 remaining patients.

Figure 6 Study C-16 Switch Cohort: SD-809 dose (mg/d) at overnight switch and at Week 8

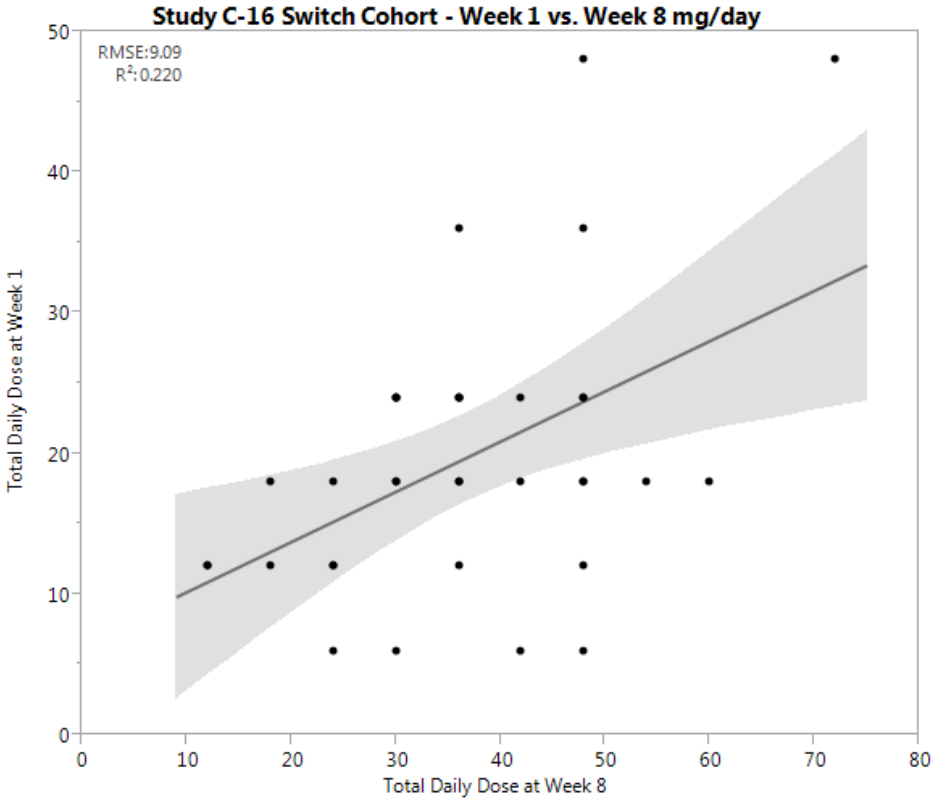

Table 18 Study C-16 Switch Cohort: mean daily dose at Week 1 and Week 8

Study C-16 Mean daily dose at Week 1 vs Week 8 (N=35)			
	SD-809 mg/d	Lower 95%	Upper 95%
Week 1	19.7	16.2	23.2
Week 8	36.7	32.1	41.3
Mean Difference of Pairs	17	12.7	21.2

The regression line fit to the data does demonstrate a roughly 2:1 ratio of initial dose to final dose. However the fit of the line is quite poor, suggesting great inter-individual variability (r^2 = 0.220). The fit does not improve with non-linear solutions.

The results at 8 weeks suggest that the initial conversion of a given Xenazine dose to half the mg in SD-809 is a safely conservative choice at which to begin. There were two patients who were poor CYP2D6 metabolizers: patient 054-7891 initially dosed at 24 mg/d SD-809 required 30 mg/d at Week 8. Patient 031-7602 initially dosed at 18 mg/d SD-809 required 48 mg/d at Week 8.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Please see the analysis of efficacy in Section 6 for Study C-15, the single pivotal trial in this application. Because of the uniformity of the study population, small size of the study and the dosage range used, it is not possible to make useful conclusions about sub-population analysis and dose response relationships.

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7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The effect created by being on medications that inhibit CYP2D6 and or by being a person who is a poor CYP 2D6 metabolizer remains unclear. The sample size is too small to make definitive conclusions about the effective dose range in this population.

We can expect to see higher doses of SD-809 used in the clinical setting. In the C-16 open label study, 28 patients were titrated above 48 mg/d.

7.2.2. Other Relevant Benefits

SD-809 with twice a day dosing has the potential to provide relief to caregivers who supervise medication administration. This convenience could be associated with fewer medication administration errors and missed doses than tetrabenazine which must be given three times daily at higher doses.

7.3. Integrated Assessment of Effectiveness

SD-809 has met the statutory standard for evidence of effectiveness in reducing the chorea of HD as measured by the Total Maximal Chorea Score, further supported by positive assessments of global improvement by both the patient and their clinical investigators.

The major finding of Trial C-15 is a mean improvement (reduction) of 2.5 points in the TMC score in the active treatment arm over placebo. Patients rated their condition as Much Improved or Very Much Improved more often in the active treatment arm over placebo (23/45 vs. 9/45) as did clinicians (19/45 vs. 6/45). These are all robustly statistically significant.

These findings find additional support when compared to the results of the pivotal trial used to provide the evidentiary basis of approval for Xenazine. In that similarly designed trial, the mean reduction of the TMC score in the tetrabenazine arm over placebo was 3.5 points. The patient's global impression of improvement also favored tetrabenazine by a wide margin but the criteria for "success" in that trial was broader and not comparable to that of Study C-15. (The patient populations were very closely matched with regard to age, years of overt disease, numbers of CAG repeats, and baseline TMC scores.)

While this finding has the aura of clinical meaningfulness, it should be emphasized that chorea is but one of the many health consequences of HD and, compared to behavioral and psychiatric

and cognitive disturbances, not the most important one. This point was emphasized by patients and caregivers during the recent FDA Voice of the Patient Symposium on HD in September 2015.

By accurately presenting the quantitative findings of the primary and key secondary outcome measures in Study C-15 in the clinical trials section of the proposed label, clinicians who treat HD will be able to help patients and their families make an informed choice about the utility of this drug.

8 Review of Safety

8.1. Safety Review Approach

Because of the small size of the safety database for this NDA application, careful attention was paid to the characterization of all adverse events in C-15, the blinded, randomized pivotal efficacy trial, and C-16, the open label long term safety study. (This also made pooling of data not possible.) The lock date for the safety database is March 31, 2015 and includes information from the 120 Day Safety Update. There have been no 15 day adverse event reports since that time.

The entire development program was inspected for idiosyncratic reactions, deaths, and serious and severe adverse events. In cases of their occurrence, the individual narrative summaries were reviewed for relevant details. Particular attention was paid to increased suicidality and depression. There is a significant background incidence of both in the Huntington's disease population. The relationship of CYP 2D6 status on adverse events was also inspected, despite the small numbers of poor metabolizers in the development program. Effect on QTc, a major safety concern in the circumstances of elevated serum levels of the drug, was also inspected.

It is important to note that this 505(b)(2) application also relies upon safety information found in the label for the RLD, Xenazine (tetrabenazine tablets , NDA 21894 initially approved in 2008, label last revised in June, 2015). Comparisons to the AE profile of SD-809 to the RLD are made in Section 8.11 Integrated Assessment of Safety.

MedDRA version 16.1 was used by the Sponsor to code adverse events in C-15 and C-16. 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 Sponsor's documentation of drug safety was reviewed by the me (Clinical Trial Reports for C-15 and C-16, Summary of Clinical Safety, ISS, and supporting information), the analyses and tables in this section were created by me using the Sponsor's SDTM and ADaM standardized datasets and JMP 11.1, JMP Clinical 11.2 and MedDRA Adverse Event Diagnosis Service (MAED) software. When used in this review, the source of Sponsor's tables is indicated in the caption.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Safety Population across the development program for SD-809 encompasses 229 persons who received at least one dose of medication.

The Phase 1 program comprises 178 healthy adult volunteers who received SD-809. The majority were single dose exposures while 24 volunteers received multiple doses. In the Phase 3 program, Study C-15 contained 45 patients who received at least one dose of drug, while open label Study C-16 contained 37 in the Switch cohort and 82 in the Rollover cohort. However, the Rollover patients who received active drug in Study C-15 (n=43) were appropriately counted only once in the Sponsor's table below.

All studies in the clinical development program for SD-809 are completed with the exception of C-16, the open label safety study. (The Switch portion of that trial has been completed.)

The Sponsor's table summarizes this program population at the time of 120 Day Safety Update:

Table 19 SD-809 Development program safety population (120 Day Safety update, p 22)

Study	Any SD-809 Exposure	≥8 Weeks	≥15 Weeks	≥28 Weeks	≥52 Weeks
Phase 3 (Subjects With Chorea Associated With Huntington's Disease)					
First-HD	45	45	--	--	--
ARC-HD (120 day update)[a]					
ARC-Rollover	82	79	71	33	8
ARC-Switch	37	36	32	19	1
Total HD Subjects Exposure[b]	**121**	**119**	**111**	**65**	**16**
Phase 1 (Healthy Volunteer Subjects)					
Total Healthy Volunteer Subjects Exposure	**178**	--	--	--	--

I used the Sponsor's updated ISS ADSL file submitted to the NDA to show the 4 possible "bins" that characterize exposure to SD-809 and the number of participants in each. (The table does not include 6 patients who took placebo in Study C-15 and then chose not to rollover into Study C-16, thus ending the trials with no exposure to SD-809):

Table 20 SD-809 Phase 3 safety population

Study C-15 Treatment Arm	Study C-16 Cohort	N
SD-809	did not rollover	2
SD-809	SD-809	43
Placebo	SD-809	39
N/A	Tetrabenazine Switch	37
Total Phase 3 HD Safety Population		121

(b) (4)

(b) (4)

(b) (4) Using the Sponsor's datasets, the average duration of exposure in Study C-15 is 84 days (range 76-102) and in Study C-16 the average duration of exposure is 195 days (range 8 - 469) as of the cutoff date. The longest exposures belong to those who had active treatment in Study C-15 and then chose to rollover.

Table 21 SD-809 Phase 3 safety population duration of exposure

Phase 3 Safety Population (N=121) - Duration of Exposure					
Epoch	≤ 3 months	≤ 6 months	≤ 9 months	≤ 12 months	>12 months
N	5	29	45	27	15

Dose exposure (total daily dose of SD-809 in mg/d) was calculated using the ADSL 120 Day Safety Update dataset by epoch of duration. The majority of individual were treated in the upper range of dosing suggested for use.

Table 22 SD-809 Average daily dose of SD-809 by duration of exposure

Phase 3 Safety Population - Duration of Exposure					
Epoch	≤ 3 months	≤ 6 months	≤ 9 months	≤ 12 months	>12 months
N	5	29	45	27	15
Total Daily Dose SD-809					
Mean mg / d	33	40	48	41	40
Range	24 - 42	12 - 72	6 - 48	18 - 48	12 - 48

The maintenance dose reached by most patients based upon their clinical response was 36 mg/d or above (76%). Note that the range of SD-809 exposure can go as high as 72 mg/d in Study C-16 and 28 patients were exposed to more than 48 mg/d at some time point.

Figure 7 Study C-16 Patients taking more than 48 mg/d at any time (n=28)

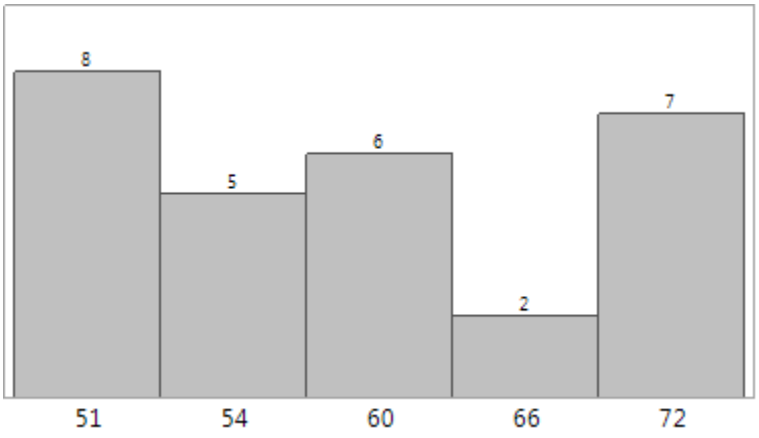

Table 23 SD-809 Maintenance doses reached by patients in Phase 3

Mg / day	N	%
48	29	35

42	15	18
36	19	23
30	6	7
24	5	6
18	2	2
12	3	4
6	1	1

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

The nature of the study population has also been discussed in the review of individual studies. As a whole, the safety population's demography is typical of the clinical HD population. There were more men than women (M = 68; F = 53) and the cohort was predominantly white (94%). Only two patients were 75 years or older.

Table 24 SD-809 Safety population: Huntington's disease characteristics

Demographic features of the SD-809 Safety Population (N=121)				
	Age	Years of HD	CAG Repeats	Baseline TMC Score
Mean	53	4.5	44	12.3
Range	23-75	0.4 -18	39-59	(3-26)
SD	12	3.8	4	4
≥ 65	n=21	5.7 (mean)	41 (mean)	11.6 (mean)

Patients with significant hepatic or renal dysfunction were excluded. The HD population in the development program reflects the general HD population for whom this drug is intended in the market place.

CYP2D6 status was investigated and 7 persons in the Safety Population were "poor metabolizers" with two patients not tested. The average duration of exposure for this small group was not different that the rest of the population: mean 224 days (range 8 – 557mg/d). The mean daily dose for this group was 29 mg/d (range 12 – 42 mg/d). Concomitant medication restrictions were closely observed.

8.2.3. **Adequacy of the safety database:**

HD is an orphan disease with a devastating natural history and control of its symptoms is an unmet medical need. This, and the fact that tetrabenazine, a close relative of

deutetrabenazine, is the RLD mitigates the usual need to adhere to strict exposure requirements for a novel agent. In comparison, the pivotal clinical trial supporting Xenazine approval was double blinded, placebo controlled, 12 weeks in duration with 54 patients in the active drug arm. The second Xenazine trial was a randomized withdrawal study in 18 patients who had been on tetrabenazine open label treatment for an average of two years. There has been no new information uncovered in this review that might suggest the need for a larger safety database.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This NDA 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-15 and Study C-16 that provide the major supporting evidence of safety and effectiveness of SD-809 were adherent to CDISC standards for SDTM and ADaM domains and variables.

As is described below, the clinical studies are small and the population fairly homogeneous with regard to demographic features. The Sponsor made many comparisons using subgroups that often contained 10 or fewer patients. As a result many of these sub-analyses should be considered very tentative at best and are not considered here.

8.3.2. Categorization of Adverse Events

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 Sponsor. It is important to note that if an AE was not considered to be plausibly related to the study drug by the Sponsor, it was not considered a TEAE and not discussed as such in the Sponsor's safety analysis.

Reviewer Comment: It is critical for the reader to understand the Sponsor's definition of Treatment Emergent Adverse Events is operationally quite conservative. In approaching this review, I assessed all AEs regardless of supposed relation to study drug. This almost always resulted in greater numbers of events than the sponsor reported. I would emphasize that AEs appear to be accurately reported in the AE datasets and these are the data I report and discuss in this safety review.

Narratives of patients suffering serious adverse events, severe adverse events, death, and AEs leading to discontinuation of study drug were provided in appendix listings. An additional line

listing of all AEs was provided. 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-15 and C-16 but other versions of MedDRA in the Phase 1 studies.

Review of the adverse events and tables derived from Sponsor submitted datasets for the placebo controlled Study C-15 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 1 or 2 patients enrolled. On the other hand there were sites with one or two enrollees that reported over a dozen AEs. The nature of the AEs reported at these sites is not different from other sites and there is no obvious reason for the differences. This wide range of reporting is not uncommon in this reviewer's experience and 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 close (SD-809 =101; Placebo=94). Severity of AEs was investigated and AEs were followed to resolution.

Table 25 Study C-15 Ratio of AEs by N by clinical site

Study C-15 Ratio of Adverse Events to N Randomized by Site					
Site ID	Patients (N) Randomized	% of Randomized	AEs (N) reported	% of AEs Reported	AEs/N Ratio
104	1	1.1%	16	7.2%	16
100	1	1.1%	12	5.4%	12
89	1	1.1%	8	3.6%	8
29	2	2.2%	14	6.3%	7
194	1	1.1%	7	3.2%	7
28	3	3.3%	19	8.6%	6.3
220	1	1.1%	6	2.7%	6
40	4	4.4%	23	10.4%	5.8
37	2	2.2%	11	5.0%	5.5
14	2	2.2%	8	3.6%	4
98	2	2.2%	8	3.6%	4
38	1	1.1%	4	1.8%	4
328	2	2.2%	7	3.2%	3.5
52	2	2.2%	6	2.7%	3
119	2	2.2%	6	2.7%	3
57	5	5.6%	11	5.0%	2.2
2	4	4.4%	8	3.6%	2
333	4	4.4%	8	3.6%	2

27	3	3.3%	6	2.7%	2
31	7	7.8%	13	5.9%	1.9
32	2	2.2%	3	1.4%	1.5
160	4	4.4%	4	1.8%	1
341	2	2.2%	2	0.9%	1
342	2	2.2%	2	0.9%	1
45	1	1.1%	1	0.5%	1
137	1	1.1%	1	0.5%	1
231	3	3.3%	2	0.9%	0.7
83	10	11.1%	3	1.4%	0.3
7	7	7.8%	2	0.9%	0.3
24	2	2.2%	0	0.0%	0
96	2	2.2%	0	0.0%	0
300	2	2.2%	0	0.0%	0
26	1	1.1%	0	0.0%	0
87	1	1.1%	0	0.0%	0
Total	90	100.0%	221	100.0%	

Verbatim terms appear to be fairly represented by Preferred Terms and only a few instances of splitting of terms appears to take place. (The most important instance of this was interpreting terms related to depression.) The following shows PTs reported more than once in the placebo controlled C-15 Safety Population (Source: AE dataset).

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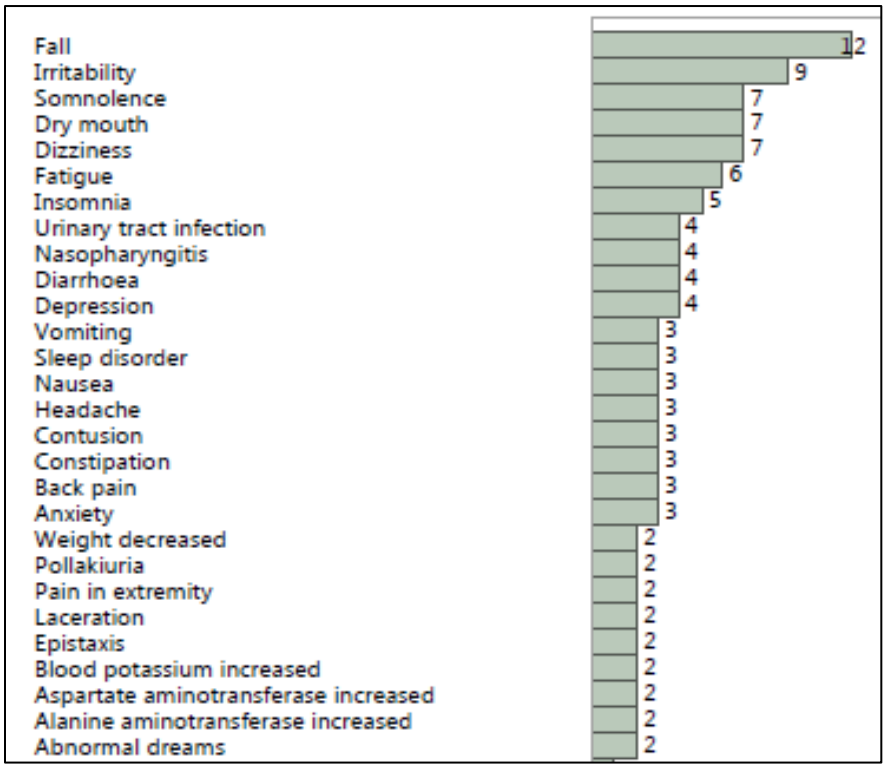
Figure 8 Study C-15 MedDRA Preferred Terms used more than once



8.3.3. Routine Clinical Tests

The obtaining of routine clinical tests was discussed above in **Section 6** when considering the design and schedule of events for Study C-15 and C-16. In addition to clinical examination and routine laboratory testing in these studies, specialized scales were used to assess adverse drug related effects at regular intervals.

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Figure 9 Clinical scales evaluating safety in Phase 3 (120 Day Safety Update, p 90)

Symptom/Disease Area	Scale
Depression	Hospital Anxiety and Depression Scale Depression Subscale
Anxiety	Hospital Anxiety and Depression Scale Anxiety Subscale
Suicidality	Columbia Suicide Severity Rating Scale
Swallowing Impairment	Swallowing Disturbance Questionnaire
Akathisia/Motor Restlessness	Barnes Akathisia Rating Scale
Daytime Sleepiness	Epworth Sleepiness Scale
Various	Unified Huntington's Disease Rating Scale Unified Parkinson's Disease Rating Scale
Cognitive Function	Montreal Cognitive Assessment

8.4. Safety Results

8.4.1. Deaths

No deaths have occurred in the HD development program. (b) (4)

(b) (6)

(b) (4)

8.4.2. Serious Adverse Events

In the development program for SD-809, there were 624 instances of AEs. Of these, 19 were labelled as SAEs occurring in 13 patients.

Additional SAEs occurred in patients not taking SD-809: one patient was on tetrabenazine in a Phase 1 pK study, two patients were in the placebo arm of Study C-15 and one volunteer was taking moxifloxacin in the TQT study.

Table 26 SD-809 Development program: all Serious Adverse Events

Patient	Age / Sex	Daily Dose (mg)	Day Event Began	Severity	Outcome	Preferred Term	System Organ Class
SD809C15-024-3121	69 F	36	193	Mild	Dose unchanged	Chest discomfort	General disorders and administration site conditions
SD809C15-027-3161	58 M	48	132	Severe	Drug stopped	Major depression	Psychiatric disorders
				Severe	and	Suicidal ideation	Psychiatric disorders
				Severe	withdrawn	Anxiety	Psychiatric disorders
SD809C15-028-3582	64 F	42	158	Moderate	Dose unchanged	Dehydration	Metabolism and nutrition disorders
				Moderate	Dose unchanged	Encephalopathy	Nervous system disorders
SD809C15-028-3583	57 F	48	148	Moderate	Drug interrupted	Depression	Psychiatric disorders
				Moderate	Drug interrupted	Suicidal ideation	Psychiatric disorders
SD809C15-031-3627	69 F	12	106	Severe	Dose unchanged	Hip fracture	Injury, poisoning and procedural complications
SD809C15-045-3641	59 F	36	83	Severe	Drug interrupted	Lumbar spinal stenosis	Musculoskeletal and connective tissue disorders
				Severe	Drug interrupted	Spondylolisthesis	Musculoskeletal and connective tissue disorders
SD809C15-083-3373	31 F	6	24	Mild	Dose unchanged	Upper limb fracture	Injury, poisoning and procedural complications
SD809C15-104-3441	61 F	48	74	Severe	Withdrawn	Agitated depression	Psychiatric disorders
			69	Severe	Drug interrupted	Cholecystitis chronic	Hepatobiliary disorders
SD809C16-007-7023	56 M	12	254	Moderate	Dose unchanged	Pneumonia	Infections and infestations
SD809C16-083-7323	67 M	48	199	Moderate	Dose unchanged	Pneumonia	Infections and infestations
SD809C16-093-7841	46 F	24	23	Moderate	Dose unchanged	Dehydration	Metabolism and nutrition disorders

SD809C16-342-7822	40 F	36	149	Severe	Withdrawn	Failure to thrive	Metabolism and nutrition disorders
SD809C16-007-3047	60 M	54	100	Severe	Dose unchanged	Penile cancer	Neoplasms benign, malignant and unspecified

The narratives and some CRFs were reviewed for these SAEs with exposure to SD-809. They were fairly characterized and none appear likely related to the drug with the possible exception of depression and suicidality which is discussed further below. All of these events clinically improved or resolved with treatment. Only one patient, SD809C15-031-3627 a 69 year old woman with a hip fracture, was a poor metabolizer of CYP 2D6.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to withdrawal from studies or requiring reductions in SD-809 dose were reported in both Study C-15 and Study C-16. Three participants (027-3161, 104-3441, and 342-7822) who had SAEs leading to withdrawal from the study are described in the SAE table above. Five patients who had dose interruptions associated with SAEs are also listed above (028-3582, 031-3627, 045-3641, 007-7023, and 093-7841).

Five additional patients in C-15 and C-16 had AEs that led to withdrawal from Study C-16.

Table 27 Phase 3 Dropouts and discontinuations due to adverse effects

Study C-16	Age / Sex	Dose (mg)	Study Day	Result	Reason
220-3521	31 F	30	290	DR WD	akathisia
007-3043	47 M	48	250	DS WD	depression and suicidal ideation
083-3365	58 M	42	102	WD	depression
083-3369	61 F	48	153	DR WD	akathisia , resolved with dose reduction, depression
333-3561	71 M	48	148	DR DS WD	depression , suicidal ideation
Dose is mg/d at which AE began. DS (dose suspension), DR (dose reduction), WD (AE led to withdrawal)					

All had a significant history of previous psychiatric disturbance. The akathisia appeared to have a temporal relationship to drug: it resolved within a few days in both cases after dose reduction.

Seventeen additional patients had dose reductions. Where the event is listed as having occurred after a dose change, the reviewer determined this to be from 1 to 4 days following the previous increase in total daily dose of SD-809. All resolved following dose reductions except in the last case, Patient 026-3141. In every case where the event follows dose change, it is highly plausible that the event was related except for the two cases of depression occurring remote from the dose change (Patients 040-3261 and 160-3484) and intermixed with concurrent

changes in antidepressant drug treatment.

Table 28 Phase 3 Event-related reductions in SD-809 dose

Study C-15	Age / Sex	Daily Dose	Study Day	Reason
002-3003	71 M	36	42	somnolence
027-3162	54 F	42	46	dizziness after dose increase
100-3422	54 F	42	53	fatigue and dizziness after dose increase
Study C-16				
040-3261	62 M	48	223	worsening depression remote from dose change
089-3681	30 F	30	30	somnolence after dose increase
160-3484	72 M	36	278	worsening depression, insomnia remote from dose change
328-3302	51 M	24	23	aggression, agitation, violent behavior, depression after dose increase
031-7601	60 F	72	121	parkinsonism, somnolence, and dysphagia
031-7603	53 M	48	30	akathisia after dose increase
089-7632	63 M	48	51	disorientation, somnolence after dose increase
199-7654	40 M	54	111	imbalance and weakness after dose increase
002-3003	71 M	36	42	somnolence after dose increase
027-3163	69 F	60	378	decreased attention after dose increase
038-3701	59 F	24	19	irritability and somnolence after dose increase
342-3861	42 F	48	57	fatigue after dose increase
031-7603	53 M	48	30	akathisia after dose increase
026-3141	58 M	24	214	hypersomnia; patient withdrew Day 298 but hypersomnia never resolved

8.4.4. Significant Adverse Events

Of the 432 individual occurrences of treatment emergent adverse events in Study C-15 and Study C-16, the majority were considered mild.

Table 29 Phase 3 Significant adverse events

Classification of TEAEs in Study C-15 and Study C-16		
Severity	Event Count	Event Count %
Severe	26	6 %
Moderate	114	26 %
Mild	292	68 %

The events considered severe occurred in 9 patients. Nine of these TEAEs in five patients (Patients 027-3161, 031-3627, 045-3641, 342-7822 and 104-3441) were also SAEs and have been addressed above. Three other patients were considered above under TEAEs that resulted in change in dose (342-7822, 104-3441 and 220-3521). The remaining TEAEs occurred in 3 patients and all resolved without dose change.

Table 30 Phase 3 Significant adverse events resolving without dose change

Patient	Age	Sex	Preferred Term	System Organ Class
SD809C16-199-7652	51	M	Somnolence	Nervous system disorders
			Faecal incontinence	Gastrointestinal disorders
			Poor quality sleep	Nervous system disorders
			Prostate infection	Infections and infestations
			Prostatomegaly	Reproductive system and breast disorders
SD809C16-199-7655	54	F	Fall	Injury, poisoning and procedural complications
			Laceration	Injury, poisoning and procedural complications
			Fall	Injury, poisoning and procedural complications
			Laceration	Injury, poisoning and procedural complications
			Laceration	Injury, poisoning and procedural complications
SD809C15-029-3181	60	F	Restlessness	Psychiatric disorders
			Urinary hesitation	Renal and urinary disorders
			Urinary tract infection	Infections and infestations
			Fatigue	General disorders and administration site conditions

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In Study C-15, 221 TEAEs occurred in 57 of 90 randomized patients: 111 events in 27 SD-809 patients and 108 events in 30 Placebo patients.

Some instances of splitting were noted. Examples of such Preferred Terms include (*abdominal pain*, *abdominal pain, upper* and *gastrointestinal pain)* and (*pruritis* and *pruritis, generalized*). Psychiatric terms (*anxiety, depression, agitated, depression, agitation,* and *restlessness*) were investigated to see if they represented different patients or not. As it turns out, correcting for these made no difference in the head count of TEAEs in these SOCs or the instance of particular syndromes except for depression or suicidality for Study C-15. There were similar numbers of patients suffering TEAEs overall in the SOCs for Nervous System Disorders, Psychiatric Disorders, and Gastrointestinal Disorders.

A head count of the TEAEs occurring in the blinded, placebo controlled Study C-15 reveals that the vast majority of these occurred only once and it is difficult to assign any importance to

them. On the other hand, this is misleading. For example, while akathisia did not occur with SD-809 in this blinded trial, cases of akathisia occurred in the open trial. These occurrences are clearly associated with dose increases of SD-809 and resolve with reduction of the dose.

The adverse events (head count, removing unrelated ones such as infections) that occurred more than once with SD-809 are as follows:

Table 31 Study C-15 AEs occurring more than once

System Organ Class	Preferred Term	SD-809 (N)	SD-809 %	Placebo (N)	Placebo %
Nervous system disorders	Somnolence	5	11.1	2	4.4
Gastrointestinal disorders	Dry mouth	4	8.9	3	6.7
General disorders and administration site conditions	Fatigue	4	8.9	2	4.4
Gastrointestinal disorders	Diarrhoea	4	8.9	0	0.0
Nervous system disorders	Dizziness	3	6.7	4	8.9
Injury, poisoning and procedural complications	Fall	3	6.7	9	20.0
Psychiatric disorders	Insomnia	3	6.7	2	4.4
General disorders and administration site conditions	Irritability	3	6.7	6	13.3
Psychiatric disorders	Anxiety	2	4.4	1	2.2
Musculoskeletal and connective tissue disorders	Back pain	2	4.4	1	2.2
Gastrointestinal disorders	Constipation	2	4.4	1	2.2

In the open label C-16 study, there appears to be no credible difference in the incidence of TEAEs in patients rolling over from the blinded trial when compared to the open-label switch over from tetrabenazine to SD-809 with the important exception of cases of somnolence (Rollover 12 % vs. Switch 30%) and falls (Rollover, 18% vs. Switch, 24%). Of interest, falls were also increased in the Placebo arm of C-15.

In open label treatment, it is apparent that sleep disturbance (both insomnia and somnolence) and mood disorders (anxiety, depression, suicidality, and irritability) are quite common. Of interest is the occurrence of akathisia, a motor restlessness associated with acute dopaminergic blockade and cases of parkinsonism. Akathisia is also a common cause of insomnia and

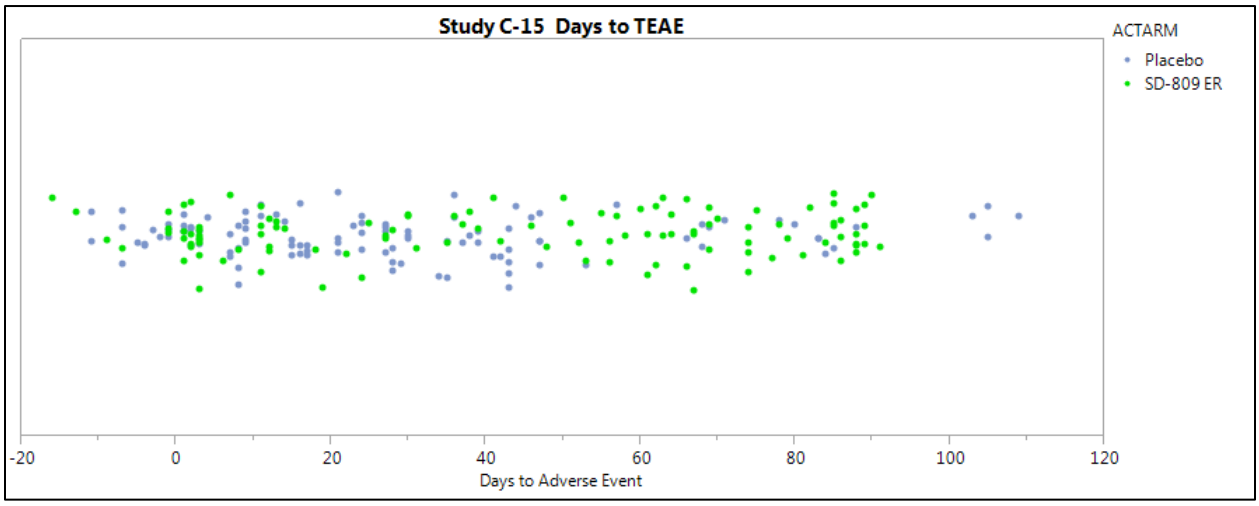
irritability.

Table 32 Study C-16 AEs

System Organ Class	Preferred Term	Open label SD-809 (N)	SD-809 %
Injury, poisoning and procedural complications	Fall	24	20.2
Psychiatric disorders	Depression	21	17.6
Nervous system disorders	Somnolence	21	17.6
Psychiatric disorders	Insomnia	17	14.3
Psychiatric disorders	Anxiety	15	12.6
Gastrointestinal disorders	Diarrhoea	10	8.4
General disorders and administration site conditions	Irritability	10	8.4
Gastrointestinal disorders	Constipation	7	5.9
Gastrointestinal disorders	Dry mouth	7	5.9
General disorders and administration site conditions	Fatigue	7	5.9
Investigations	Weight decreased	7	5.9
Nervous system disorders	Akathisia	6	5.0
Gastrointestinal disorders	Nausea	6	5.0
Psychiatric disorders	Suicidal ideation	6	5.0
Gastrointestinal disorders	Dysphagia	5	4.2
Gastrointestinal disorders	Vomiting	5	4.2
Psychiatric disorders	Apathy	4	3.4
Psychiatric disorders	Sleep disorder	4	3.4
Musculoskeletal and connective tissue disorders	Back pain	3	2.5
Nervous system disorders	Chorea	3	2.5
Nervous system disorders	Cognitive disorder	3	2.5
Nervous system disorders	Drooling	3	2.5
General disorders and administration site conditions	Gait disturbance	3	2.5
Nervous system disorders	Memory impairment	3	2.5
Renal and urinary disorders	Micturition urgency	3	2.5
Nervous system disorders	Parkinsonism	3	2.5

Adverse events occurred throughout the C-15 study period. (Day 0 represents randomization to treatment).

Figure 10 Study C-15 Distribution of occurrences of AEs by study day



For both treatment arms, more adverse events occurred more commonly during the initial 8 week titration phase than during the rest of the study (but proportional to the titration period being 2/3 of the study duration). By total numbers of events counted, SD-809 treatment had more somnolence as an AE but fewer falls (Table 33, below). The nature of the adverse events was not otherwise qualitatively different between the arms. (Other events that occurred only once were omitted from the table.)

Table 33 Study C-15 AE count by treatment arm

Preferred Term	Total Event Count	
	SD-809 ER	Placebo
Somnolence	6	2
Fall	5	11
Diarrhoea	4	0
Dry mouth	4	3
Fatigue	4	2
Frequent bowel movements	2	0
Hangover	2	0
Insomnia	2	2
Irritability	2	4

8.4.6. Laboratory Findings

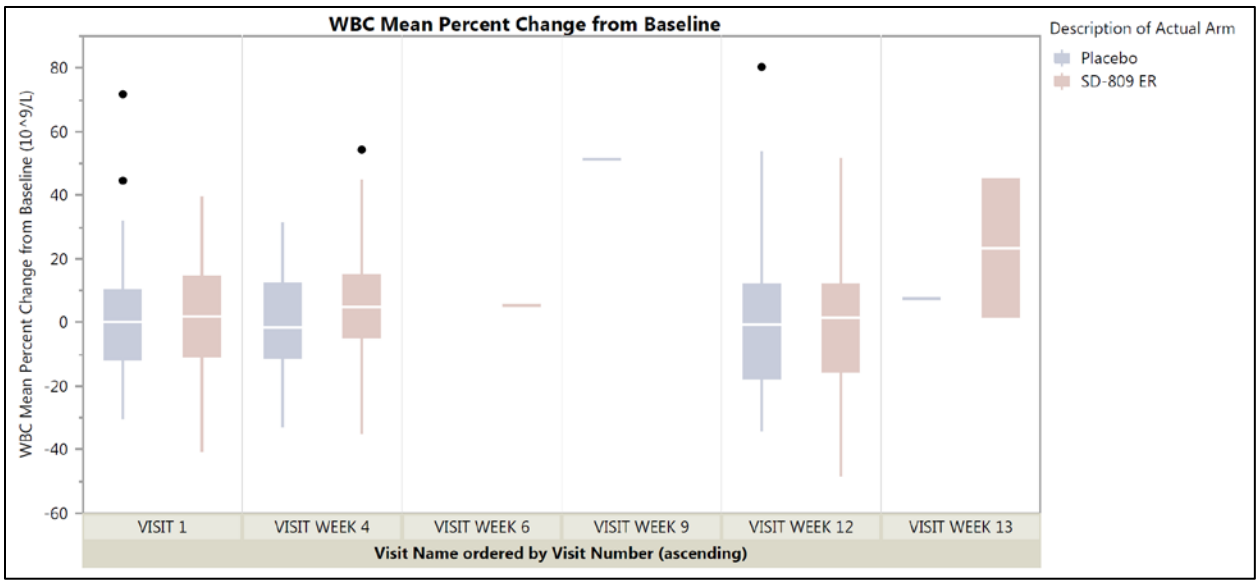
There was no a priori non-clinical signal suggesting that deutetrabenazine should affect clinical

laboratory. The Sponsor's analysis was reviewed and shift tables created in JMP Clinical from the SDTM LB dataset. Clinical laboratory evaluations did not reveal any clinically important differences in mean test values between the patients in the SD-809 and placebo groups in Study C-15. There was also no change noted in the mean laboratory values obtained over time in the open label single arm Study C-16.

That said, some changes in laboratory values were reported as adverse events:

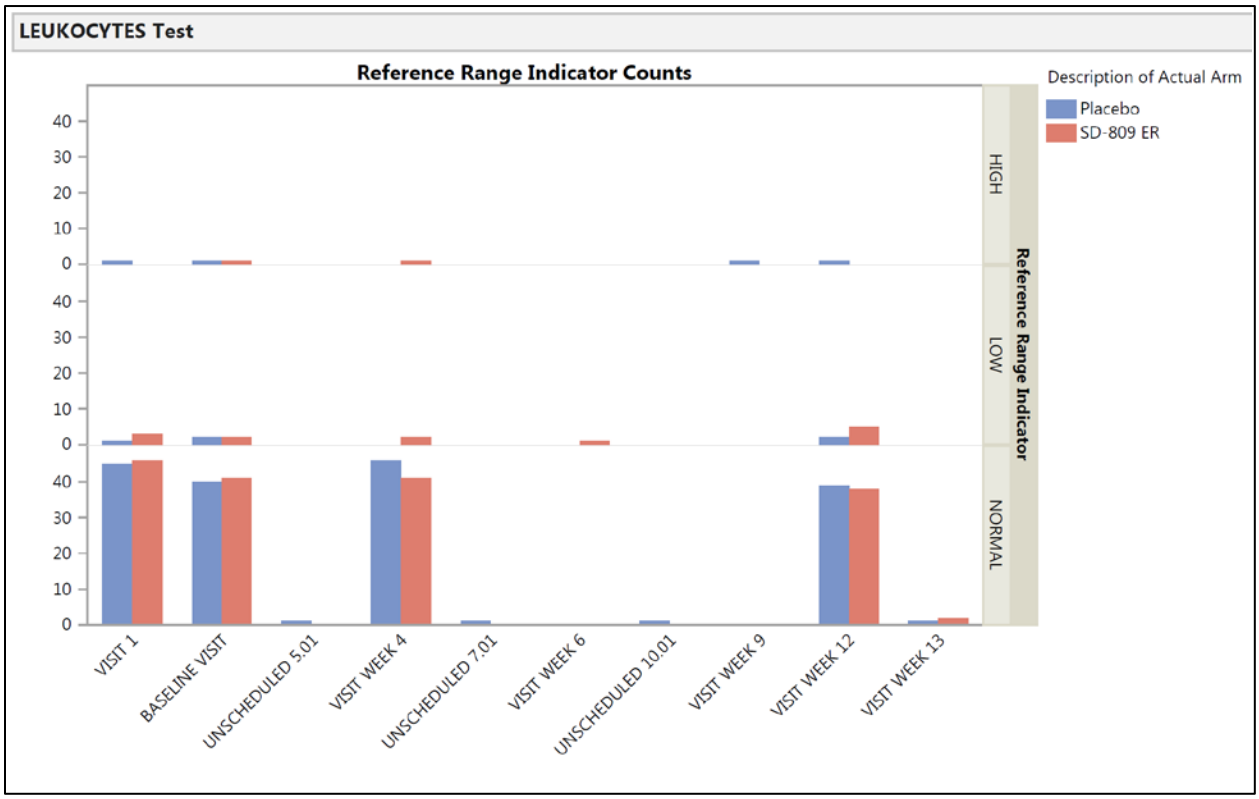
Hematology
One patient taking SD-809 in C-15 experienced an AE of *white blood cell count increased* and one in the SD-809 group experienced an AE of *white blood cell count decreased*. No other AEs related to hematology laboratories were reported in either group. None were reported in C-16. The following is a graphical illustration of shift from baseline for white blood cells over the course of C-15.

Figure 11 Study C-15 Total white blood cell count change from baseline by visit



The following illustrates the numbers of WBC tests at each visit that are high, low, or in the normal range.

Figure 12 Study C-15 WBC tests outside of the normal range by visit



Reviewer Comment: These graphical illustrations are included by the reviewer as an example of JMP Clinical analysis of laboratory testing; this was performed for each laboratory parameter in the LB dataset.

Chemistry

An increase in ALT and AST occurred in a single patient (342-3863) in the SD-809 arm of Study C-15. The elevation was reported as an AE (values at Week 12 were 10 times and 4.8 times the ULN for ALT and AST, respectively); total bilirubin and alkaline phosphatase were normal at the time of the aminotransferase elevation and remained normal during follow-up. The patient had no symptoms of hepatitis, no laboratory evidence for hepatitis A, B, or C, no history of alcohol abuse, and an abdominal ultrasound was normal. The laboratory abnormalities subsequently were attributed by a consulting gastroenterologist to concomitant use of sertraline. Approximately 2 months after discontinuing sertraline, AST and ALT had returned to nearly normal (1.1 times the ULN). Furthermore, the patient has been rechallenged and treated with SD-809 for 6 weeks without further significant changes in aminotransferases.

There were nine other instances of changes reported as AEs in a variety of chemistry parameters, none of which were sustained. (In Study C-15, there were 20,284 tests of individual clinical laboratory parameters drawn in 375 blood and 367 urine collections.)

8.4.7. **Vital Signs**

Mean heart rate and blood pressure were stable over time when compared to placebo in Study C-15. The same is true of changes in systolic and diastolic blood pressures when changing from lying to standing. Review of individual subject orthostatic blood pressure and heart rate data showed that orthostatic events (defined as a decrease in systolic blood pressure ≥20 mm Hg, or a decrease in diastolic blood pressure of ≥10 mmHg) occurred in 5 (11%) subjects in the SD-809 group and 10 (22%) subjects in the placebo group. There were no AEs reported that included the "orthostatic" in the Preferred Term in either C-15 or C-16. Two SD-809 patients reported dizziness as an AE and no one reported syncope in C-15.

8.4.8. **Electrocardiograms (ECGs)**

Electrocardiograms were performed at baseline and Week 12 in the Safety Population in Study C-15. As reported by the Sponsor, there were no clinically significant differences between the treatment groups in any of the mean ECG parameters. The mean (SD) QTc interval was slightly higher in the SD-809 group compared with the placebo group at both screening (SD-809: 415.1 [18.0] ms versus placebo: 411.6 [18.7] ms) and Week 12(SD-809: 417.4 [17.6] ms versus placebo: 410.7 [20.9] ms). One patient in the SD-809 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.

No ECG-related AEs were reported for any patient in the SD-809 group. Four AEs identified via ECG were experienced by two patients in the placebo group.

Eighteen patients were taking citalopram or escitalopram in Study C-16. No increases of QTc were noted over the course of the study and values remained well within the normal range.

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Table 34 Study C-16 QTcF duration by week (120 Day Safety Update)

Time Point	ARC-Rollover (N=8)		ARC-Switch (N=10)	
	n	QTcF Duration (ms) mean (SD)	n	QTcF Duration (ms) mean (SD)
Baseline	8	418.5 (17.43)	10	420.5 (14.53)
Week 1 (ARC-Switch) or Week 2 (ARC-Rollover)	8	417.1 (15.75)	8	414.6 (19.31)
Week 4	7	414.3 (15.97)	7	404.7 (12.96)
Week 8	8	412.4 (19.72)	9	417.4 (13.94)

8.4.9. QT

A Thorough QT (TQT) study was performed in healthy volunteers by the Sponsor and submitted for review by the FDA Interdisciplinary Review Team (IRT) for QT studies.

Assay sensitivity was assured by using moxifloxacin as an active control. The IRT's opinion was that *"the largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated … indicating that assay sensitivity was established."*

Single-dose administration of SD-809 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.

The Sponsor modeled the potential for QT prolongation at supratherapeutic exposure to peak concentrations of major active SD-809 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 SD-809 48 mg per day. The Sponsor'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 Sponsor's interpretation was that this had no clinical impact.

The IRT agreed that there *was "no significant QTc prolongation effect of SD-809 (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 SD-809 (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*

in the QT interval of approximately 8 ms reported in the Xenazine Prescribing Information."

However, the IRT reviewer opined that there is a limitation to the interpretation of this study because *"the plasma α and β-HTBZ concentrations achieved with the single dose of 24 mg SD-809 do not cover the expected steady state exposure (Cmax) following the highest therapeutic dose of 24 mg b.i.d. and the worst case clinical scenario (CYP2D6 poor metabolizer or administered a strong CYP2D6 inhibitor). Similar to Xenazine, a statistic significant exposure response relationship between the sum concentration of the active metabolites (α+β) and QT has been observed. Clinically relevant QT prolongation might be expected in some patients at the highest therapeutic dose of 24 mg b.i.d., especially in CYP2D6 poor metabolizer or patients co-administered a strong CYP2D6 inhibitor."*

(b) (4)

The IRT suggests (and this reviewer agrees) that because of the clear limitation of this TQT study, the same QT-related language as found in the Xenazine label should be retained: "Effects at higher exposures to either XENAZINE or its metabolites have not been evaluated."

8.4.10. Immunogenicity

Immunogenicity is not relevant to this small molecule submission.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Depression and Suicidality

Studies have found that between a 1/3 and 3/4 (depending on methodology used) of the HD population have manifest psychiatric symptoms. Depression and anxiety are the most common psychiatric symptoms and their presence is unrelated to disease stage. They also occur more frequently in pre-symptomatic individuals.

Suicide also occurs more frequently in early symptomatic individuals(Hubers et al., 2012; Hubers et al., 2013; Schoenfeld et al., 1984) and also in pre-symptomatic gene carriers (Farrer, 1986). As a result, the Hospital Anxiety and Depression Scale (HADS) and the Columbia Suicide Severity Rating Scale (C-SSRS) were employed at every Phase 3 patient encounter as a screening and assessment tools.

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

subtypes of depression and suicidality were grouped together. These include situational depression, post-partum depression, mood swings, mood disorder, bipolar disorder, and so forth. The aim was to be as inclusive as possible. In the SDTM MH dataset, 60 such psychiatric diagnoses were recorded in the Medical History of 55 out of 90 randomized patients in C-15 (SD-809 = 26; Placebo, = 29). This includes two patients in the SD-809 arm and one patient in the Placebo arm with a history of previous suicidal ideation.

Psychiatric AEs in Study C-15 were reviewed. Two patients in the SD-809 arm (SD809C15-083-3369 and SD809C15-104-3441) had an AE consistent with increased depression; the latter patient also had suicidal ideation. Three patients in the placebo arm also had an AE consistent with increased depression (SD809C15-333-3564, SD809C15-194-3501, and SD809C15-052-3323). Of note, all five participants had a prior medical history of a depressive disorder that was recorded at enrollment.

Patient 104-3441 is included above in **Section 8.4.2**; her SAE was rated "severe" and resulted in her withdrawal from the trial. The others, whose AEs were rated as "mild", did not require dose changes and resolved while remaining in the trial.

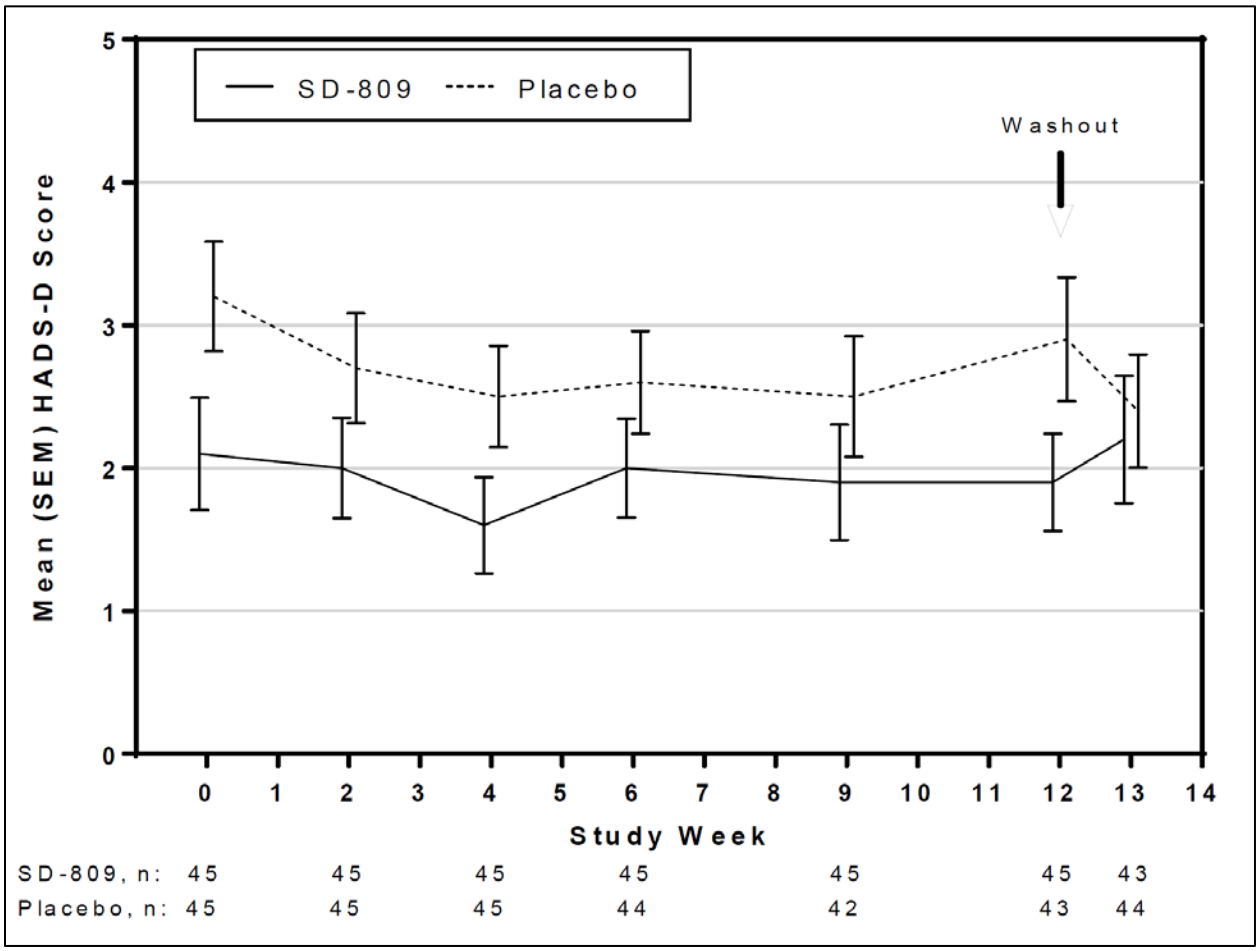
In this instance, the Sponsor's analysis of depression and suicidality is affected by their application of the definition of TEAE. As measured by the C-SSRS and reported by the Sponsor, the number of participants with prior lifetime history of suicidal ideation (assessed at screening) was similar between the SD-809 (7 patient [15.6%]) and placebo groups (8 patients [17.8%]). In Study C-15 Clinical Study Report, the Sponsor states *"In the current study, 4% of SD-809 subjects and 7% of placebo subjects experienced adverse events related to depression. These results are supported by the lack of a difference between the SD-809 and placebo groups on the HADS-D assessment and no signal of suicidal ideation or behavior on the C-SSRS."* Their conclusion appears in part to be based on the fact that after the baseline queries, there was only a single positive response by one patient in the placebo arm to Question 1 or 2 on suicidal ideation in the C-SSRS.

Reviewer comment: Despite the considerable prevalence of mood disorder and suicidality recorded in the medical history of the study participants, the C-SSRS patient questionnaire did not reveal as much as their medical history at enrollment did. This may call into question the method of presentation of the survey during the study, a lack of candor in a patient population well aware of the stigma related to psychiatric illness, and perhaps the general utility of the C-SSRS as a screening tool.

Similarly, the Sponsor, in using the MedDRA higher level group term of Depressed Mood Disorders and Disturbances found that a total of two (4.4%) subjects in the SD-809 group and three (6.7%) subjects in the placebo group experienced at least one AE of preferred terms including depression. All of these subjects had a medical history of depression at screening.

The following illustrates the Sponsor's assessment of the HADS depression subscale over the C-15 study (HADS score ≥ 11 was exclusionary from the trial; higher score means worse depression).

Figure 13 Study C-15 HADS depression scores by week (CSR, p 116)

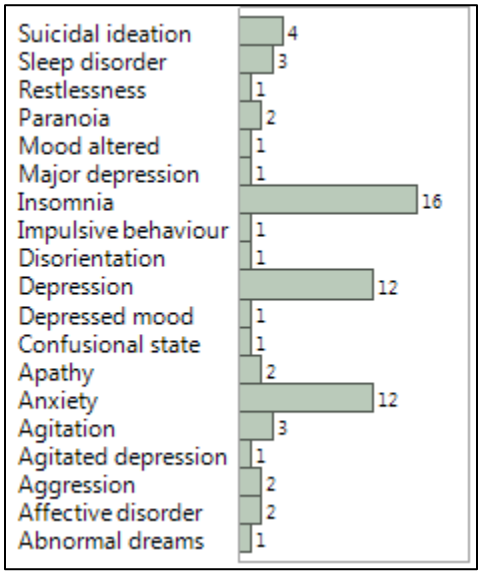


Reviewer Comment: In the analysis of suicidality and depression in Study C-16 beginning below, there is a major difference between the Sponsor's analysis and mine. Whereas this reviewer treated all AEs of depression and suicidal ideation as AEs without regard to cause, the Sponsor analyzed only the events they felt were treatment emergent, i.e.: their occurrence had some suggestion of relationship to study drug. A previous medical history of depression or suicidality appears to have been a sufficient reason to consider an AE of depression or suicidality as potentially drug unrelated.

In addition, in analyzing depression, the Sponsor states that it was performed by grouping AEs

whose terms that included the word "depression." To look at this further, I looked at all PTs that mapped to the Psychiatric Disorders System Organ Class in the AE dataset for Study C-16.

Table 35 Study C-16 Preferred Terms related to Psychiatry Disorders SOC



As shown in the table above, the terms "mood" and "affective" capture additional patients with AEs. As is also evident in the discussion that follows, "suicidal ideation" as an AE did not capture everyone who is listed in the discussion of suicidality and depression below. This may reflect the Sponsor's arbitrary procedure for only analyzing AEs that they feel are likelier to be attributable to drug. Noting how many patients have previous psychiatric histories makes that approach suspect.

In Study C-16, open label SD-809 had a similar experience. Depression related Preferred Terms occurred in 26 patients and 5 had suicidal ideation as well. Suicidal ideation occurred in one patient where depression had not been recorded as an AE.

- SAEs: SD809C15-027-3161 and SD809C15-028-3583.
- Withdrawn: SD809C15-007-3043, SD809C15-027-3161, SD809C15-083-3365, and SD809C15-333-3561.
- Depression AE in C-15 re-occurs as AEs in Study C-16: SD809C15-083-3369, SD809C15-194-3501, and SD809C15-328-3302

Table 36 Study C-16 Depression and suicidal ideation

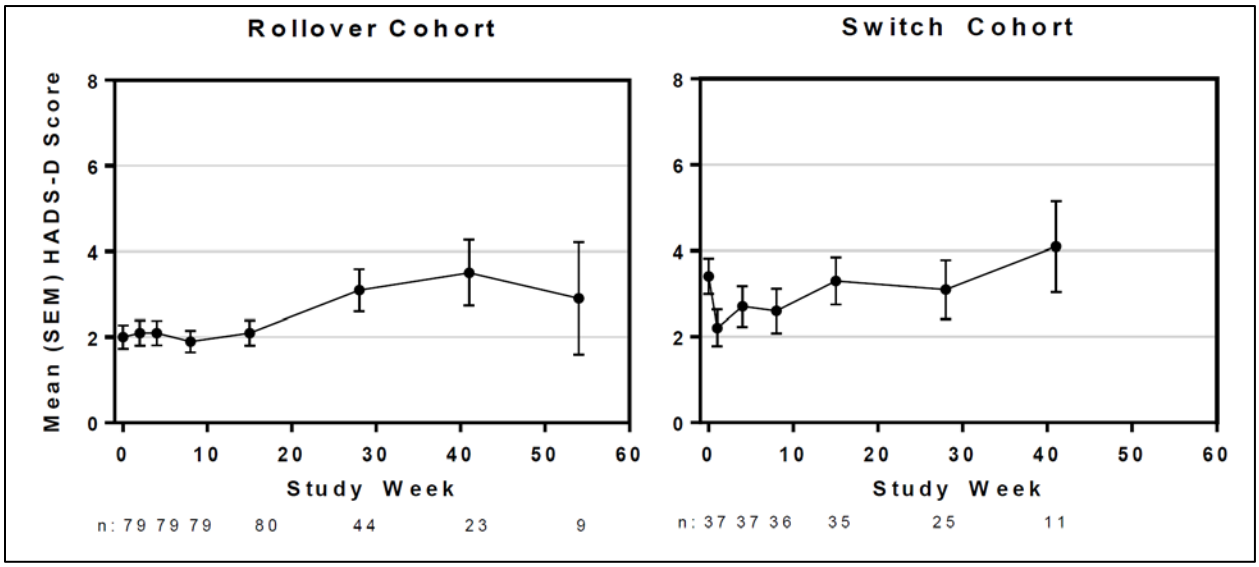
Rollover Cohort	Age	Sex	Race	Medical History	AE Depression	AE Suicidal ideation	AE Study day	Investigator Action

SD809C15-002-3003	71	M	WHITE	N	Y	Y	234	DOSE REDUCED
SD809C15-007-3043	47	M	WHITE	y	Y	Y	250	WITHDRAWN
SD809C15-007-3046	55	M	WHITE	Y	Y		125	DOSE NOT CHANGED
SD809C15-024-3122	62	F	WHITE	Y	Y		90	DOSE NOT CHANGED
SD809C15-026-3141	58	M	WHITE	Y	Y		60	DOSE NOT CHANGED
SD809C15-027-3161	58	M	WHITE	N	Y	Y	132	WITHDRAWN
SD809C15-028-3583	57	F	WHITE	N	Y		148	DRUG INTERRUPTED
SD809C15-031-3623	50	M	WHITE	N	Y		83	DOSE NOT CHANGED
SD809C15-031-3624	33	M	WHITE	Y	Y		135	DOSE NOT CHANGED
SD809C15-032-3222	52	M	BLACK	Y	Y		47	DOSE NOT CHANGED
SD809C15-040-3261	62	M	WHITE	Y	Y		223	DOSE REDUCED
SD809C15-057-3343	66	F	WHITE	Y	Y		62	DOSE NOT CHANGED
SD809C15-057-3344	33	M	WHITE	Y	Y		130	DOSE NOT CHANGED
SD809C15-083-3365	58	M	WHITE	Y	Y		102	WITHDRAWN
SD809C15-083-3369	61	F	WHITE	Y	Y		15	DOSE NOT CHANGED
SD809C15-160-3484	72	M	WHITE	Y	Y		278	DOSE REDUCED
SD809C15-194-3501	71	M	WHITE	Y	Y		56	DOSE NOT CHANGED
SD809C15-220-3521	31	F	WHITE	Y	Y		35	DOSE REDUCED
SD809C15-231-3782	66	M	WHITE	Y	Y		2	DOSE NOT CHANGED
SD809C15-328-3302	51	M	WHITE	N	Y		23	DRUG INTERRUPTED
SD809C15-333-3561	71	M	WHITE	N	Y	Y	256	WITHDRAWN
Switch Cohort								
SD809C16-007-7021	56	F	WHITE	Y	Y		21	DOSE NOT CHANGED
SD809C16-007-7023	56	M	WHITE	Y	Y	Y	54	DOSE REDUCED
SD809C16-031-7602	61	M	WHITE	N		Y	122	DOSE NOT CHANGED
SD809C16-054-7891	44	M	WHITE	Y	Y		37	DOSE NOT CHANGED
SD809C16-057-7302	49	F	WHITE	Y	Y		13	DOSE NOT CHANGED
SD809C16-342-7822	40	F	WHITE	Y	Y		127	DOSE REDUCED

Similar to the analysis of Study C-15, the Sponsor applied their narrow definition of TEAE and found that eight (10.7%) subjects in the Rollover Cohort experienced an AE related to depression during the study, and two (5.4%) subjects in the Switch Cohort experienced AEs of depression.

The averaging of the HADS depression scale by the Sponsor obscures these individuals:

Figure 14 Study C-16 HADS depression scores by week (120 Day Safety Update, p 44)



In Study C-16, the C-SSRS did much better in identifying those individuals with a lifetime history of suicidality and it performed better when used during the trial to detect suicidal ideation as an AE: 120d SU p45

Table 37 Study C-16 Positive C-SSRS during the study

	Rollover Cohort (N=81) n (%)	Switch Cohort (N=37) n (%)
C-SSRS, Lifetime History (Assessed at Screening)		
Suicidal Ideation[a]	13 (16.0)	4 (10.8)
C-SSRS, Any Postbaseline Time Point (Since Last Visit)		
Suicidal Ideation[a]	5 (6.2)	2 (5.4)
Suicidal Behavior[b]	1 (1.2)	0
Completed Suicide	0	0

8.5.2. Akathisia

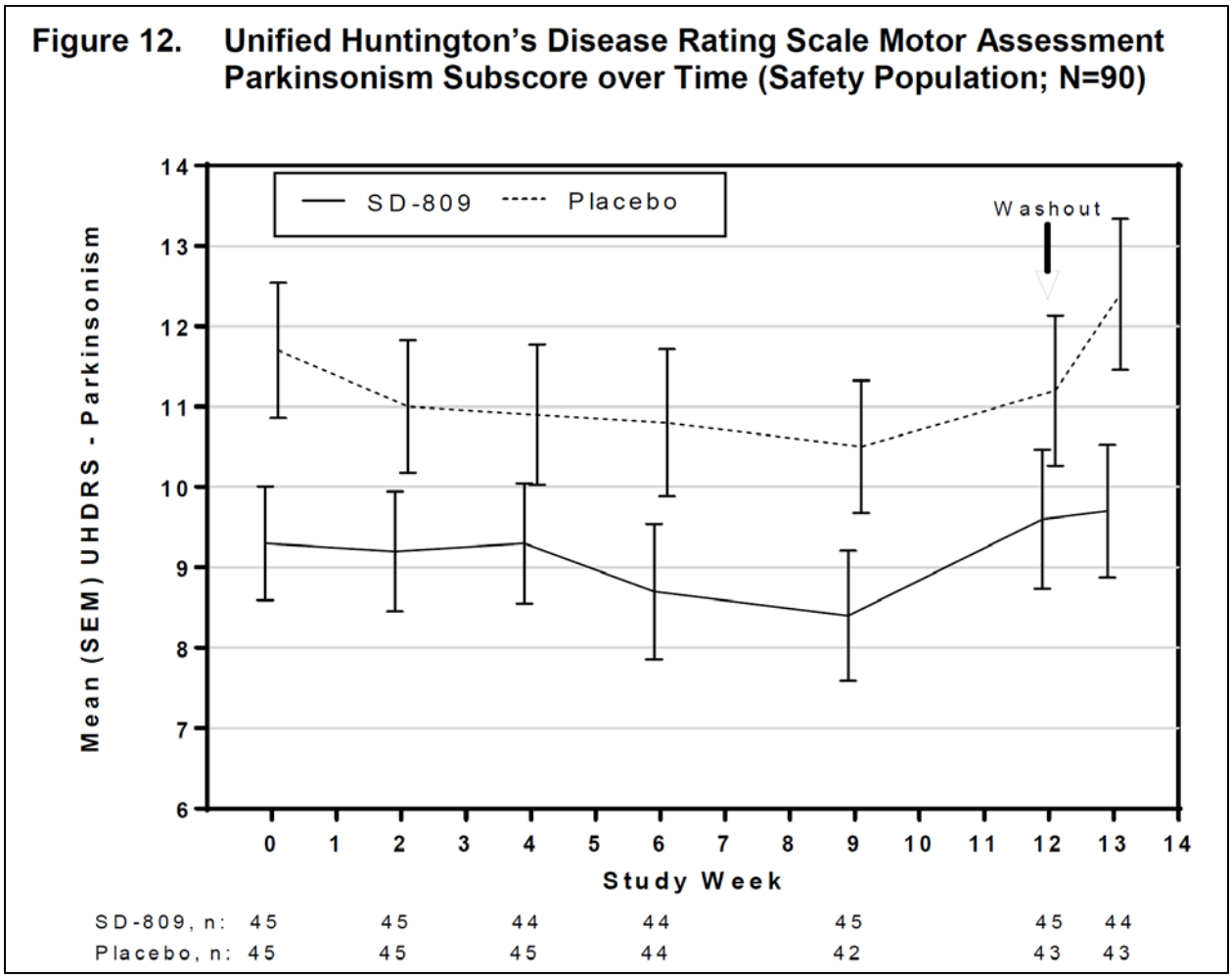
Because akathisia can be difficult to distinguish clinically from restlessness, all Preferred Terms that could represent akathisia (akathisia, hyperkinesia, psychomotor hyperactivity, and restlessness) were included in this analysis. Motor restlessness occurred in 5% of the treated population of the open label study, but only one of the participants taking SD-809 in the double

blind study. Nevertheless, this phenomenon remains important as akathisia is a potent magnifier of depressive symptoms and is known to provoke suicidality. It led to withdrawal from Study C-16 for two individuals. The restlessness can also be taken for increased chorea which could potentially lead to an unfortunate dose increase, not dose reduction.
The Barnes Akathisia Rating Scale scores did not differentiate between the two treatment arms in Study C-15.

8.5.3. **Parkinsonism**

Parkinsonism was described as an AE in none of the C_15 patients and three patients in C-16, one of whom was taking 72 mg daily. This resolved with dose reduction. Parkinsonism was rated by the Parkinson subscale score of the UHDRS Total Motor Score. The scores in both treatment arms remained unchanged over the course of the study. There was in general less Parkinsonism in patients in the SD-809 treatment arm that in the placebo arm but by the Sponsor's ANCOVA analysis using baseline as the covariate this was not a statistically significant difference.

Figure 15 Study C-15 UHDRS Parkinsonism score by week (CSR, p 123)



8.5.4. **Dysphagia**

Swallowing was evaluated by administration of the Swallowing Disturbance Questionnaire. In the open label SD-809 study, dysphagia was reported as an adverse event in 5 patients (4.2%). In the double blind study, none of the SD-809 patients had dysphagia as an AE, while 1 placebo patient did. Because dysphagia may result in aspiration pneumonia, this was also looked at. No patients developed pneumonia in Study C-15 while two patients developed pneumonia as an SAE in Study C-16. Both resolved without dose reductions and while continuing on medication.

8.5.5. Sedation and somnolence

Somnolence was the most commonly reported TEAE. In Study C-15, somnolence as an AE occurred in 5 (11%) patients taking SD-809 and only 2 patients in the placebo arm (4.4%). These occurred during the initial weeks when SD-809 was being titrated upwards between days 3 and 52 of the study in the dosage range of 6 to 48 mg. In four of the cases in the SD-809 arm, it was sufficiently severe that dose reductions were made, and in all cases but one this resolved the AE. In Study C-16, three events occurred and two resolved with dose reductions. Hypersomnolence caused one patient to withdraw from the open label study. It should be noted that fatigue was also a reason for dose reductions and also occurred more commonly with active drug treatment. It is impossible to discern whether this Preferred Term represents some occurrences of somnolence. The Epworth Sleepiness Scale showed no difference between the treatment arms.

8.6. Safety Analyses by Demographic Subgroups

The population was insufficiently diverse to make subgroup analysis statistically valid beyond the categories of age and gender. These did not reveal any adverse effect on the safety of SD-809.

A total of 17 patients (8 in the SD-809 group and 9 in the placebo group) were using a strong CYP2D6 inhibitor at baseline. Patients taking stable doses of drugs that inhibit CYP 2D6 at baseline did not appear to have more adverse events, but the small numbers of patients and events would be insufficient to pick up anything less than a large drug effect. There were no SAEs in this group. Only 5 patients (SD-809 = 3; Placebo = 2) who were poor metabolizers of CYP 2D6 were randomized in C-15. There were too few AEs to reach any conclusion. In both C-15 and C-16, all AEs in this group were mild or moderate in severity. One exception was a patient (328-3302, noted above) who had worsening of depression, with agitation and violent behavior. The behavior subsided after dose reduction.

8.7. Specific Safety Studies/Clinical Trials

No specific safety studies were performed during the SD-809 development program.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies were submitted in this application.

8.8.2. Human Reproduction and Pregnancy

No reproductive studies were submitted in this application.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric assessments were submitted in this application.

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

There is no evidence that this drug is habituating or subject to abuse. The clinical studies in the development program for SD-809 did not reveal any tendency for drug-seeking behavior, although queries were not made in a systematic manner.

The Sponsor conducted a literature search in PubMed and Web of Science for the period January, 1966 to April, 2015 using a wide range of search terms. The search did not identify any human studies or case reports of tetrabenazine abuse.

The Sponsor reports that "…overdoses with Xenazine (tetrabenazine), the listed drug for this application, at doses ranging from 100 mg to 1 g, have been reported in the literature and were associated with the following adverse reactions: acute dystonia, oculogyric crisis, nausea and vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, rubor, and tremor."

In this application, participants in Study C-15 had a one week washout prior to rolling over into Study C-16. No behavioral or autonomic signs of withdrawal were reported, though it is not known how such observations were made beyond a general query by the investigator. Chorea symptoms at a severity consistent with each individual's baseline ratings did reappear during the week's washout.

Reviewer's comment: The active metabolites of SD-809, α-HTBZ and β-HTBZ, have half-lives of 10.5 and 5.9 hours, respectively. It is therefore likely that a week would have been sufficient period in which to observe behavioral evidence of habituation. A withdrawal study performed with tetrabenazine had similar results (Frank et al., 2008).

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

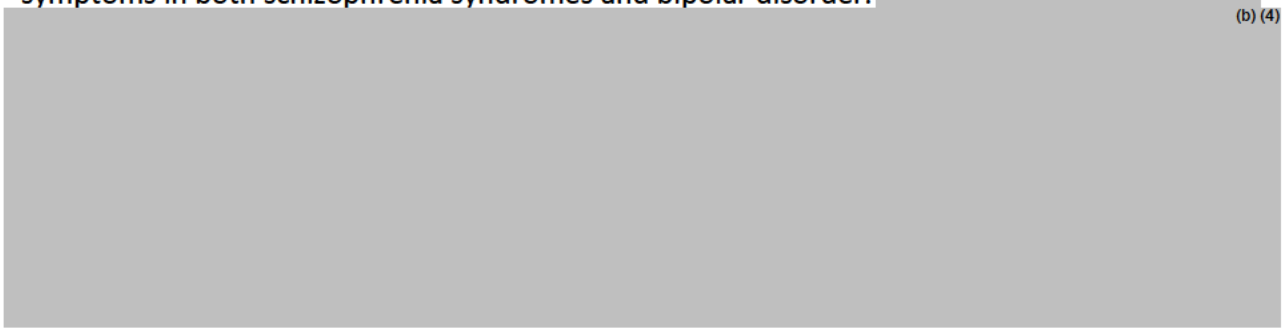
SD-809 is not currently commercially available in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

This drug could be used in certain circumstances not studied in this application. For example, it may be used to treat HD patients with greater depression, i.e. HADS depression score above 11 points or a prominent history of suicidality. It is not known if treatment with SD-809 would confer a greater risk of activation of suicidal behavior in this vulnerable group. It is also

expected that SD-809 would be prescribed to children with hyperkinetic movement disorders in association with degenerative neurological disease (as has the RLD), although the pediatric HD population tends to be much more severely affected by rigidity and has less chorea. The older population is a lesser concern; fewer HD patients are diagnosed in later life.

Other conditions for which this drug may be used include the most common cause of chorea, tardive dyskinesia related to chronic neuroleptic use. Neuroleptics are used to treat psychotic symptoms in both schizophrenia syndromes and bipolar disorder. (b) (4)



From both a clinical and scientific perspective, it would be reasonable to expect that this drug is going to be tried in most hyperkinetic movement disorders. In general, these neurological disorders are poorly controlled and a drug with a novel mechanism is likely to invite informal clinical experimentation by health care practitioners.

8.10. Additional Safety Issues From Other Disciplines

The Clinical Pharmacology and Pharmacological Toxicology reviews have raised an issue concerning the metabolites of SD-809. SD-809 may be metabolized to different proportions of breakdown products compared to the RLD. Metabolites of SD-809 that are larger in proportion than those of the RLD may need qualification as to their non-clinical safety, especially with regard to their carcinogenic and embryotoxic potential. The clinical development program for SD-809 was not designed to shed any new light on these potential safety issues.

There are also outstanding CMC issues with regard to contaminants related to manufacturing of the drug substance. Final inspection reports of the manufacturing facility are also pending (see Section 4 above).

8.11. Integrated Assessment of Safety

Within the limitation posed by a small development program with limited duration of exposure, it is possible to say that the adverse events profile of SD-809 is very similar to the RLD. However, comparisons between the populations of the two development programs cannot be made easily. In general, while the events themselves are similar, they tend to be less numerous

in the SD-809-development program. The major areas of concern about SD-809's safe use are addressed here.

Depression and suicidality

As discussed earlier, depression and suicide are much more common in the HD than the general population. That was certainly the case in the trial population where over half had previous medical histories consistent with depression and about 15% had a history of suicidal ideation. The use of screening scales (HADS and C-SSRS) for increased depression and suicidality during the course of Study C-15 detected little. The Adverse Event datasets were more informative; five patients who had previous histories of depression had increased symptoms, including one SD-809 patient with suicidal ideation. These events occurred in both the active and placebo arms. The open label, long term safety study with a much longer exposure to SD-809 had many more instances of depression (n=27) and suicidality (n=6) as an AE. It is not possible to know if this represents an increased risk with treatment of SD-809, and given the background rate of affective disorder in HD, the size of the population to see added risk due to treatment would be impossibly large.

By comparison, in 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 (HuntingtonStudyGroup, 2006). In two open-label studies (29 patients receiving Xenazine for up to 48 weeks and, 75 patients receiving Xenazine for up to 80 weeks), the rate of depression/worsening depression was 35% (Frank, 2009). In all of the HD chorea studies of Xenazine (n=187), one patient committed suicide, one attempted suicide, and six had suicidal ideation.

The boxed warning in the RLD label addresses the concern.

Figure 16 Boxed warning (Xenazine label)

WARNING: DEPRESSION AND SUICIDALITY

See full prescribing information for complete boxed warning.

- **Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.2)**
- **Balance risks of depression and suicidality with the clinical need for control of chorea when considering the use of XENAZINE (5.1)**
- **Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)**
- **Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.2)**
- **Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)**
- **XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression (4, 5.2)**

Akathisia

Motor restlessness occurred in 5% of the treated population of the open label study, but none of the participants of the double blind study. Nevertheless, this phenomenon remains important as akathisia is a potent magnifier of depressive symptoms and is known to provoke suicidality in psychiatrically susceptible individuals (Hansen, 2001). It led to withdrawal from Study C-16 for two individuals. The restlessness can also be taken for increased chorea which could potentially lead to an unfortunate dose increase, not dose reduction.

By comparison, in the 12-week, double-blind, placebo-controlled Xenazine study, akathisia was observed in 10 (19%) of Xenazine-treated patients and none of the placebo treated patients (HuntingtonStudyGroup, 2006). In the 80-week open- label study, akathisia was observed in 20% of Xenazine-treated patients but akathisia was not observed in a 48- week open-label study. This discrepancy is not explained (Frank, 2009).

Parkinsonism

Parkinsonism was described as an AE in one of the C-15 patients and in 3 of the open label patients, one of whom was taking 72 mg daily. This resolved with dose reduction.

By comparison, in the 12-week double-blind, placebo-controlled symptoms suggestive of parkinsonism (i.e., bradykinesia, hypertonia and rigidity) were observed in 15% of Xenazine-

treated patients compared to none of the placebo treated patients. In the 48-week and 80-week open-label studies, symptoms suggestive of parkinsonism were observed in 10% and 3% of Xenazine-treated patients, respectively.

Dysphagia

In the open label SD-809 study, dysphagia was reported as an adverse event in 5 patients (4.2%). In the double blind study, none of the SD-809 patients had dysphagia as an AE, while 1 placebo patient did. Dysphagia may be associated with aspiration pneumonia. No patients developed pneumonia in Study C-15 while two patients developed pneumonia as an SAE in Study C-16. Both resolved without dose reductions and while continuing on medication.

By comparison, in the 12- week, double-blind, placebo-controlled study dysphagia was observed in 4% of Xenazine-treated patients and 3% of placebo-treated patients. In the 48-week and 80-week open-label studies, dysphagia was observed in 10% and 8% of Xenazine-treated patients, respectively.

Sedation and somnolence

In Study C-15, somnolence as an AE occurred in 5 (11%) patients taking SD-809 and only 2 patients in the placebo arm (4.4%). In four of the cases in the SD-809 arm, it was sufficiently severe that dose reductions were made, and in all cases but one this resolved the AE. In Study C-16, three events occurred and two resolved with dose reductions. Hypersomnolence caused one patient to withdraw from the open label study. It should be noted that fatigue was also a reason for dose reductions and also occurred more commonly with active drug treatment. It is impossible to discern whether this Preferred Term represents some occurrences of somnolence.

By comparison, in the 12-week, double-blind, placebo-controlled Xenazine trial, sedation/somnolence occurred in 17 of 54 (31%) in the Xenazine arm and in 1 (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. In all but one case, decreasing the dose of Xenazine resulted in decreased sedation. In the 48-week and 80-week open-label studies, sedation/somnolence occurred in 17% and 57% of Xenazine treated patients, respectively.

9 Advisory Committee Meeting and Other External Consultations

Advisory Committee input was not sought for this application.

10 Labeling Recommendations

10.1. Prescribing Information

Review of the prescribing information is deferred at this time.

10.2. Patient Labeling

A medication guide exists for the RLD and one should be required of this product as well. Specific areas of focus common to both products are depression and suicidality, interactions with medications and avoidance in patients with illnesses that affect the metabolism and excretion of SD-809.

10.3. Nonprescription Labeling

This section is not applicable to this product.

11 Risk Evaluation and Mitigation Strategies (REMS)

The RLD was subject to REMS that investigated strategies to minimize the occurrence of serious side effects of drug use. Those REMS were successfully concluded (see above, Section 3.1). During the review of SD-809, no new information was discovered that would suggest the need for additional REMS, nor have any new, novel, or previously undescribed adverse drug reactions been described that would warrant this intervention at this time.

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

None.

11.2. Conditions of Use to Address Safety Issue(s)

None.

11.3. Recommendations on REMS

No REMS are recommended at this time. There is adequate information presented in the label, Physician Prescribing Information, and the Medication Guide to provide sufficient guidance to healthcare providers, the patient, and the patient's caregivers to ensure the safe use of SD-809 in the medical treatment of chorea caused by Huntington's Disease.

12 Postmarketing Requirements and Commitments

Based upon review of the clinical data submitted in this application, no clinical post marketing commitment or requirement is deemed necessary.

13 Appendices

13.1. References

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13.2. Financial Disclosure

See also Financial Disclosures in Section 6.1.2 of this review. These same disclosures apply to Study C-16, as well.

Covered Clinical Study (Name and/or Number): SD-809-C-15 A Randomized, Double Blind, Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea associated with Huntington Disease

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 38		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 38		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Study C-15 - Full listing of Adverse Events (Head Count)

Created from the Sponsor's SDTM AE and DM datasets with JMP 11.1

System Organ Class	Preferred Term	SD-809	SD-809 %	Placebo	Placebo %
Vascular disorders	Hot flush	1	2.2		
	Hypertension	1	2.2		
Skin and subcutaneous tissue disorders	Pruritus	1	2.2		
	Pruritus generalised	1	2.2		
	Night sweats			1	2.2
	Rash			1	2.2
Respiratory, thoracic and mediastinal disorders	Nasal congestion	1	2.2		
	Chronic obstructive pulmonary disease			1	2.2
	Epistaxis			2	4.4
	Hiccups			1	2.2
	Erectile dysfunction	1	2.2		
Renal and urinary disorders	Pollakiuria	1	2.2	1	2.2
	Micturition urgency	1	2.2		
	Urinary hesitation	1	2.2		
	Urinary incontinence	1	2.2		
Psychiatric disorders	Insomnia	3	6.7	2	4.4
	Anxiety	2	4.4	1	2.2
	Abnormal dreams	1	2.2	1	2.2
	Depression	1	2.2	3	6.7
	Agitated depression	1	2.2		
	Agitation	1	2.2		
	Restlessness	1	2.2		
	Suicidal ideation	1	2.2		

	Compulsions			1	2.2
	Impulsive behaviour			1	2.2
	Sleep disorder			3	6.7
Nervous system disorders	Somnolence	5	11.1	2	4.4
	Dizziness	3	6.7	4	8.9
	Cognitive disorder	1	2.2		
	Drooling	1	2.2		
	Dyskinesia	1	2.2		
	Migraine	1	2.2		
	Akathisia			1	2.2
	Headache			3	6.7
	Loss of consciousness			1	2.2
	Syncope			1	2.2
Musculoskeletal and connective tissue disorders	Back pain	2	4.4	1	2.2
	Jaw disorder	1	2.2		
	Muscle spasms	1	2.2		
	Trigger finger	1	2.2		
	Muscle twitching			1	2.2
	Musculoskeletal discomfort			1	2.2
	Pain in extremity			2	4.4
Metabolism and nutrition disorders	Decreased appetite	1	2.2		
Investigations	Alanine aminotransferase increased	2	4.4		
	Aspartate aminotransferase increased	2	4.4		
	Weight decreased	1	2.2	1	2.2
	Blood alkaline phosphatase increased	1	2.2		

	Blood cholesterol increased	1	2.2		
	Blood glucose increased	1	2.2		
	Blood iron decreased	1	2.2		
	Blood testosterone decreased	1	2.2		
	Blood urea increased	1	2.2		
	Specific gravity urine increased	1	2.2		
	Urine ketone body present	1	2.2		
	Urine leukocyte esterase	1	2.2		
	Urine protein/creatinine ratio increased	1	2.2		
	White blood cell count decreased	1	2.2		
	White blood cell count increased	1	2.2		
	Blood potassium increased			2	4.4
	Blood triglycerides increased			1	2.2
Injury, poisoning and procedural complications	Fall	3	6.7	9	20.0
	Contusion	2	4.4	1	2.2
	Laceration	1	2.2	1	2.2
	Arthropod sting			1	2.2
	Excoriation			1	2.2
	Face injury			1	2.2
	Joint injury			1	2.2
	Limb injury			1	2.2

	Lip injury			1	2.2
	Rib fracture			1	2.2
	Wound			1	2.2
Infections and infestations	Urinary tract infection	3	6.7	1	2.2
	Nasopharyngitis	2	4.4	2	4.4
	Gastroenteritis viral	1	2.2		
	Influenza	1	2.2		
	Oral herpes	1	2.2		
	Pyelonephritis	1	2.2		
	Sinusitis	1	2.2		
	Cystitis			1	2.2
	Gastroenteritis			1	2.2
	Lower respiratory tract infection			1	2.2
	Upper respiratory tract infection			1	2.2
Hepatobiliary disorders	Cholecystitis chronic	1	2.2		
General disorders and administration site conditions	Fatigue	4	8.9	2	4.4
	Irritability	3	6.7	6	13.3
	Chest pain	1	2.2		
	Gait disturbance	1	2.2		
	Hangover	1	2.2		
Gastrointestinal disorders	Dry mouth	4	8.9	3	6.7
	Diarrhoea	4	8.9		
	Constipation	2	4.4	1	2.2
	Nausea	1	2.2	2	4.4

	Abdominal pain	1	2.2		
	Abdominal pain upper	1	2.2		
	Dyspepsia	1	2.2		
	Frequent bowel movements	1	2.2		
	Gastrointestinal pain	1	2.2		
	Dysphagia			1	2.2
	Flatulence			1	2.2
	Salivary hypersecretion			1	2.2
	Toothache			1	2.2
	Vomiting			3	6.7
Eye disorders	Conjunctivitis	1	2.2		
	Vision blurred			1	2.2
Ear and labyrinth disorders	Meniere's disease	1	2.2		
	Tinnitus			1	2.2
Cardiac disorders	Arrhythmia			1	2.2
	Atrial fibrillation			1	2.2
	Atrioventricular block first degree			1	2.2
	Coronary artery disease			1	2.2
	Ventricular extrasystoles			1	2.2

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/s/

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05/24/2016

GERALD D PODSKALNY
05/24/2016