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APPLICATION NUMBER:

208082Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 208082
Submission date: 10/3/2016 Resubmission
Drug: deutetrabenazine
Applicant: Teva Pharmaceuticals
Indication: Treatment of chorea associated with Huntington's disease

Reviewing Division: Division of Neurology Products

Discussion and conclusion:
The initial pharm/tox review of this NDA noted that there was insufficient information to confirm that the human metabolites, particularly major human metabolites, were comparable between tetrabenazine and deutetrabenazine. Such a comparison was necessary to understand whether the safety of tetrabenazine supported deutetrabenazine. The resubmission has clarified the human metabolite profiles sufficiently such that the pharm/tox reviewer and supervisor conclude that the nonclinical information provided supports the approval of the NDA for the above indication. I agree.

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/s/

PAUL C BROWN
03/30/2017

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208-082
Supporting document:	17, 20, 23, 26
Applicant's letter date:	1/15/2016; 4/8/2016; 5/9/2016; 10/3/2016
CDER stamp date:	1/15/2016; 4/8/2016; 5/9/2016; 10/3/2016
Product:	AUSTEDO (SD-809; deutetrabenazine)
Indication:	Treatment of chorea associated with Huntington's disease
Applicant:	Teva Pharmaceuticals, Inc.; La Jolla, CA
Review Division:	Neurology Products (DNP)
Reviewer:	Christopher D. Toscano, Ph.D., DABT
Supervisor:	Lois M. Freed, Ph.D.
Division Director:	Billy Dunn, M.D.
Project Manager:	Stacy M. Metz, Pharm. D.

Disclaimer

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1 Executive Summary

1.1 Introduction

The sponsor of NDA 208-082, Teva Pharmaceuticals, Inc., was provided with a Complete Response (CR) letter on May 27, 2016. In the CR letter, the sponsor was informed that the "*clinical pharmacology studies were not adequate to determine whether all major human metabolites of deutetrabenazine have been identified*." Specifically, based on the information provided during the development of deutetrabenazine (SD-809), metabolites M1 (SD-1021) and M4 (SD-1018) were thought to be major human metabolites (MHM). Based on the fact that there was limited information on the level of these metabolites circulating in animals dosed with deutetrabenazine, the sponsor was informed in the CR letter that "*if the results of the pending clinical pharmacology analyses identify additional major circulating human metabolites, you will need to demonstrate that each has been adequately assessed in the appropriate nonclinical studies…"* A review of the nonclinical studies provided in the initial submission was filed (Toscano CD, Nonclinical Review, February 4, 2016).

After internal discussions about the clinical pharmacology information provided in the NDA resubmission (October 3, 2016), it has been determined that metabolites M1 and M4 are not major human metabolites as defined by ICH M3(R2) because they do not circulate at levels greater than 10% of the total drug-related exposure (see Clinical Pharmacology Review for detailed assessment). Because nonclinical studies of these metabolites are no longer needed to support approval of the NDA, the nonclinical studies provided in the resubmission to support the safety of metabolite M1 and M4 will only be discussed briefly in Section 1.2 of this review. As stated in the February 4, 2016, nonclinical review, the nonclinical studies provided in the initial submission are adequate to support the approval of NDA 208-082.

1.2 Discussion of Nonclinical Findings

In the resubmission, the sponsor provided a series of pharmacology, pharmacokinetic, and genetic toxicology studies of metabolites M1 and M4. M1 binding to the rat adrenergic α_2 receptor and the human adrenergic $_{\alpha 2C}$ receptor was demonstrated in a series of adequately conducted in vitro high-throughput screens (DPR-2016-030, DPR-2016-032, DPR-2016-033); M4 did not demonstrate relevant binding in similar studies (DPR-2016-029, DPR-2016-031). The pharmacokinetic studies of M1 and M4 after oral dosing of rat, mouse, and rabbit with SD-809 or tetrabenazine (TBZ) were performed to determine if exposure to these metabolites had been adequate in nonclinical studies previously conducted by the sponsor or those described in the Xenazine label (DS-2016-016, DP-2016-037, DP-2016-038, DP-2016-054, DP-2016-056, SD-809-NC-062, DP-2016-043, DP-2016-045). Since it has been subsequently demonstrated that these metabolites are not MHMs, these studies are not required to support the approval of the NDA. There were no findings of concern in the in vitro (DP-2016-001, DP-2016-002, DP-2016-003) or in vivo pharmacokinetic studies provided in the resubmission and the results of these studies were consistent with what was described in the sponsor's meeting package (July 22, 2016). M4 and M1 were negative in an adequately conducted in vitro bacterial reverse mutation assay and an

adequately conducted in vitro chromosomal aberration study, respectively (DS-2016-027, DS-2016-024). Computational toxicology assessment of the mutagenicity of M1 and M4 was negative (DRK16-0826, DRK16-0834). There were no test article-related findings when M1 was tested in a zebrafish developmental toxicity screen (DS-2016-038). In summary, there were no test article-related findings of concern in the nonclinical studies provided to support the resubmission.

1.3 Recommendations

1.3.1 Approvability: The nonclinical studies reviewed under the initial submission are adequate to support the approval of NDA 208-082 (see February 4, 2016, review for additional details).

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Labeling recommendations can be found in the February 4, 2016, nonclinical review.

2 Drug Information:

For detailed drug information, refer to Toscano CD, "Pharmacology/Toxicology NDA Review and Evaluation", NDA 208-082, February 4, 2016.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology:

- DPR-2016-029, VMAT2 and off-target binding SD-1018 (SD-809 M4)
- DPR-2016-030, VMAT2 and off-target binding SD-1021 (SD-809 M1)
- DPR-2016-031, VMAT2 and off-target binding SD-1026 (TBZ M4)
- DPR-2016-032, VMAT2 and off-target binding SD-1027 (TBZ M1)
- DPR-2016-033, binding of SD-1018 (SD-809 M4) and SD-1026 (TBZ M4) to adrenergic α2C (human) receptors

Pharmacokinetics

Analytical Methods and Validation Reports:

- SD-809-NC-061, Validation of a Method for the Determination of SD-1021 Metabolite and SD-1018 Metabolites of SD-809 (d6-tetrabenazine) in Rat Plasma by LC/MS/MS
- DP-2016-090, An Analytical Method Validation and Stability Study of SD-809 Metabolite M4 (SD-1018) in Dimethyl sulfoxide Formulations

Absorption:

- DS-2016-016, A 9-day, twice daily (BID) oral (gavage) pharmacokinetic evaluation of M1 (SD-1021 or SD-1027), M4 (SD-1018 or SD-1026), SD-809, and SD-808 (tetrabenazine) in Sprague Dawley rats.
- DP-2016-037, Pharmacokinetics of SD-809 in Male and Female CD-1 Mice after Single or Repeated Oral Doses
- DP-2016-038, Pharmacokinetics of Tetrabenazine in Male and Female C57/BL6 Mice after Single or Repeated Oral Doses

- DP-2016-054, Pharmacokinetics of SD-809 and Tetrabenazine in Male and Female CD-1 and CF-1 Mice After Single Oral Dose SD-809 or Tetrabenazine
- DP-2016-056, Pharmacokinetics of SD-809 and Tetrabenazine in Female New Zealand White Rabbit after Single Oral Dose SD-809 or Tetrabenazine
- SD-809-NC-062, Pharmacokinetics of SD-1021 in rat
- DP-2016-043, In Life Report for DP-2016-054
- DP-2016-045, In Life Report for DP-2016-056

Pharmacokinetic Drug Interactions:

- DP-2016-001, In Vitro Evaluation of SD-1018 (SD-809 Metabolite M4) as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
- DP-2016-002, In Vitro Evaluation of SD-1018 (SD-809 Metabolite M4) as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes
- DP-2016-003, In Vitro Evaluation of SD-1018 (SD-809 Metabolite M4) as an Inhibitor and a Substrate of Human P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 Transporters

Genetic Toxicology:

- DS-2016-027, SD-1018: Salmonella-E. Coli/Mammalian Microsome Reverse Mutation Assay
- DS-2016-024, SD-1021: In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes
- DRK16-0826, Computational Toxicity Report for Metabolite M4 in SD-809 (TEV-50717)
- DRK16-0834, Computational Toxicity Report for Metabolite M1 in SD-809 (TEV-50717)

Developmental Toxicology:

- DS-2016-038, Zebrafish Developmental Toxicity Screen of TEV-48317 and SD-1021

3.2 Studies Not Reviewed: None

3.3 Previous Reviews Referenced

- Toscano CD, “Pharmacology/Toxicology NDA Review and Evaluation,” NDA 208-082, February 4, 2016.

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/s/

CHRISTOPHER D TOSCANO
01/18/2017

LOIS M FREED
01/18/2017
I concur.

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 208082
Submission date: 5/29/2015
Drug: deutetrabenazine
Applicant: Teva Pharmaceuticals
Indication: Treatment of chorea associated with Huntington's disease

Reviewing Division: Division of Neurology Products

Discussion:
This NDA referred to the Agency's finding of safety for the approved drug, tetrabenazine (Xenazine). A comparison of the human metabolites associated with the two drugs is necessary to understand if the safety of tetrabenazine supports deutetrabenazine. The primary pharm/tox review and the supervisory review discuss the metabolites and note that the clinical pharmacology review is unable to confirm that the human metabolites, particularly major human metabolites (those that compose greater than 10% of total drug in circulation), are comparable between the two drugs. The pharm/tox reviewer and supervisor recommend that the human major metabolite profiles be clarified sufficiently such that the Agency can determine whether the existing finding of safety for tetrabenazine applies to deutetrabenazine.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that there needs to be an adequate bridge for the major human metabolites in order for the Agency to make a safety decision.

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PAUL C BROWN
05/24/2016

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: March 31, 2016

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 208-082 (SD-809; d_6-tetrabenazine; AUSTEDO; Auspex Pharmaceuticals)

NDA 208-082 was submitted on May 29, 2015, to support marketing approval of SD-809 (deutetrabenazine) for treatment of the chorea of Huntington's disease. The NDA is a 505(b)(2) submission, with Xenazine (tetrabenazine; NDA 21-894) as the Reference Listed Drug (RLD). Clinical development was conducted under IND 112975.

The nonclinical program consists of the following pivotal studies of SD-809:

- Pharmacology
- PK/ADME
- Toxicology
    - 3-month oral toxicity study of SD-809 and tetrabenazine (TBZ) in rat
    - Embryofetal development study of SD-809 and TBZ 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

These data were reviewed in detail by Dr. Toscano (*cf. Pharmacology/Toxicology NDA Review and Evaluation, NDA 208-082, Christopher D. Toscano, Ph.D., February 3, 2016*). Based on that review, Dr. Toscano has concluded that "It is not possible to determine if the nonclinical studies…support bridging to the…RLD…" because of the inadequacy of the sponsor's evaluation of the in vivo metabolic profile of SD-809 in humans.

The following is a summary of the nonclinical data provided for SD-809 and potential review issues; a comprehensive description and discussion of these data are provided in Dr. Toscano's review.

Pharmacology

SD-809 is a deuterated form of the RLD (TBZ), with substitution of two d-methoxy ($-OCD_3$) groups in place of the two methoxy ($-OCH_3$) groups of TBZ. SD-809, like TBZ, is an inhibitor of the vesicular monoamine transporter, type 2 (VMAT2). Binding affinities for VMAT2 were similar for the deuterated and non-deuterated active metabolites (α- and β-HTBZ) (sponsor's table below), as were binding affinities to a panel of other receptors/binding sites.

Table 1. Inhibition of VMAT2 Binding by Deuterated and Nondeuterated α-HTBZ and β-HTBZ; K_i and IC_{50} Values

	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

Safety Pharmacology

The sponsor assessed CNS safety pharmacology in the pivotal 3-month oral toxicity study in Sprague-Dawley rat but only in males (6/group, Week 12), which was justified by the higher plasma exposures and more severe clinical signs in males. An in vitro hERG assay indicated IC_{50}'s of >10 µM for the active metabolites of SD-809 and TBZ (identified in Table 1 above). In vivo cardiovascular or respiratory safety pharmacology studies were not conducted.

PK/ADME

PK/ADME studies of SD-809 and TBZ were conducted in CD-1 mouse and rat (Sprague-Dawley [non-pregnant and pregnant], Lister Hooded), as well as in vitro metabolism studies in rat and human liver preparations (S9, microsomes, or hepatocytes).

In general, the PK/ADME of SD-809 was similar to that of TBZ. The major, active, metabolites quantified were d_6 α- and β-dihydrotetrabenazine (d_6 α- and β-HTBZ) In Sprague-Dawley rat, acute oral doses (2.5 and 15 mg/kg) of SD-809 resulted in up to 2.4-fold higher plasma AUCs for parent and metabolites, d_6 α- and β-HTBZ, compared to TBZ and metabolites, α- and β-HTBZ, 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 SD-809 and TBZ.

In vivo metabolism studies were not conducted in animals. The sponsor stated that "None are planned as human exposure to the metabolites of the listed tetrabenazine will be used to qualify the SD-809 metabolites" (*Pharmacokinetics Written Summary, pg. 8 of 25*). However, the OCBP team has concluded that because of deficiencies in the evaluation of the in vivo metabolic profile in humans, it is unclear, based on the available data, whether

or not all major circulating metabolites of SD-809 in humans have been identified. The primary deficiencies are as follows:

- Inconsistent values obtained for metabolite M1 (2-methylpropanoic acid metabolite of β-HTBZ), using semi-quantitative methods, resulting in an inability to determine whether or not M1 is a major metabolite in humans. It was not identified as a major human metabolite of TBZ, either by the sponsor or in TBZ labeling.
- The inability of the sponsor to demonstrate, using semi-quantitative methods, that a known (based on TBZ labeling) major human metabolite of TBZ, 9-O-desmethyl-β-HTBZ, is a major human metabolite of SD-809 or TBZ. This deficiency increases the overall concern regarding the adequacy of these methods, as noted for M1.
- Lack of information on an unidentified peak on the radiochromatograms of pooled plasma samples, which appears "much higher" with SD-809 compared to TBZ.

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 available data do suggest that M4 (monohydroxy TBZ) is a major human metabolite of SD-809 and TBZ; however, M4 is not identified as such in labeling for TBZ.

General Toxicology and Reproductive and Development Toxicology

The only pivotal studies of SD-809 conducted by the sponsor were a 3-month oral toxicity study and an embryofetal development study in Sprague-Dawley rat. In the 3-month study, SD-809 was administered at doses of 0, 2.5, 5, and 15 mg/kg BID; TBZ was administered at a single dose level (15 mg/kg BID). In the embryofetal development study, SD-809 was administered at doses of 0, 2.5, 5, and 15 mg/kg BID on gestation days 6-17; TBZ was administered at a single dose level (15 mg/kg BID) during the same period. Based on his review of the data, Dr. Toscano concluded that SD-809 exhibited no unique toxicities, based on direct comparison to TBZ.

Genetic Toxicology

SD-809 and metabolites, d_6 α- and β-HTBZ, were negative when tested in separate in vitro (Ames, chromosomal aberration assay in human peripheral blood lymphocytes) assays. SD-809 and TBZ (0, 20, 40, 80 mg/kg QD x 3 for both) were negative in an in vivo mouse micronucleus assay.

Conclusions and Recommendations

The sponsor was informed multiple times during clinical development (*cf. Memorandum of Meeting Minutes, PIND 112975, 12/9/2011; Memorandum of Meeting Minutes, End of*

Phase 2, IND 112975, 12/26/2012) and review of the NDA (*cf. email communication, October 15, 2015; Mid-Cycle Communication, NDA 208082, 12/2/2015; Late-Cycle Meeting Background Package, NDA 208082, 2/19/2016*) of the importance of providing an adequate comparison of the in vivo metabolic profile of SD-809 with that of the RLD. However, the OCBP team has concluded that the sponsor has not adequately characterized the in vivo metabolic profile of SD-809 in humans. 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.

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LOIS M FREED
03/31/2016

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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208-082
Supporting document/s:	3
Applicant's letter date:	5/29/2015
CDER stamp date:	5/29/2015
Product:	Austedo (SD-809; deutetrabenazine)
Indication:	Treatment of chorea associated with Huntington's disease
Applicant:	Teva Pharmaceuticals; La Jolla, CA
Review Division:	Neurology Products (DNP)
Reviewer:	Christopher D. Toscano, Ph.D., DABT
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Billy Dunn, M.D.
Project Manager:	Stacy Metz, Pharm.D.

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TABLE OF CONTENTS

1 EXECUTIVE SUMMARY 3

1.1 Introduction 3
1.2 Brief Discussion of Nonclinical Findings 3
1.3 Recommendations 3

2 DRUG INFORMATION 10

2.1 Drug 10
2.2 Relevant INDs, NDAs, BLAs and DMFs 11
2.3 Drug Formulation 11
2.4 Comments on Novel Excipients 11
2.5 Comments on Impurities/Degradants of Concern 12
2.6 Proposed Clinical Population and Dosing Regimen 15
2.7 Regulatory Background 15

3 STUDIES SUBMITTED 16

4 PHARMACOLOGY 21

4.1 Primary Pharmacology 21
4.2 Secondary Pharmacology 21
4.3 Safety Pharmacology 22

5 PHARMACOKINETICS/ADME/TOXICOKINETICS 23

5.1 PK/ADME 23

6 GENERAL TOXICOLOGY 29

6.1 Single-Dose Toxicity 29
6.2 Repeat-Dose Toxicity 33

7 GENETIC TOXICOLOGY 48

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames) 48
7.2 *In Vitro* Assays in Mammalian Cells 55
7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay) 64

9 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY 67

9.2 Embryonic Fetal Development 67

11 INTEGRATED SUMMARY AND SAFETY EVALUATION 76

1 Executive Summary

1.1 Introduction:

Austedo (SD-809) is a deuterated form of tetrabenazine (TBZ), a drug substance approved under the trade name Xenazine (NDA 21-894) for the treatment of chorea associated with Huntington's disease. By deuterating TBZ, the sponsor plans to take advantage of the kinetic isotope effect (KIE) of deuterium to alter the metabolism of TBZ and increase exposure to the active metabolites, α- and β-dihydrotetrabenazine. The sponsor has requested approval of Austedo under 505(b)(2), with Xenazine serving as the reference listed drug (RLD).

1.2 Brief Discussion of Nonclinical Findings

The pivotal toxicology studies conducted to support the approval of SD-809 consist of a 3-month oral toxicity study and an embryofetal development (EFD) study in rat, with TBZ as a comparator, and a complete genetic toxicology battery. Overall, there were no adverse findings unique to SD-809, relative to TBZ. It is important to note that there is uncertainty regarding the adequacy of the available information on the human metabolism of SD-809; therefore, it is unclear if all major human metabolites of SD-809 have been adequately tested. The sponsor has provided adequate nonclinical information to support the proposed specifications for the known impurities in SD-809.

1.3 Recommendations

1.3.1 Approvability

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 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.

1.3.2 Additional Non Clinical Recommendations

- If the Clinical Pharmacology review team determines that there is a marked difference in the profile of MHMs between SD-809 and the RLD, the sponsor will need to provide additional nonclinical information to support the safety of these metabolites. For example, quantification of the level of each metabolite of concern at steady state in the 3-month repeat dose pivotal study and EFD studies would be necessary. If any of the SD-809 specific MHMs are found not to be covered in the pivotal studies conducted in rat or if there are MHMs of SD-809 that are not described in the labeling of the RLD, additional nonclinical studies may be required to demonstrate the safety of the metabolite(s), including a

chronic study in a single species (up to 6 months in rodent and 9 months in nonrodent), reproductive and development studies (e.g., EFD and pre- and postnatal development), and a carcinogenicity assessment.

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1.3.3 Labeling

Labeling Section	Sponsor Proposed	Reviewer Recommended
Highlights of Prescribing Information	Indications and Usage AUSTEDO is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease. (1) Use in Specific Populations • Pregnancy: Based on animal data, [redacted] (b) (4) may cause fetal harm. (8.1)	*No change recommended*
5 Warnings and Precautions	**5.12 Binding to Melanin-Containing Tissues** Since deutetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that [redacted] (b) (4) may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of the eye has been conducted in the chronic toxicity studies in a pigmented species such as dogs. Ophthalmologic monitoring in humans was inadequate to exclude the possibility of injury occurring after long-term exposure. The clinical relevance of deutetrabenazine's binding to melanin-containing tissues is unknown. Although there are no specific recommendations for periodic ophthalmologic monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects *[see Clinical Pharmacology (12.2)].*	*No change recommended*

8.1 Pregnancy	**8.1 Pregnancy** *Risk Summary* (b) (4) *Animal Data* (b) (4) (b) (4)	**8.1 Pregnancy** *Risk Summary* There are no adequate and well-controlled studies in pregnant women. AUSTEDO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Animal Data* A dose-dependent increase in the incidence of 7th cervical rib occurred in fetuses of pregnant rats given oral doses of 5, 10, or 30 mg/kg/day BID deutetrabenazine or 30 mg/kg/day BID tetrabenazine throughout the period of organogenesis. The lowest dose of deutetrabenazine was similar to the maximum recommended human dose [MRHD] of 48 mg/day AUSTEDO on a mg/m^2 basis. Deutetrabenazine has not been assessed in embryo-fetal development studies in pregnant rabbits. Tetrabenazine had no effects on embryo-fetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m^2 basis). Because neither rat nor rabbit dosed with tetrabenazine produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately addressed the potential effects of tetrabenazine on embryo-fetal development in humans. Deutetrabenazine has not been assessed in a pre-and postnatal developmental study. When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and

	(b) (4) (b) (4)	offspring postnatal mortality was observed at 15 and 30 mg/kg/day, and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD of tetrabenazine on a mg/m^2 basis. *Labor and Delivery* The effect of AUSTEDO on labor and delivery in humans is unknown. **8.3 Females and Males of Reproductive Potential** *Infertility* AUSTEDO has not been assessed on impairment of fertility. In a study conducted with tetrabenazine, no effects on mating and fertility indices or sperm parameters (motility, count, density) were observed in rats. In female rats, disrupted estrous cyclicity was observed *[see Nonclinical Toxicology (13.1)].* VMAT2 inhibition may elevate serum prolactin concentrations [see *Warnings and Precautions (5.10)*].
12.1 Mechanism of Action	**12.1 Mechanism of Action** The precise mechanism by which AUSTEDO (deutetrabenazine) exerts its anti-chorea effects is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. The major circulating metabolites (α-dihydrotetrabenazine [HTBZ] and β-HTBZ) of deutetrabenazine, are reversible inhibitors of VMAT2, resulting in decreased uptake of	**12.1 Mechanism of Action** The precise mechanism by which AUSTEDO (deutetrabenazine) exerts its anti-chorea effects is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. The major circulating metabolites (α-dihydrotetrabenazine [HTBZ] and β-HTBZ) of deutetrabenazine, are reversible inhibitors of VMAT2, resulting in decreased uptake of monoamines into synaptic vesicles

	monoamines into synaptic vesicles and depletion of monoamine stores. (b) (4) (b) (4)	and depletion of monoamine stores.
	12.2 Pharmacodynamics **Melanin Binding** Deutetrabenazine or its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. After a single oral dose of radiolabeled deutetrabenazine, radioactivity was still detected in eye and fur at 35 days following dosing.	**12.2 Pharmacodynamics** *No change recommended*
13 Nonclinical Toxicology	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** No carcinogenicity studies were performed with deutetrabenazine. No increase in tumors was observed in $p53^{+/-}$ transgenic mice treated orally with tetrabenazine at doses of 0, 5, 15, and 30 mg/kg/day for 26 weeks. Deutetrabenazine and its α-HTBZ and β-HTBZ metabolites were	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** <u>Carcinogenesis</u> No carcinogenicity studies were performed with deutetrabenazine. No increase in tumors was observed in $p53^{+/-}$ transgenic mice treated orally with tetrabenazine at doses of 0, 5, 15, and 30 mg/kg/day for 26 weeks. When compared to humans receiving a 50 mg dose of tetrabenazine, mice dosed with a 30 mg/kg dose of tetrabenazine produce about one sixth the levels of 9-desmethyl-beta-DHTBZ, a major human metabolite. Therefore, this study may not have adequately characterized the potential of tetrabenazine to be carcinogenic in humans. <u>Mutagenesis</u> Deutetrabenazine and its α-HTBZ and β-HTBZ metabolites were

	negative [redacted] in the *in vitro* bacterial reverse mutation assay and in the *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, in the presence or absence of metabolic activation. [redacted] Oral administration of tetrabenazine (doses of 5, 15, or 30 mg/kg/day) to female rats prior to and throughout mating, and continuing through day 7 of gestation, resulted in disrupted estrous cyclicity at doses greater than 5 mg/kg/day [redacted] No effects on mating and fertility indices or sperm parameters (motility, count, density) were observed when males were treated orally with tetrabenazine at doses of 5, 15 or 30 mg/kg/day [redacted] prior to and throughout mating with untreated females.	negative for genotoxicity in the *in vitro* bacterial reverse mutation assay and in the *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, in the presence or absence of metabolic activation. Deutetrabenazine was negative in *in vivo* micronucleus tests in male and female mice. <u>Impairment of Fertility</u> No fertility study has been conducted with deutetrabenazine. Oral administration of deutetrabenazine (doses of 5, 10, or 30 mg/kg/day) to female rats for 3 months resulted in disruption of estrous cyclicity at all dose levels; the lowest dose was similar to the MRHD of SD-809 on a mg/m^2 basis. Oral administration of tetrabenazine (doses of 5, 15, or 30 mg/kg/day) to female rats prior to and throughout mating, and continuing through day 7 of gestation, resulted in disrupted estrous cyclicity at doses greater than 5 mg/kg/day (less than the MRHD of tetrabenazine on a mg/m^2 basis). No effects on mating and fertility indices or sperm parameters (motility, count, density) were observed when males were treated orally with tetrabenazine at doses of 5, 15 or 30 mg/kg/day (up to 3 times the MRHD of tetrabenazine on a mg/m^2 basis) prior to and throughout mating with untreated females. Because rats dosed with tetrabenazine do not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately assessed the potential of tetrabenazine to impair fertility in humans.

2 Drug Information

2.1 Drug

CAS Registry Number: 1392826-25-3

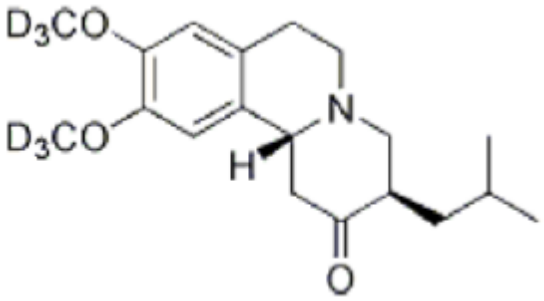
Generic Name: deutetrabenazine

Code Name: SD-809, d6-tetrabenazine, d6-TBZ

Chemical Name: (RR, SS)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d3)-3-(2-methylpropyl)-2Hbenzo[a]quinolizin-2-one

Molecular Formula/Molecular Weight: $C_{19}H_{21}D_6NO_3$; 323.46

Structure:



Pharmacologic Class: Vesicular monoamine transporter 2 (VMAT2) inhibitor

2.2 Relevant IND: IND 112,975 (Auspex; SD-809)

2.3 Drug Formulation: The sponsor's table (provided below) describes the formulation of the drug product.

Table 1. SD-809 Tablet Composition

Component	Amount per Tablet (mg)			Function	Standard/Grade
Deutetrabenazine	6.00	9.00	12.00	Active ingredient	In-house/GMP
Mannitol (b) (4)				(b) (4)	USP/NF, EP
Microcrystalline Cellulose					NF, EP
Povidone (b) (4)					USP/NF, EP
Polysorbate 80					NF, EP
(b) (4)					USP/NF, EP
Polyethylene Oxide (b) (4)					NF
Magnesium Stearate					NF, EP
Butylated Hydroxyanisole					NF, EP
Butylated Hydroxytoluene					NF, EP
(b) (4)					Supplier
					Supplier
					USP/NF, EP
					USP/NF, EP
Total					(b) (4)

2.4 Comments on Novel Excipients: The excipients in the drug product are listed in the Inactive Ingredient Database and are present at levels that are lower than those in previously approved drug products.

2.5 Comments on Impurities/Degradants of Concern: The sponsor proposes the following specifications for the drug substance (sponsor's Table 1, below).

Table 1: Specifications for Deutetrabenazine

Test	Acceptance Criteria	Analytical Method
Description	White to yellow crystalline powder	Visual
Identification*	IR Spectrum of the sample should match with the standard	USP<197K>
	The retention time of the principal peak in the test solution chromatogram should match to the principal peak retention time of the standard solution chromatogram obtained from the Assay by HPLC	HPLC
(b) (4)	(b) (4)	
	Not more than (b) (4)	USP<921>
Residue on Ignition*	Not more than	USP<281>
Elemental Impurities*	(b) (4) NMT (b) (4) NMT NMT NMT	USP<233> (b) (4)
Related Substances (%w/w)	(b) (4) NMT (b) (4) NMT NMT NMT NMT NMT Unspecified and unidentified impurities: NMT Total impurities: NMT	HPLC
Residual solvents*	(b) (4) NMT (b) (4) NMT NMT NMT	GC
Assay (b) (4)	NLT (b) (4)	HPLC
Deuterium content*	Not less than (b) (4)	(b) (4)

* Test not performed for stability purposes
(b) (4); NMT = Not More Than; NLT = Not Less Than

With the exception of (b) (4), the proposed specification for each individual impurity is less than the qualification threshold of 0.15%. The following table contains the information on the drug batches used for drug substance validation and drug product registration (sponsor's table, below).

Table 1. Description of (b) (4) Deutetrabenazine Batches

Drug Substance Batch #	Batch Size (kg)	Date of Manufacture	Use of Batch
DT4130001	(b) (4)	November 2013	Drug Substance Validation
DT4130002		November 2013	
DT4130003		November 2013	
DT4130004		December 2013	
(b) (4) 112394St41012002		October 2012	Drug Product Registration
112394St41112003		November 2012	
112394St41112004		November 2012	

The structures and level of impurities in the drug substance batches used in the IND studies and the batches used to formulate the drug product are provided in the sponsor's tables, below.

Organic Impurity	Origin	Control[a]	Acceptance Criterion	Results from Process Validation Lots
(b) (4)				

Table 7. Related Substances

Batch #	(b) (4)
DT4130001	
DT4130002	
DT4130003	
DT4130004	
(b) (4) 12394St41012002	
12394St41112003	
12394St41112004	

ND=not detected

With regard to the potential mutagenicity of the drug substance impurities mentioned above, the sponsor has performed a computational toxicology assessment of (b) (4) (b) (4) (Derek Nexus and Multicase); a full genetic toxicology battery was performed on

(b) (4), as a mixture with SD-809, and an in vitro assessment was performed for (b) (4) It appears, from the information provided in the initial NDA submission, that a computational toxicology assessment was not performed for (b) (4), (b) (4) The sponsor was informed of this potential deficiency during the Mid-Cycle Communication Meeting (November 3, 2015). A QSAR assessment for these four impurities was performed by the CDER Computational Toxicology Consultation Service; none of the four impurities was positive for mutagenicity in DEREK Nexus, Leadscope Model Applier, or CASE Ultra. The sponsor provided the results of an in silico assessment upon request and the result was also negative. Therefore, there is no concern regarding the mutagenic potential of (b) (4).

Two of the impurities in the drug substance are carried over to the drug product, (b) (4) (b) (4) (sponsor's tables, below).

Table 4. Batch Analysis of SD-809 Tablets – 6 mg

Attribute	Specification	N451173B	N451857B	N452166B
Related Substances	(b) (4)			

Table 5. Batch Analysis of SD-809 Tablets – 9 mg

Attribute	Specification	N451737B	N451738B	N452168B
Related Substances	(b) (4)			

Table 6. Batch Analysis of SD-809 Tablets – 12 mg

Attribute	Specification	N451174B	N451739B	N452167B
Related Substances	(b) (4)			

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) Although the currently detected levels do not exceed the qualification threshold of 200 µg/ 48 mg SD-809 or (b) (4) the sponsor states that the level of this (b) (4) in the drug product. Therefore, the sponsor has proposed a specification for this impurity/degradant of (b) (4)% in the drug product. Based on a MRHD of 48 mg and a 60 kg human, the total daily dose of (b) (4) would be (b) (4) mg/kg at (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). 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.

Table 7. (b) (4) Human Dose and Human Dose Equivalents in Rat and Mouse

90-Day GLP Rat Toxicology [a] and Embryofetal Rat Development [b] Studies			Intended Maximum Labeled Dose [d]		Safety Factor [e]
SD-809 dose (mg/kg/day)	(b) (4) dose (mg/kg/day) [f]	(b) (4) HED [g] (mg/kg/ day)	SD-809 dose (mg/kg/day)	(b) (4) dose (mg/kg/day)	
10	(b) (4)				
GLP Mouse Micronucleus Study [c]			**Intended Maximum Labeled Dose [d]**		**Safety Factor [e]**
SD-809 dose (mg/kg/day)	(b) (4) dose (mg/kg/day) [f]	(b) (4) HED [g] (mg/kg/ day)	SD-809 dose (mg/kg/day)	(b) (4) dose (mg/kg/day)	
80	(b) (4)				

Abbreviation: HED, human equivalent dose.
[a] Section 2.6.7.7; Reference: SD-809-NC-025.
[b] Section 2.6.7.13; Reference: SD-809-NC-052.
[c] Section 2.6.7.9; Reference: SD-809-NC-044.
[d] Assumes a daily 48 mg dose of SD-809 containing (b) (4) (b) (4) in a 60 kg adult.
[e] Nonclinical dose as HED (mg/kg/day) divided by (b) (4) human dose (mg/kg/day).
[f] Assumes dose formulation contained (b) (4) (b) (4) (lowest measured value in SD-809-NC-050-Section 2.6.5.2).
[g] HED from mice and rats obtained by dividing the mouse and rat dose by 12.3 and 6.2, respectively (FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. July 2005).

The sponsor conducted both a bacterial reverse mutation assay and an in vitro chromosomal aberration study with SD-809 containing (b) (4). Both studies were adequately conducted and SD-809 with (b) (4) was negative for mutagenicity and clastogenicity.

2.6 Proposed Clinical Population and Dosing Regimen: Huntington's disease patients will be treated with a starting dose of 6 mg/day QD and titrated up at weekly intervals by 6 mg/day to a tolerated dose that reduces chorea. Doses of 12 mg/day or higher should be given BID. The maximum recommended human daily dose (MRHD) is 48 mg BID.

2.7 Regulatory Background: At the pre-NDA meeting held on March 19, 2015, the Division stated that the nonclinical studies appeared to be sufficient to support an NDA for SD-809 (Meeting Minutes, IND 112975, 4/17/2015). It was noted in the nonclinical filing review that the nonclinical studies submitted in NDA 208-082 were the same that were provided in the pre-NDA meeting packet, as mentioned above (Nonclinical Filing Review, NDA 208-082, 7/14/2015).

3 Studies Submitted

3.1 Studies Reviewed (sponsor's table)

Type of Study / Description	Test System	Method of Administration	Testing Facility	Study Number
Primary Pharmacodynamics				
Displacement of [^{3}H]-dihydrotetrabenazine binding to native VMAT2	Synaptic vesicles isolated from rat forebrain homogenates	In vitro	(b) (4)	SD-809-NC-008
Secondary Pharmacodynamics				
Off-target activity: binding screen to 64 targets	Membranes prepared from - Tissues - Cell lines	In vitro		SD-809-NC-009
Off-target activity: human dopamine D2s receptor and sigma (nonselective) receptor	Membranes prepared from - CHO-K1 cell line - Guinea pig brain homogenate	In vitro		SD-809-NC-010
Off-target activity: opioid (nonselective) receptor	Membranes prepared from rat forebrain homogenate	In vitro		SD-809-NC-011
Off-target activity: Alpha-1-adrenergic (nonselective) receptor and serotonin (nonselective) receptor	Membranes prepared from - Rat forebrain homogenate - Rat cortex homogenate	In vitro		SD-809-NC-012
Off-target activity: Alpha-2-adrenergic (nonselective) receptor	Membranes prepared from rat cortex homogenate	In vitro		SD-809-NC-013
Safety Pharmacology				
hERG channel inhibition	hERG channel expressed in Chinese Hamster Ovary (CHO) cell line	In vitro		SD-809-NC-009
Functional observational battery	Rat; assessment included in a three-month rat GLP toxicology and toxicokinetic study	Oral (gavage)		SD-809-NC-025
Pharmacodynamic Drug Interactions: No studies conducted				
Analytical Methods				
Validation of a method to determine tetrabenazine and SD-809 concentrations	Aqueous formulations	NA	(b) (4)	SD-809-NC-018
Qualification of HPLC/MS/MS to determine concentrations of deuterated and non-deuterated α-HTBZ; deuterated and non-deuterated β-HTBZ	Rat plasma	NA		SD-809-NC-020
Validation and stability study of deuterated and non-deuterated α-HTBZ; deuterated and non-deuterated β-HTBZ	DMSO formulations	NA		SD-809-NC-022
Validation of HPLC/MS/MS, and stability study of tetrabenazine, α-HTBZ and β-HTBZ	Rat plasma	NA		SD-809-NC-023
Validation of HPLC/MS/MS and stability of SD-809, deuterated α-HTBZ, and deuterated β-HTBZ	Rat plasma	NA		SD-809-NC-024
Concentration assessment of SD-809 and (b) (4) based on pH	Aqueous formulations	NA		SD-809-NC-050
Cross validation and stability study of SD-809 containing (b) (4) (b) (4)	DMSO formulations	NA		SD-809-NC-068
Method validation and stability study of (b) (4)	DMSO formulations	NA		SD-809-NC-069
Method validation and stability study of metabolite M1 (SD-1021)	DMSO and aqueous formulations	NA		SD-809-NC-070

			(b) (4)	
Absorption				
Single-Dose Toxicity with Toxicokinetics	Sprague-Dawley Male and Female Rats	Oral		SD-809-NC-004
Repeat-Dose Toxicokinetics	CD-1 Male Mice	Oral		SD-809-NC-036
Repeat-Dose Toxicity with Toxicokinetics	Sprague-Dawley Male Rats	Oral		SD-809-NC-006
Repeat-Dose Toxicity with Toxicokinetics	Sprague-Dawley Male and Female Rats	Oral		SD-809-NC-025
Embryo-fetal developmental toxicity with toxicokinetics	Gravid Sprague-Dawley Female Rats	Oral		SD-809-NC-052
14-Day Toxicity Study with Toxicokinetics (oral gavage)	Sprague-Dawley Male and Female Rats	Oral		SD-809-NC-076
Distribution				
[^{14}C] Excretion and Tissue Distribution Study	Male Rat (Lister-Hooded for distribution, Sprague-Dawley for blood-to-brain ratio study)	Oral administration of [^{14}C]-SD-809 and non-deuterated reference compound, [^{14}C]-tetrabenazine		SD-809-NC-042
Metabolism				
Characterization of metabolites of substrates SD-809 and tetrabenazine	Human and rat liver S9 fraction	In vitro		SD-809-NC-049
Characterization of metabolites of substrates deuterated and non-deuterated α-HTBZ and β-HTBZ	Human liver microsomes	In vitro		SD-809-NC-015
Metabolic stability of SD-809, tetrabenazine, deuterated and non-deuterated α-HTBZ and β-HTBZ	Human, monkey, dog, rat, and mouse liver microsomes	In vitro	Auspex Pharmaceuticals, Inc.	SD-809-NC-001
Metabolic stability of SD-809, tetrabenazine, deuterated and non-deuterated α-HTBZ andβ-HTBZ	Human liver S9 and cytosol fraction	In vitro	Auspex Pharmaceuticals, Inc.	SD-809-NC-002
Metabolic stability of SD-809, tetrabenazine, deuterated and non-deuterated α-HTBZ and β-HTBZ	Human recombinant CYP1A2, CYP3A4, or CYP2D6	In vitro	Auspex Pharmaceuticals, Inc.	SD-809-NC-003
In vitro metabolic stability of deuterated and non-deuterated α-HTBZ and β-HTBZ with and without CYP inhibitors	Human liver microsomes	In vitro	(b) (4)	SD-809-NC-041
Excretion				
[^{14}C] Excretion and Tissue Distribution Study	Lister Hooded Male Rat	Oral administration of [^{14}C]-SD-809 and [^{14}C]-tetrabenazine		SD-809-NC-042
Pharmacokinetic Drug Interactions				
No studies conducted				
Other Studies (Metabolite M1 [SD-1021])				
Evaluation of metabolite M1 as in inhibitor of CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; time dependent and metabolism dependent	Human liver microsomes	In vitro		SD-809-NC-071
Evaluation of metabolite M1 as in inducer of CYP enzymes CYP1A2, CYP2B6, and CYP3A4	Human hepatocytes	In vitro		SD-809-NC-072
Evaluation of metabolite M1 as a substrate of transporters	Madin-Darby canine kidney cells MDCKII-MDR1 and MDCKII-BCRP	In vitro		SD-809-NC-073
Evaluation of metabolite M1 as an inhibitor of transporters	Caco-2 and MDCKII-BCRP cells; HEK3 cells expressing organic anion transporters and organic cation transporters	In vitro		SD-809-NC-073

Overview of Toxicology Studies			Test Article: Deutetrabenazine (SD-809), deuterated α-HTBZ, deuterated β-HTBZ			
Type of Study	**Species and Strain**	**Duration of Dosing**	**Doses**	**GLP Compliance**	**Testing Facility**	**Study Number**
Single-Dose Toxicity						
Single-Dose Toxicity with Toxicokinetics	Sprague-Dawley Male and Female Rats	Single dose [a]	0 (0.5% CMC) SD-809: 2.5, 15 mg/kg Tetrabenazine: 2.5, 15 mg/kg	No	(b) (4)	SD-809-NC-004
Repeat-Dose Toxicity						
Repeat-Dose Toxicity with Toxicokinetics	Sprague-Dawley Male Rats	14 days [a]	0 (0.5% CMC, 0.1% polysorbate 80) SD-809: 7.5, 15, 25 mg/kg/dose BID Tetrabenazine: 25 mg/kg/dose BID	No		SD-809-NC-006
	Sprague-Dawley Male and Female Rats	3 months [a]	0 (0.5% CMC, 0.1% polysorbate 80) SD-809: 2.5, 5, 15 mg/kg/dose BID Tetrabenazine: 15 mg/kg/dose BID	Yes		SD-809-NC-025
Genotoxicity						
Bacterial system [b]	S typhimurium TA1537, TA98, TA100, TA1535 E.coli WP2uvrA	2 days [b,c]	SD-809 (containing (b) (4)): 0 (DMSO), 100, 250, 500, 1000, 2500, and 5000 µg/plate	Yes		SD-809-NC-056
Mammalian system [b]	Human Peripheral Blood Lymphocytes	3, 22 hours [b,c]	SD-809 (containing (b) (4)): 3 hours without activation: 0, (DMSO), 100, 175, and 325 µg/mL SD-809 (containing (b) (4)):, 3 hours with activation: 0 (DMSO), 50, 100, and 175 µg/mL SD-809 (containing (b) (4)): 22 hours without activation: 0 (DMSO) 50, 75, and 125 µg/mL	Yes		SD-809-NC-057
Bacterial system	S typhimurium TA1537, TA98, TA100, TA1535 E.coli WP2uvrA	2 days [c]	Deuterated α-HTBZ (SD-948): 0 (DMSO), 25, 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate [d]	Yes		SD-809-NC-032

Overview of Toxicology Studies			Test Article: Deutetrabenazine (SD-809), deuterated α-HTBZ, deuterated β-HTBZ			
Type of Study	**Species and Strain**	**Duration of Dosing**	**Doses**	**GLP Compliance**	**Testing Facility**	**Study Number**
	S typhimurium TA1537, TA98, TA100, TA1535 E. coli WP2uvrA	2 days[c]	Deuterated β-HTBZ (SD-949): 0 (DMSO), 25, 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate [e]	Yes	(b) (4)	SD-809-NC-034
Mammalian system	Human Peripheral Blood Lymphocytes	3, 22 hours[c]	Deuterated α-HTBZ (SD-948): 0 (DMSO), 43.6, 68.2, 106, 133, and 325 µg/mL[f]	Yes		SD-809-NC-033
	Human Peripheral Blood Lymphocytes	3, 22 hours[c]	Deuterated β-HTBZ (SD-949): 0 (DMSO), 27.9, 85.2, and 325 µg/mL[g]	Yes		SD-809-NC-035
In vivo micronucleus	CD-1 Male and Female Mice	3 days[a]	Range-finding phase: 0 (0.5% CMC, 0.1% polysorbate 80) SD-809, once daily for 3 days: 25, 50, 100 mg/kg/dose Tetrabenazine, once daily for 3 days: 25, 50, 100 mg/kg/dose Definitive phase: 0 (0.5% CMC, 0.1% polysorbate 80) SD-809, once daily for 3 days: 20, 40, 80 mg/kg/dose Tetrabenazine, once daily for 3 days: 20, 40, 80 mg/kg/dose	Yes		SD-809-NC-044
Carcinogenicity: No study conducted. Not Applicable						
Reproductive and Developmental Toxicity						
Preliminary Embryofetal Development	Sprague-Dawley Gravid Female Rats	11 days (Gestational Days 6-17)[a]	0 (0.5% CMC, 0.1% polysorbate 80) SD-809: 5, 15, 25 mg/kg/dose BID	No	(b) (4)	SD-809-NC-051
Embryofetal Development	Sprague-Dawley Gravid Female Rats	11 days (Gestational Days 6-17)[a]	0 (0.5% CMC, 0.1% polysorbate 80) SD-809: 2.5, 5, 15 mg/kg/dose, BID Tetrabenazine: 15 mg/kg/dose, BID	Yes		SD-809-NC-052
Local Tolerance: No study conducted. Not Applicable						

Overview of Toxicology Studies			Test Article: Deutetrabenazine (SD-809), deuterated α-HTBZ, deuterated β-HTBZ			
Type of Study	**Species and Strain**	**Duration of Dosing**	**Doses**	**GLP Compliance**	**Testing Facility**	**Study Number**
Other Toxicity Studies						
	Metabolite M1 (SD-1021)					
Genotoxicity: Bacterial system	S typhimurium TA1537, TA98, TA100, TA1535 E.coli WP2uvrA	2 days [c]	Metabolite M1 (SD-1021): 0 (DMSO), 100, 250, 500, 1000, 2500, and 5000 µg/plate	Yes	(b) (4)	SD-809-NC-066
Genotoxicity: Mammalian system	Human Peripheral Blood Lymphocytes	3, 22 hours [c]	Metabolite M1 (SD-1021): 0 (DMSO), 90, 180, and 360 µg/mL	Yes		SD-809-NC-067
Genotoxicity: (Q)SAR	MultiCASE Derek Nexus	NA	NA	NA		SD-809-NC-063, SD-809-NC-064
	Impurities (b) (4)					
Genotoxicity of (b) (4) Bacterial system	Strains: TA1537, TA98, TA100, TA1535 and Escherichia coli strain WP2uvrA	2 days [c]	SD-809 containing (b) (4) 0 (DMSO), 100, 250, 500, 1000, 2500, and 5000 µg/plate	Yes	(b) (4)	SD-809-NC-056
Genotoxicity of (b) (4) Mammalian system	Human Peripheral Blood Lymphocytes	3, 22 hours [c]	SD-809 containing (b) (4) 3 hours without activation: 0 (DMSO), 100, 175, and 325 µg/mL SD-809 containing (b) (4) 3 hours with activation: 0 (DMSO), 50, 100, and 175 µg/mL SD-809 containing (b) (4) 22 hours without activation: 0 (DMSO), 50, 75, and 125 µg/mL	Yes		SD-809-NC-057
Genotoxicity of (b) (4) Bacterial system	S typhimurium TA1537, TA98, TA100, TA1535 E.coli WP2uvrA	2 days [c]	(b) (4) 0 (DMSO), 100, 250, 500, 1000, 2500, and 5000 µg/plate	Yes		SD-809-NC-058

Overview of Toxicology Studies			Test Article: Deutetrabenazine (SD-809), deuterated α-HTBZ, deuterated β-HTBZ			
Type of Study	**Species and Strain**	**Duration of Dosing**	**Doses**	**GLP Compliance**	**Testing Facility**	**Study Number**
Genotoxicity of (b) (4) Mammalian system	Human Peripheral Blood Lymphocytes	3, 22 hours[c]	(b) (4) 3 hours without activation: 0 (DMSO), 100, 175, and 325 µg/mL (b) (4) 3 hours with activation: 0 (DMSO), 150, 225, and 300 µg/mL (b) (4) 22 hours without activation: 0 (DMSO), 25, 50, 75 µg/mL	Yes	(b) (4)	SD-809-NC-059
Genotoxicity of (b) (4) (Q)SAR	MultiCASE Derek Nexus	NA	NA	NA		SD-809-NC-074, SD-809-NC-075
Repeat-Dose Toxicity with Toxicokinetics of (b) (4)	Sprague-Dawley Male and Female Rats	14 days [a]	0 (0.5% CMC, 0.1% polysorbate 80) SD-809: 5 mg/kg/dose BID SD-809 with (b) (4) 5 mg/kg/dose BID	Yes		SD-809-NC-076

BID = twice daily; NA = not applicable; CMC = Carboxymethyl cellulose; DMSO = Dimethyl sulfoxide; HTBZ = dihydrotetrabenazine.

[a] Method of administration: oral gavage.

[b] Studies conducted as part of qualification of (b) (4) impurity (b) (4) of SD-809). Results are described under "Other Toxicity Studies" Section 17.

[c] Method of administration: in vitro.

[d] Nondeuterated α-HTBZ (SD-946) reported in SD-809-NC-028 and Section 8.2.

[e] Nondeuterated β-HTBZ (SD-947) reported in SD-809-NC-030 and Section 8.4.

[f] Nondeuterated α-HTBZ (SD-946) reported in SD-809-NC-029 and Section 8.6.

[g] Nondeuterated β-HTBZ (SD-947) reported in SD-809-NC-031 and Section 8.8.

Overview of Toxicokinetics Studies		Test Article: Deutetrabenazine (SD-809), deuterated α-HTBZ, deuterated β HTBZ		
Type of Study	**Test System**	**Doses**	**GLP Compliance**	**Study Number**
Single Dose Toxicity Study with Toxicokinetics (oral gavage)	Sprague-Dawley Male and Female Rats	0: 0.5% CMC SD-809: 2.5, 15 mg/kg Tetrabenazine: 2.5, 15 mg/kg	No	SD-809-NC-004
14-Day Dose Range Finding and Toxicokinetic Study (oral gavage)	Sprague-Dawley Male Rats; Samples on Day 0 and Day 13	0: 0.5% CMC, 0.1% polysorbate 80 SD-809: 7.5, 15, 25 mg/kg BID Tetrabenazine: 25 mg/kg BID	No	SD-809-NC-006
3-Month Toxicity Study with Toxicokinetics (oral gavage)	Sprague-Dawley Male and Female Rats; Samples on Day 0, Day 34 and Day 91	0: 0.5% CMC, 0.1% polysorbate 80 SD-809: 2.5, 5, 15 mg/kg BID Tetrabenazine: 15 mg/kg BID	Yes	SD-809-NC-025
Embryo-fetal developmental toxicity with toxicokinetics (oral gavage)	Sprague-Dawley Gravid Female Rats; Samples on Dosing Day 0 (Gestational Day 6) and Dosing Day 11 (Gestational Day 17)	0: 0.5% CMC, 0.1% polysorbate 80 SD-809: 2.5, 5, 15 mg/kg BID Tetrabenazine: 15 mg/kg BID	Yes	SD-809-NC-052
14-Day Toxicity Study with Toxicokinetics (oral gavage)	Sprague-Dawley Male and Female Rats; Samples on Day 0 and Day 13	0: 0.5% CMC, 0.1% polysorbate 80 SD-809: 5 mg/kg/dose BID SD-809 with (b) (4) 5 mg/kg/dose BID	No	SD-809-NC-076

CMC = Carboxymethyl cellulose; BID = twice daily dosing; HTBZ = dihydrotetrabenazine.

3.2 Studies Not Reviewed: None

3.3 Previous Reviews Referenced: None

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4 Pharmacology

4.1 Primary Pharmacology

The in vitro binding affinity for the active metabolites of TBZ (α- and β-dihydrotetrabenazine) and the deuterated versions of these metabolites to the vesicular monoamine transporter 2 (VMAT2) was examined in competitive binding assays (SD-809-NC-008). The sponsor uses the following terminology for each test article throughout the application: α-dihydrotetrabenazine (SD-946), β-dihydrotetrabenazine (SD-947), d6-α-dihydrotetrabenazine (SD-948), and d6-β-dihydrotetrabenazine (SD-949). The IC_{50} and K_i for each compound at VMAT2 are provided in the sponsor's table, below. There was no apparent impact of deuteration on the binding activity of α-dihydrotetrabenazine and β-dihydrotetrabenazine.

Table 1. Inhibition of VMAT2 Binding by Deuterated and Nondeuterated α-HTBZ and β-HTBZ; K_i and IC_{50} Values

	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)

4.2 Secondary Pharmacology

Off-target binding of the deuterated and non-deuterated forms of α-dihydrotetrabenazine and β- dihydrotetrabenazine was assessed in an in vitro binding screen (SD-809-NC-009; sponsor's table 2, below). For targets with > 50% inhibition, there appeared to be no impact of deuteration on the binding of the test article, with the exception of β- dihydrotetrabenazine at the opioid receptor.

Table 2. Percentage Inhibition of Radioligand Binding to Off-target Receptors by 10 µM of Deuterated and Nondeuterated α-HTBZ-and β-HTBZ

	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.

The off-target binding was confirmed in a separate set of in vitro studies that were conducted for each of the targets listed in the sponsor's table, above (SD-809-NC-010, SD-809-NC-011, SD-809-NC-012, SD-809-NC-013). The IC_{50} for each test article, both deuterated and non-deuterated, are provided in the sponsor's table 3 below; there was little impact of deuteration on the binding of α-dihydrotetrabenazine and β-dihydrotetrabenazine.

Table 3. Inhibition of Radioligand Binding to Off-target Receptors by Deuterated and Nondeuterated α-HTBZ and β-HTBZ; IC_{50} 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.

4.3 Safety Pharmacology

A functional observational battery was conducted with SD-809 as part of the 3-month study in rat (reviewed below). There was no respiratory safety pharmacology study performed with SD-809. An in vitro assessment of hERG inhibition was performed with 10 µM of the deuterated and non-deuterated forms of α-dihydrotetrabenazine and β-dihydrotetrabenazine; inhibition was < 50% (SD-809-ND-009). There were no in vivo cardiovascular safety pharmacology studies performed with SD-809.

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5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Analytical Methods & Validation Reports: Validated methods were used to assess the levels of:

- TBZ (SD-808) and SD-809 in aqueous formulations (SD-809-NC-018)
- SD-946, SD-947, SD-948, and SD-949 in rat plasma (SD-809-NC-020)
- (b) (4) of SD-809, under acidic conditions (SD-809-NC-050)
- Metabolite 1 (M1) in DMSO (SD-809-NC-069 and SD-809-NC-070).

Absorption:

Study SD-809-NC-036: "Toxicokinetics of SD-808 (Tetrabenazine) and SD-809 (d6-Tetrabenazine) Following a Single Oral Gavage Dose or Three Consecutive Daily Oral Gavage Doses to Male CD-1 Mice." CD-1 mice (n= 18 males/group) were given a single dose or three consecutive daily doses of 40 mg/kg SD-808 (Lot 30046-036C2; 99.8% purity) or 40 mg/kg SD-809 (Lot 30046-039C2; 99.9% purity) in 0.5% carboxymethylcellulose/ 0.1% Tween 80 by oral gavage. The PK parameters for TBZ, SD-809, and related metabolites (α-dihydrotetrabenazine and β-dihydrotetrabenazine) are provided in the sponsor's table, below.

Table 3-2. Group Mean Pharmacokinetic Summary Data

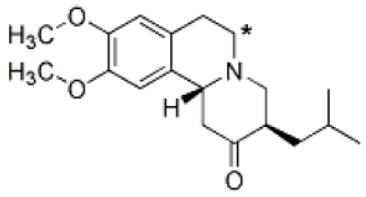
Compound	Dose (mg/kg)	Group	Day	Analyte	C_{max} (ng/mL)	SE C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	SE AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
Tetrabenazine (SD-808)	40	1	1	SD-946 α-HTBZ Metabolite	337	133	0.500	214	66.6	1.24
				SD-947 ß-HTBZ Metabolite	98.9	18.7	0.500	81.0	9.77	1.04
		3	3	SD-946 α-HTBZ Metabolite	188	46.2	0.500	145	25.3	0.578
				SD-947 ß-HTBZ Metabolite	70.2	11.4	0.500	75.8	8.59	0.745
d_6-Tetrabenazine SD-809	40	2	1	SD-948 α-HTBZ Metabolite	259	17.6	0.500	205	14.1	0.849
				SD-949 ß-HTBZ Metabolite	105	13.7	0.500	111	9.75	0.682
		4	3	SD-948 α-HTBZ Metabolite	286	108	0.500	208	56.5	1.23
				SD-949 ß-HTBZ Metabolite	109	37.1	0.500	107	21.4	1.28

Distribution:

Study SD-809-NC-042: "[^{14}C]-SD-809 and [^{14}C]-tetrabenazine: Rat Excretion and Tissue Distribution Studies." Male Sprague Dawley or Lister hooded rats were given a single dose of 5 mg free base/kg of either radiolabelled compound by oral gavage (structures provided below).

Common name: [^{14}C]-Tetrabenazine ([^{14}C]-SD-808)

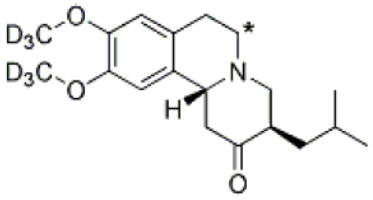
Chemical structure:



* Position of ^{14}C-label

Common name: [^{14}C]-d_6-Tetrabenazine ([^{14}C]-SD-809)

Chemical structure:



* Position of ^{14}C-label

For the determination of brain distribution and calculation of blood/brain ratio, nine SD rats were given a single oral dose of radiolabelled TBZ or SD-809 (0.37 MBq/rat). Brain and plasma samples were taken from 3 rats/group at 1, 4, and 8 hours after dosing. Blood/brain ratio was slightly higher in rats dosed with TBZ at 1 hour after dosing and markedly higher at 4 hours after dosing, relative to rats dosed with SD-809 (sponsor's table, below). Brain distribution was similar between both test articles at 8 hours after dosing.

Table 2. Concentrations of Radioactivity Measured in Whole Blood and Brain Collected from Male Sprague Dawley Rats Following a Single 5 mg/kg Dose of [^{14}C]-SD-809 or [^{14}C]-Tetrabenazine

		Time Postdose (hours)		
		1	4	8
SD-809	Whole	0.565 (0.21)	0.509 (0.05)	0.324 (0.03)
Tetrabenazine	Blood	0.808 (0.16)	0.520 (0.17)	0.275 (0.02)
SD-809	Brain	0.562 (0.28)	0.458 (0.04)	0.191 (0.03)
Tetrabenazine		0.751 (0.17)	0.328 (0.09)	0.168 (0.03)
SD-809	Ratio	1.039 (0.11)	1.109 (0.06)	1.698 (0.07)
Tetrabenazine	(Blood/Brain)	1.083 (0.06)	1.580 (0.22)	1.664 (0.31)

Section 2.6.5.5.2; Reference: SD-809-NC-042.
Mean (standard deviation) Radioactivity (µg equivalents / g tissue), n=3 per time point, per test article.

Male Lister hooded rats (n=7/ test article) were given a single oral dose of radiolabelled TBZ or radiolabelled SD-809 (5 mg/kg; 0.37 MBq/rat). One rat per group was euthanized at 1 hour, 4 hours, 24 hours, 48 hours, 7 days, 21 days, or 35 days after dosing. Tissue concentrations were quantitated using whole-body autoradiography; the results are provided in the sponsor's tables, below. The lower limit of quantification (LLOQ) was 0.053 and 0.052 µg Eq/g for TBZ and SD-809, respectively.

[^{14}C]-Tetrabenazine, expressed as µg equivalents/g

Tissue	Time after dose administration						
	1 hour	4 hours	1 day	2 days	7 days	21 days	35 days
Adrenal gland	3.04	2.13	0.671	0.294	0.071	BLQ	BLQ
Blood (heart)	0.822	0.458	0.065	BLQ	BLQ	BLQ	BLQ
Eye*	12.9	22.3	9.46	5.67	3.54	0.980	0.160
Kidney cortex	3.64	4.33	0.604	0.284	0.099	BLQ	BLQ
Kidney medulla	2.38	2.01	0.662	BLQ	BLQ	BLQ	BLQ
Liver	6.13	4.65	0.984	0.446	0.085	BLQ	BLQ
Lung	1.25	0.909	0.072	0.057	BLQ	BLQ	BLQ
Muscle	0.894	0.580	0.056	BLQ	BLQ	BLQ	BLQ
Nasal mucosa	1.47	2.79	0.855	0.411	BLQ	BLQ	BLQ
Pigmented fur	BLQ	BLQ	BLQ	BLQ	BLQ	5.66	2.14
Skin (non-pigmented)	1.22	0.982	0.078	BLQ	BLQ	BLQ	BLQ
Skin (pigmented)	2.06	2.03	0.333	0.418	0.268	BLQ	BLQ
Urinary bladder contents	23.0	14.4	1.14	NS	BLQ	BLQ	BLQ
Uveal tract	51.3	88.4	36.2	15.9	6.63	2.97	4.26
Remaining tissues (excl. GI Tract)	0.114 - 4.47	0.065 - 3.87	BLQ - 0.384	BLQ - 0.119	BLQ	BLQ	BLQ
GI Tract	1.55 – 72.6	0.964 - 42.4	0.053 - 3.26	BLQ - 0.384	BLQ	BLQ	BLQ

* Result determined by oxidation and liquid scintillation counting (LSC)
BLQ Below Limit of accurate Quantification (Less than 0.053 µg equivalents/g)
NS Tissue not sectioned

[^{14}C]-SD-809,expressed as µg equivalents/g

Tissue	Time after dose administration						
	1 hour	4 hours	1 day	2 days	7 days	21 days	35 days
Adrenal gland	3.17	2.40	0.558	0.249	BLQ	BLQ	BLQ
Blood (heart)	0.819	0.595	BLQ	BLQ	BLQ	BLQ	BLQ
Eye*	3.26	30.0	16.7	10.8	5.50	2.33	0.400
Kidney cortex	3.42	2.59	0.582	0.368	0.125	BLQ	BLQ
Kidney medulla	2.66	2.23	0.120	0.052	BLQ	BLQ	BLQ
Liver	5.89	4.63	0.793	0.522	0.070	BLQ	BLQ
Lung	1.50	0.853	0.055	BLQ	BLQ	BLQ	BLQ
Muscle	0.987	0.610	BLQ	BLQ	BLQ	BLQ	BLQ
Nasal mucosa	2.34	1.74	NS	0.452	0.104	BLQ	BLQ
Pigmented fur	BLQ	BLQ	BLQ	2.95	3.93	3.28	3.59
Skin (non-pigmented)	0.988	0.677	0.073	BLQ	BLQ	BLQ	BLQ
Skin (pigmented)	2.42	3.26	1.28	0.161	BLQ	BLQ	BLQ
Urinary bladder contents	31.8	24.1	1.45	NS	NS	BLQ	BLQ
Uveal tract	34.3	129†	37.8	25.3	12.7	5.06	3.57
Remaining tissues (excl. GI Tract)	0.077 - 4.89	0.089 - 3.78	BLQ - 0.399	BLQ - 0.165	BLQ - 0.066	BLQ	BLQ
GI Tract	0.390 - 20.2	1.23 – 91.6†	BLQ - 1.93	BLQ - 0.507	BLQ	BLQ	BLQ

* Result determined by oxidation and liquid scintillation counting (LSC)
BLQ Below Limit of accurate Quantification (Less than 0.052 µg equivalents/g)
NS Tissue not sectioned
† Above limit of accurate quantification (>89.2 µg equivalents/g)

The pattern of organ distribution was similar between animals dosed with TBZ or SD-809. Feces was the main route of excretion (~60%), with urine accounting for 26-29% of dose radioactivity, for TBZ and SD-809.

Metabolism:

Given that the kinetic isotope effect (KIE) of deuterium is known to impact the metabolism of test articles, it is expected that the metabolism of SD-809 will differ from that of TBZ. A number of studies were conducted to evaluate those differences.

Study SD-809-NC-001: "In vitro stability of Tetrabenazine, SD-809, alpha-dihydrotetrabenazine, beta-dihydrotetrabenazine, d6-alpha-dihydrotetrabenazine, and d6-beta-dihydrotetrabenazine in Human, Rat, Dog, Monkey, and Mouse Liver Microsomes." TBZ (1 μM), SD-809 (1 μM), alpha-dihydrotetrabenazine (0.25 μM), beta-dihydrotetrabenazine (0.25 μM), d6-alpha-dihydrotetrabenazine (0.25 μM), and d6-beta-dihydrotetrabenazine (0.25 μM) were incubated separately for 30 to 60 minutes with liver microsomes from human, rat, dog, monkey, and mouse. Deuteration had a minimal effect on the half-life of TBZ in the presence of human liver microsomes (increased by 8%). However, the stability of alpha- and beta-dihydrotetrabenazine, when incubated with human liver microsomes, was markedly increased by deuteration (48% to 139%, respectively), but to a lesser extent when incubated with liver microsomes from rat, dog, monkey, or mouse (sponsor's Table 2, below).

Table 2. Microsomal Stability of Tetrabenazine, alpha-HTBZ, beta-HTBZ, SD-809, d_6-alpha-HTBZ and d_6-beta-HTBZ Incubated with Rat, Dog, Mouse and Monkey Liver Microsomes

Species [a]	Rat	Dog	Monkey	Mouse
Tetrabenazine $t_{1/2}$ (min) [b]	17.7	5.93	3.00	4.50
SD-809 $t_{1/2}$ (min)	17.8	5.93	3.00	4.50
% change by deuteration	0.56	0	0	0
alpha-HTBZ $t_{1/2}$ (min) [c]	243	80.7	58.9	35.1
d_6-alpha HTBZ $t_{1/2}$ (min)	236	92.8	26.7	28.4
% change by deuteration	-2.88	15.0	-54.7	-19.1
beta-HTBZ $t_{1/2}$ (min) [c]	99.9	47.8	30.9	59.0
d_6-beta HTBZ $t_{1/2}$ (min)	106	55.0	19.1	43.9
% change by deuteration	6.11	15.1	-38.2	-25.6

a: Average of duplicates, one experiment per species

b: In vitro procedures and sample preparation #3, Bioanalytical method #4

c: In vitro procedures and sample preparation #4, Bioanalytical method #4

Study SD-809-NC-002: "SD-809: In Vitro Stability of Tetrabenazine, SD-809, alpha-dihydrotetrabenazine, beta-dihydrotetrabenazine, d6-alpha-dihydrotetrabenazine and d6-beta-dihydrotetrabenazine in Human S9 Liver Fraction." Tetrabenazine, SD-809, alpha-dihydrotetrabenazine, beta-dihydrotetrabenazine, d6-alpha-dihydrotetrabenazine and d6-beta-dihydrotetrabenazine were incubated separately (at 0.25 μM) with human hepatic S9 fraction or cytosol for one hour. Both TBZ and SD-809 were below the limit

of quantification (BLQ) after the 60 minute incubation period. In general, deuteration increased the stability of α- and β-dihydrotetrabenazine (48.5% and 105%, respectively) in the presence of human S9 fraction or cytosol.

Study SD-809-NC-003: "SD-809: In Vitro Stability of Tetrabenazine, SD-809, alpha-dihydrotetrabenazine, beta-dihydrotetrabenazine, d6-alpha-dihydrotetrabenazine and d6-beta-dihydrotetrabenazine in Human CYP1A2, 2D6, and 3A4." The stability of TBZ, SD-809, and the alpha and beta metabolites of these compounds were tested in the presence of recombinant human CYP450 1A2, 3A4, and 2D6. TBZ and SD-809 were extensively metabolized by CYP3A4 ($t_{1/2}$= 5-6 min) but not by CYP1A2 or CYP2D6. The half-life of alpha- and beta-dihydrotetrabenazine was the shortest in the presence of CYP2D6 (28 and 23 minutes, respectively) and markedly longer in the presence of CYP3A4 (71 and 176 minutes, respectively). There was limited metabolism of these two metabolites in the presence of CYP1A2. Deuteration increased the half-life of alpha- and beta- dihydrotetrabenazine in the presence of CYP2D6 (226% and 138%, respectively) but not in the presence of CYP3A4.

Study SD-809-NC-015: "In Vitro Stability of Deuterated (d6) and Non-Deuterated (d0) α-dihydrotetrabenazine and β-dihydrotetrabenazine by Human Liver Microsomes." Deuterated and non-deuterated forms of α- and β-dihydrotetrabenazine were incubated for 60 minutes with human liver microsomes. Metabolites were assessed using an HPLC-MS/MS method. There were no novel metabolites detected for the deuterated compounds, relative to the non-deuterated (sponsor's table, below).

Test article	Test article (μM)	Metabolites					
		9-*O*-desmethyl-HTBZ	10-*O*-desmethyl-HTBZ	Oxidation product 1	Oxidation product 2	Oxidation product 3	Oxidation product 4
d_0-α-HTBZ	5	+	+	+	+	+	ND
d_6-α-HTBZ		+	+	+	+	+	ND
d_0-β-HTBZ		+	+	+	+	+	+
d_6-β-HTBZ		+	+	+	+	ND	ND

\+ Metabolite was detected in 60-min incubation samples.

ND Metabolite was not detected.

The oxidation products were all m+16 amu.

Metabolites were detected in incubation with an equimolar mixture of d_6-HTBZ and d_0-HTBZ.

Study SD-809-NC-41:"Contribution of CYP1A2, CYP2D6, and CYP3A4/5 Enzymes to the In Vitro Metabolism of d6- and d0-α-dihydrotetrabenazine and β-dihydrotetrabenazine in Human Liver Microsomes." Deuterated and non-deuterated forms of α- and β-dihydrotetrabenazine (1 μM) were incubated with human liver microsomes in the presence of CYP1A2, 2D6, or 3A4/5 inhibitors (10 μM furafylline, 1 μM quinidine, or 50 μM troleandomycin, respectively). The contribution of each CYP isoform toward the formation of the desmethylated metabolites is provided in the sponsor's table, below. It is apparent that CYP2D6 plays a major role in the formation of the desmethylated metabolites of the deuterated and non-deuterated forms of TBZ.

Metabolite	Percent contribution (%)		
	CYP1A2	CYP2D6	CYP3A4/5
d_0-9-*O*-desmethyl-α-HTBZ	13.2	83.0	22.5
d_0-10-*O*-desmethyl-α-HTBZ	5.6	84.5	11.2
d_0-9-*O*-desmethyl-β-HTBZ	ND	89.4	ND
d_0-10-*O*-desmethyl-β-HTBZ	ND	91.8	ND
d_3-9-*O*-desmethyl-α-HTBZ	15.2	68.5	ND
d_3-10-*O*-desmethyl-α-HTBZ	ND	ND	ND
d_3-9-*O*-desmethyl-β-HTBZ	12.3	89.3	9.6
d_3-10-*O*-desmethyl-β-HTBZ	28.9	ND	ND

ND Not determined

Study SD-809-NC-049: "In Vitro Metabolism of Deuterated (d6) and Non-deuterated (d0) Tetrabenazine by Liver S9 Fractions from Rat and Human." Deuterated and non-deuterated forms of TBZ were incubated for 60 minutes with rat or human liver S9 fractions. Using an HPLC-MS/MS method, the production of six metabolites was monitored (sponsor's table, below). Metabolite production appeared to be similar between rat and human and did not differ with deuteration status.

Metabolite	d_0-TBZ (5 µM)		d_6-TBZ (5 µM)	
	Rat	Human	Rat	Human
9-*O*-desmethyl-β-HTBZ	+	+	+	+
10-*O*-desmethyl-β-HTBZ	+	+	+	+
9-*O*-desmethyl-α-HTBZ	+	+	+	+
10-*O*-desmethyl-α-HTBZ	+	+	+	+
β-HTBZ	+	+	+	+
α-HTBZ	+	+	+	+

\+ Metabolite was detected in 60-min incubation samples.

Metabolites were also detected in incubation with an equimolar mixture of d_6-TBZ and d_0-TBZ.

Other Pharmacokinetic Studies:

Study SD-809-NC-071: "In Vitro Evaluation of SD-1021 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes." SD-1021, which is also known as Metabolite 1 or M1 (2-methylpropanoic acid β-dihydrotetrabenazine), was incubated with human liver microsomes to determine the ability to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. SD-1021 was not a direct, time-dependent, or metabolism-dependent inhibitor of any of the CYPs examined in this study when tested up to 100 µM.

Study SD-809-NC-072: "In Vitro Evaluation of SD-1021 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes." Primary cultures of human hepatocytes were incubated with up to 100 µM SD-1021 to determine the ability of this metabolite of SD-809 to induce CYP1A2, CYP2B6, or CYP3A4. SD-1021 did not induce CYP1A2; however, mRNA levels of CYP2B6 and CYP3A4 were increased by 2- to 3-fold.

Study SD-809-NC-073: "In Vitro Evaluation of SD-1021 as an Inhibitor and Substrate of Human P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 Transporters." The ability of SD-1021 (up to 3 µM) to inhibit the activity of P-gp and BCRP was tested in a monolayer of Caco-2 and MDCKII-BCRP cells. The ability of SD-1021 (up to 3 µM) to inhibit OATP1B1, OATP1B3, OAT1, OAT3, and OCT2 transporters was evaluated in HEK293 cells. SD-1021 was not a substrate for these transport proteins.

6 General Toxicology

6.1 Single-Dose Toxicity

Study SD-809-NC-004: "Exploratory Toxicity and Toxicokinetics of Tetrabenazine and d6-tetrabenazine (SD-809) Following a Single Oral Gavage Dose in Male and Female Sprague-Dawley Rats." Sprague-Dawley rats were given a single oral dose of vehicle (0.5% carboxymethylcellulose), TBZ (Lot 30046-0362C2, 99.7%), or SD-809 (30046-039C2, 99.7%) by oral gavage as detailed in the sponsor's table, below. Animals were euthanized 14 days after dosing.

Group	Test Article	Animal IDs	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	# Animals per sex per Group
1	Vehicle	1M001–1M006 1F001–1F006	0	0	10	6 (12 total)
2	Tetrabenazine	2M001–2M006 2F001–2F006	2.5	0.25	10	6 (12 total)
3	Tetrabenazine	3M001–3M006 3F001–3F006	15	1.5	10	6 (12 total)
4	SD-809	4M001–4M006 4F001–4F006	2.5	0.25	10	6 (12 total)
5	SD-809	5M001–5M006 5F001–5F006	15	1.5	10	6 (12 total)
Toxicokinetic Groups						
6	Tetrabenazine	6M001–6M003 6F001–6F003	2.5	0.25	10	3 (6 total)
7	Tetrabenazine	7M001–7M003 7F001–7F003	15	1.5	10	3 (6 total)
8	SD-809	8M001–8M003 8F001–8F003	2.5	0.25	10	3 (6 total)
9	SD-809	9M001–9M003 9F001–9F003	15	1.5	10	3 (6 total)

Lethargy was observed in HDM and HDF in the TBZ and SD-809 groups. There were no test article-related effects on body weight, food consumption, or clinical pathology parameters evaluated on Days 2 and 24 post dose or on organ weights or gross pathology assessed on Day 14. Deuteration increased the circulating levels of α- and β-dihydrotetrabenazine; other known circulating metabolites were not assessed (sponsor's tables, below). The NOAEL was 2.5 mg/kg TBZ or SD-809.

Table 3.2. Individual Animal and Group Mean Toxicokinetic Summary Data

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
Tetrabenazine	PO	6	2.5	SD-946 (α-HTBZ)	F	6F001	4.17	1.00	2.09	NC
						6F002	8.76	1.00	23.8	1.60
						6F003	5.59	1.00	15.6	1.77
						N	3	3	3	2
						Mean	6.17	1.00	13.8	1.69
						SD	2.35	0.00	11.0	0.115
					M	6M001	44.1	1.00	150	2.00
						6M002	31.9	1.00	124	2.14
						6M003	36.5	1.00	145	2.08
						N	3	3	3	3
						Mean	37.5	1.00	139	2.07
						SD	6.16	0.00	13.6	0.0726
					F + M	N	6	6	6	5
						Mean	21.8	1.00	76.7	1.92
						SD	17.7	0.00	69.7	0.226

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
SD-809	PO	8	2.5	SD-948 (d_6-α-HTBZ)	F	8F001	3.72	1.00	11.0	2.57
						8F002	14.4	1.00	42.5	1.68
						8F003	11.6	1.00	44.0	2.38
						N	3	3	3	3
						Mean	9.91	1.00	32.5	2.21
						SD	5.54	0.00	18.6	0.472
					M	8M001	88.9	0.500	387	2.31
						8M002	38.2	1.00	195	2.17
						8M003	66.7	1.00	283	2.25
						N	3	3	3	3
						Mean	64.6	0.833	288	2.24
						SD	25.4	0.289	95.9	0.069
					F + M	N	6	6	6	6
						Mean	37.3	0.917	160	2.23
						SD	34.2	0.204	153	0.302

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
Tetrabenazine	PO	6	2.5	SD-947 (β-HTBZ)	F	6F001	0.00	NC	0.00	NC
						6F002	0.00	NC	0.00	NC
						6F003	0.00	NC	0.00	NC
						N	3	0	3	0
						Mean	0.00	NC	0.00	NC
						SD	0.00	NC	0.00	NC
					M	6M001	0.00	NC	0.00	NC
						6M002	0.00	NC	0.00	NC
						6M003	0.00	NC	0.00	NC
						N	3	0	3	0
						Mean	0.00	NC	0.00	NC
						SD	0.00	NC	0.00	NC
					F + M	N	6	0	6	0
						Mean	0.00	NC	0.00	NC
						SD	0.00	NC	0.00	NC

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
SD-809	PO	8	2.5	SD-949 (d_6-β-HTBZ)	F	8F001	1.24	1.00	1.18	NC
						8F002	1.74	1.00	1.87	NC
						8F003	1.23	1.00	1.21	NC
						N	3	3	3	0
						Mean	1.40	1.00	1.42	NC
						SD	0.292	0.00	0.392	NC
					M	8M001	2.06	0.500	2.97	1.30
						8M002	0.00	NC	0.00	NC
						8M003	0.00	NC	0.00	NC
						N	3	1	3	1
						Mean	0.687	0.500	0.988	1.30
						SD	1.19	NC	1.71	NC
					F + M	N	6	4	6	1
						Mean	1.05	0.875	1.20	1.30
						SD	0.868	0.250	1.14	NC

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
Tetrabenazine	PO	7	15	SD-946 (α-HTBZ)	F	7F001	276	1.00	748	1.52
						7F002	212	0.500	534	2.01
						7F003	181	0.500	497	1.69
						N	3	3	3	3
						Mean	223	0.667	593	1.74
						SD	48.4	0.289	136	0.248
					M	7M001	395	1.00	1510	1.75
						7M002	340	0.500	967	1.61
						7M003	571	0.500	1810	1.44
						N	3	3	3	3
						Mean	435	0.667	1430	1.60
						SD	121	0.289	428	0.158
					F + M	N	6	6	6	6
						Mean	329	0.667	1010	1.67
						SD	142	0.258	539	0.201

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
SD-809	PO	9	15	SD-948 (d_6-α-HTBZ)	F	9F001	142	1.00	500	2.00
						9F002	389	1.00	1360	1.80
						9F003	130	1.00	402	1.64
						N	3	3	3	3
						Mean	220	1.00	755	1.81
						SD	146	0.00	530	0.177
					M	9M001	751	0.500	2620	1.94
						9M002	885	0.500	2410	1.27
						9M003	735	1.00	2440	1.54
						N	3	3	3	3
						Mean	790	0.667	2490	1.58
						SD	82.4	0.289	114	0.335
					F + M	N	6	6	6	6
						Mean	505	0.833	1620	1.70
						SD	330	0.258	1010	0.271

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
Tetrabenazine	PO	7	15	SD-947 (β-HTBZ)	F	7F001	11.8	1.00	21.7	0.742
						7F002	15.8	0.500	23.7	0.651
						7F003	41.2	0.500	60.9	0.772
						N	3	3	3	3
						Mean	22.9	0.667	35.5	0.722
						SD	15.9	0.289	22.1	0.0632
					M	7M001	16.3	0.500	30.2	0.953
						7M002	11.1	0.500	17.6	0.940
						7M003	13.3	0.500	22.1	0.839
						N	3	3	3	3
						Mean	13.6	0.500	23.3	0.911
						SD	2.61	0.00	6.40	0.0627
					F + M	N	6	6	6	6
						Mean	18.3	0.583	29.4	0.816
						SD	11.4	0.204	16.0	0.118

Compound	Route	Group	Dose (mg/kg)	Analyte	Gender	Animal ID	C_{max} (ng/mL)	T_{max} (h)	AUC_{all} (h*ng/mL)	$HL_{\lambda z}$ (h)
SD-809	PO	9	15	SD-949 (d_6-β-HTBZ)	F	9F001	33.9	0.500	83.0	0.934
						9F002	25.6	1.00	49.7	0.916
						9F003	22.9	1.00	48.2	0.917
						N	3	3	3	3
						Mean	27.5	0.833	60.3	0.922
						SD	5.73	0.289	19.7	0.0102
					M	9M001	26.8	0.500	58.7	1.26
						9M002	24.1	1.00	48.7	0.842
						9M003	15.0	0.500	30.6	0.852
						N	3	3	3	3
						Mean	22.0	0.667	46.0	0.984
						SD	6.18	0.289	14.2	0.237
					F + M	N	6	6	6	6
						Mean	24.7	0.750	53.2	0.953
						SD	6.12	0.274	17.2	0.154

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6.2 Repeat-Dose Toxicity

Study Title: A 14-Day Twice-Daily Oral (gavage) Comparative Dose Range-Finding and Toxicokinetic Study of SD-809 (d6-tetrabenazine) in Male Sprague-Dawley Rats

Study no.:	SD-809-NC-006
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6/3/2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	TBZ, Lot 30046-036C2, 99.8% SD-809, Lot 30046-039C2, 99.8%

Key Study Findings

- **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 TBZ.**
- **Exposure to the alpha and beta metabolites was higher in rats dosed with the deuterated TBZ, relative to the non-deuterated form.**

Methods

Doses:	0, 7.5, 15, 25 mg/kg BID (15, 30, 50 mg/kg/day, respectively) SD-809; 25 mg/kg TBZ BID (SD-808; 50 mg/kg/day)
Frequency of dosing:	14 days; twice daily separated by 12 hours
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% polysorbate 80
Species/Strain:	Crl:CD(SD) male rats
Number/Sex/Group:	Toxicology: 5 males/group; Toxicokinetic: 6 males/group
Age:	45 days

Dosing Solution Analysis: All dosing solutions were within +/- 15% of the nominal concentration.

Mortality & Clinical Signs: All animals survived to the scheduled necropsy. Intermittent tremors, flattened body, and palpebral closure occurred in all animals dosed with SD-809 or TBZ, but not in control animals. Rigid muscle tone and hypoactivity occurred in MD and HD animals dosed with SD-809 and animals dosed with TBZ. There were no clinical signs that were unique to SD-809-dosed animals.

Body Weights & Feed Consumption: Absolute BW was decreased at the end of the dosing period in all SD-809 (12.8%, 18%, 16.9%, LD, MD, HD, respectively) and TBZ (16%) dose groups, relative to control. Food consumption was decreased by 8-15% in rats dosed with SD-809 and by 20% in rats dosed with TBZ.

Hematology: WBC, lymphocyte count, monocyte count, reticulocyte count, and platelet count were decreased, relative to control, in animals dosed with SD-809 or TBZ.

Hematology Parameter	7.5 mg/kg BID SD-809	15 mg/kg BID SD-809	25 mg/kg BID SD-809	25 mg/kg BID TBZ
WBC	-20%	-23%	-19%	-19%
Lymphocytes	-22%	-29%	-21%	-22%
Monocytes	-24%	-38%	-29%	-57%
Reticulocytes	-16%	-18%	-16%	15%
Platelets	-18%	-16%	-28%	-37%

Table: Percent change in hematology parameter (absolute count), relative to control.

Clinical Chemistry: Liver enzymes were elevated in rats dosed with SD-809 or TBZ. ALT was increased in MD (21%) and HD (46%) SD-809 and TBZ (27%) dose groups, relative to control. AST was increased in MD (36%) and HD (57%) SD-809 and TBZ (31%) dose groups, relative to control.

Gross Pathology: There were no test article-related findings at necropsy.

Toxicokinetics: Exposure to the alpha and beta metabolites was higher in rats dosed with SD-809 relative to TBZ (sponsor's table, below).

Text Table 1. Summary of Toxicokinetic Parameters

Treatment:	SD-809						SD-808	
Dose (mg/kg/dose):	7.5		15		25		25	
Analyte: [a]	SD-948 (d_6-α-HTZB)						SD-946 (α-HTZB)	
Parameter (Units)	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13
AUC_{last} (ng·h/mL)	801	846	2102	1524	4479	1950	2935	1292
C_{max} (ng/mL)	296	323	584	516	1237	599	921	376
T_{max} (h)	0.5	0.5	1	0.5	1	0.5	1	1
Analyte: [a]	SD-949 (d_6-β-HTZB)						SD-947(β-HTZB)	
Parameter (Units)	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13
AUC_{last} (ng·h/mL)	9.62	11.3	23.4	28.6	64.7	66.0	NR	36.2
C_{max} (ng/mL)	7.36	7.51	13.0	17.2	34.2	27.9	10.3	20.1
T_{max} (h)	0.5	0.5	1	0.5	1	0.5	0.5	1

[a] = SD-948 and SD-949 are metabolites of SD-809; SD-946 and SD-947 are metabolites of tetrabenazine (SD-808).
HTZB = dihydrotetrabenazine.
NR = Not reportable

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

Study no.:	SD-809-NC-076
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/17/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-809; Lot DT21213001; 99.8% (b) (4); LOT 30138-047C1; 99.5%

Key Study Findings

- **Inclusion of (b) (4) in SD-809 did not result in unique adverse effects in male or female rats, relative to SD-809 alone.**

Methods

Doses:	See sponsor's tables, below
Frequency of dosing:	14 days; twice daily separated by 6 hours
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% polysorbate 80
Species/Strain:	Crl:CD(SD) male rats
Number/Sex/Group:	See sponsor's table below
Age:	40 days

Study 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.

Dosing Solution Analysis: All dosing solutions were within +/- 15% of the nominal concentration.

Mortality & Clinical Signs: With the exception of one TK group female dosed with SD-

809 and [redacted], all animals survived to the scheduled necropsy. The TK female was found dead on day 12; the death did not appear to be related to the test article. There were no test article-related clinical signs in any of the dose groups.

Body Weights & Food Consumption: Absolute BW was decreased at the end of the dosing period by 11% in males dosed with SD-809 containing [redacted] and 7% in males dosed with SD-809 alone, both relative to control. Absolute BW was not affected by either treatment in females. Food consumption was decreased by 21% and 30%, relative to control, in rats dosed with SD-809 containing the impurity or SD-809 alone, respectively.

Hematology & Clinical Chemistry: Hematology assessments were conducted on Day 14. Total leukocyte cell count (33%), reticulocyte count (19%-23%), absolute lymphocyte count (38%), and absolute monocyte count (44%) were decreased by a similar magnitude in both male dose groups, relative to control. There were no test article-related effects on the hematology parameters in females. Clinical chemistry was not affected by either test article in males or females.

Ophthalmic Examination: Conducted on study days 11 and 12 using an indirect ophthalmoscope and a slit lamp biomicroscope; no test article-related findings were observed.

Organ Weights: Relative to control, absolute spleen and thymus weights were decreased in males dosed with SD-809 with (24-25%) and without (9%) the impurity. There were no test article-related effects on organ weights in females.

Gross Pathology: There were no test article-related findings. Histopathology was not performed.

Toxicokinetics: Inclusion of 5% [redacted] did not appear to markedly affect the circulating levels of the alpha and beta metabolites of SD-809. Exposure to the parent compound was slightly higher in males when co-administered with the impurity (sponsor's tables, below).

Text Table 4. Summary of SD-809 Toxicokinetic Parameters

Dosage Level [a]	AUC_{last} (ng•h/mL)		C_{max} (ng/mL)		T_{max} (h)	
	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13
Males						
95%SD-809/[redacted]	3.83	3.59	6.96	6.46	0.5	0.5
SD-809	2.20	2.06	3.61	3.48	0.5	0.5
Females						
95%SD-809/[redacted]	2.87	5.74	4.90	5.82	0.5	0.5
SD-809	4.33	7.35	2.95	4.90	0.5	0.5

[a] = Dosage levels were 10 mg/kg/day for both SD-809 and 95%SD-809/[redacted]

Text Table 5. Summary of SD-948 Toxicokinetic Parameters

Dosage Level [a]	AUC_{last} (ng•h/mL)		C_{max} (ng/mL)		T_{max} (h)	
	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13
Males						
95%SD-809/(b) (4)	656	574	196	221	0.5	0.5
SD-809	839	627	202	164	0.5	0.5
Females						
95%SD-809/(b) (4)	127	94.3	32.7	23.6	1.0	1.0
SD-809	191	157	39.4	41.9	0.5	1.0

[a] = Dosage levels were 10 mg/kg/day for both SD-809 and 95%SD-809/(b) (4)

Text Table 6. Summary of SD-949 Toxicokinetic Parameters

Dosage Level [a]	AUC_{last} (ng•h/mL)		C_{max} (ng/mL)		T_{max} (h)	
	Day 0	Day 13	Day 0	Day 13	Day 0	Day 13
Males						
95%SD-809/(b) (4)	4.01	4.58	3.38	3.80	0.5	0.5
SD-809	4.26	3.78	2.61	2.21	0.5	0.5
Females						
95%SD-809/(b) (4)	1.36	6.96	1.98	2.94	0.5	0.5
SD-809	4.39	7.48	2.61	3.57	0.5	1.0

[a] = Dosage levels were 10 mg/kg/day for both SD-809 and 95%SD-809/(b) (4)

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Study title: A 3-Month (Twice-Daily) Oral Gavage Toxicity and Toxicokinetic Study of Deuterated Tetrabenazine in Sprague Dawley Rats

Study no.:	SD-809-NC-025
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/14/2011
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-809, CCS-1209d6/STG-05/00111, 99.3% TBZ (SD-808), CCS-1209d0/STG-05/00111, 99.2%

Key Study Findings

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

Methods

Doses:	See sponsor's table, below.
Frequency of dosing:	Twice daily for 28 or 91 days
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% polysorbate 80
Species/Strain:	Sprague Dawley rat; Crl:CD(SD)
Number/Sex/Group:	See sponsor's table, below
Age:	44 days
Deviation from study protocol:	The deviations did not affect the validity of the study.

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Study Design:

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.

Dosing Solution Analysis: Dosing solutions were +/- 15% of the nominal concentration.

Mortality: A CM from the TK group was found dead on Day 71. There was no evidence of gavaging error; cause of death is unknown. All other animals survived until the scheduled necropsy.

Clinical Signs: A summary of the clinical signs observed during the dosing period are provided in the sponsor's table, below.

----- M A L E -----

TABLE RANGE: DAY 0 TO DAY 91 / GROUP:	1	2	3	4	5
NORMAL					
TIME OF DOSE					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	3245/25	3300/25	3139/25	2154/25	2345/25
1 HOUR POST-DOSING					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	1624/25	1645/25	1354/25	175/25	188/25
4 HOURS POST-DOSING					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	1618/25	1646/25	1580/25	1242/25	1253/25
BEHAVIOR/CNS					
TIME OF DOSE					
-TWITCHING	0/0	0/0	1/1	1/1	2/2
-EXCESSIVE CHEWING OF CAGE	0/0	3/2	0/0	0/0	1/1
-STRAUB TAIL	0/0	0/0	0/0	15/2	42/1
-HYPER-REACTIVITY TO TOUCH	0/0	0/0	1/1	6/4	0/0
-PARTIAL CLOSURE LEFT EYE	1/1	0/0	0/0	0/0	0/0
-EXCESSIVE STRUGGLING DURING DOSING	0/0	1/1	3/3	2/2	4/4
1 HOUR POST-DOSING					
-TWITCHING	0/0	0/0	0/0	9/8	2/2
-TREMORS, INTERMITTENT	0/0	0/0	41/8	1085/25	1060/25
-CONVULSIONS UPON HANDLING	0/0	0/0	0/0	1/1	1/1
-STRAUB TAIL	0/0	0/0	0/0	9/1	35/1
-PARTIAL CLOSURE LEFT EYE	0/0	5/3	238/24	1440/25	1433/25
-PARTIAL CLOSURE RIGHT EYE	0/0	4/2	218/24	1438/25	1427/25
UNSCHED OBS (>75,<210 MINS)					
-TREMORS, INTERMITTENT	0/0	0/0	0/0	25/25	18/18
-PARTIAL CLOSURE LEFT EYE	0/0	0/0	0/0	25/25	22/22
-PARTIAL CLOSURE RIGHT EYE	0/0	0/0	0/0	25/25	22/22
4 HOURS POST-DOSING					
-TWITCHING	0/0	0/0	0/0	2/2	2/2
-TREMORS, INTERMITTENT	0/0	0/0	3/2	173/24	184/23
-TREMORS, CONTINUOUS	0/0	0/0	0/0	5/5	0/0
-IMPAIRED USE OF LEFT FORELIMB	0/0	0/0	0/0	1/1	0/0
-STRAUB TAIL	0/0	0/0	0/0	5/1	28/1
-PARTIAL CLOSURE LEFT EYE	0/0	1/1	23/10	330/24	328/24
-PARTIAL CLOSURE RIGHT EYE	0/0	1/1	27/11	313/24	316/24
TIME OF DOSE					
-TWITCHING EAR(S)	0/0	0/0	7/5	2/2	3/2
-INCREASED ACTIVITY	0/0	4/3	169/18	1137/25	953/25
1 HOUR POST-DOSING					
-TAIL SHEATH MISSING	0/0	0/0	0/0	1/1	0/0
-TWITCHING EAR(S)	0/0	7/6	110/24	1091/25	1069/25

1- 0 MG/KG/DOSE 2- 2.5 MG/KG/DOSE 3- 5 MG/KG/DOSE 4-15 MG/KG/DOSE-SD 5-15 MG/KG/DOSE-TB

----- F E M A L E -----

TABLE RANGE: DAY 0 TO DAY 91 / GROUP:	1	2	3	4	5
BEHAVIOR/CNS					
TIME OF DOSE					
-STRAUB TAIL	0/0	0/0	0/0	3/1	0/0
-EXCESSIVE STRUGGLING DURING DOSING	0/0	0/0	0/0	0/0	1/1
1 HOUR POST-DOSING					
-TREMORS, INTERMITTENT	0/0	0/0	0/0	51/18	55/16
-STRAUB TAIL	0/0	0/0	0/0	2/1	0/0
-PARTIAL CLOSURE LEFT EYE	0/0	0/0	2/2	168/22	243/25
-PARTIAL CLOSURE RIGHT EYE	0/0	0/0	1/1	163/22	220/25
4 HOURS POST-DOSING					
-TREMORS, INTERMITTENT	0/0	0/0	0/0	18/10	11/9
-STRAUB TAIL	0/0	0/0	0/0	2/1	0/0
-PARTIAL CLOSURE LEFT EYE	0/0	0/0	2/2	35/15	52/19
-PARTIAL CLOSURE RIGHT EYE	0/0	0/0	1/1	37/16	57/21
TIME OF DOSE					
-TWITCHING EAR(S)	0/0	0/0	0/0	1/1	3/3
-INCREASED ACTIVITY	0/0	0/0	2/2	91/21	99/24

1- 0 MG/KG/DOSE 2- 2.5 MG/KG/DOSE 3- 5 MG/KG/DOSE 4-15 MG/KG/DOSE-SD 5-15 MG/KG/DOSE-TB

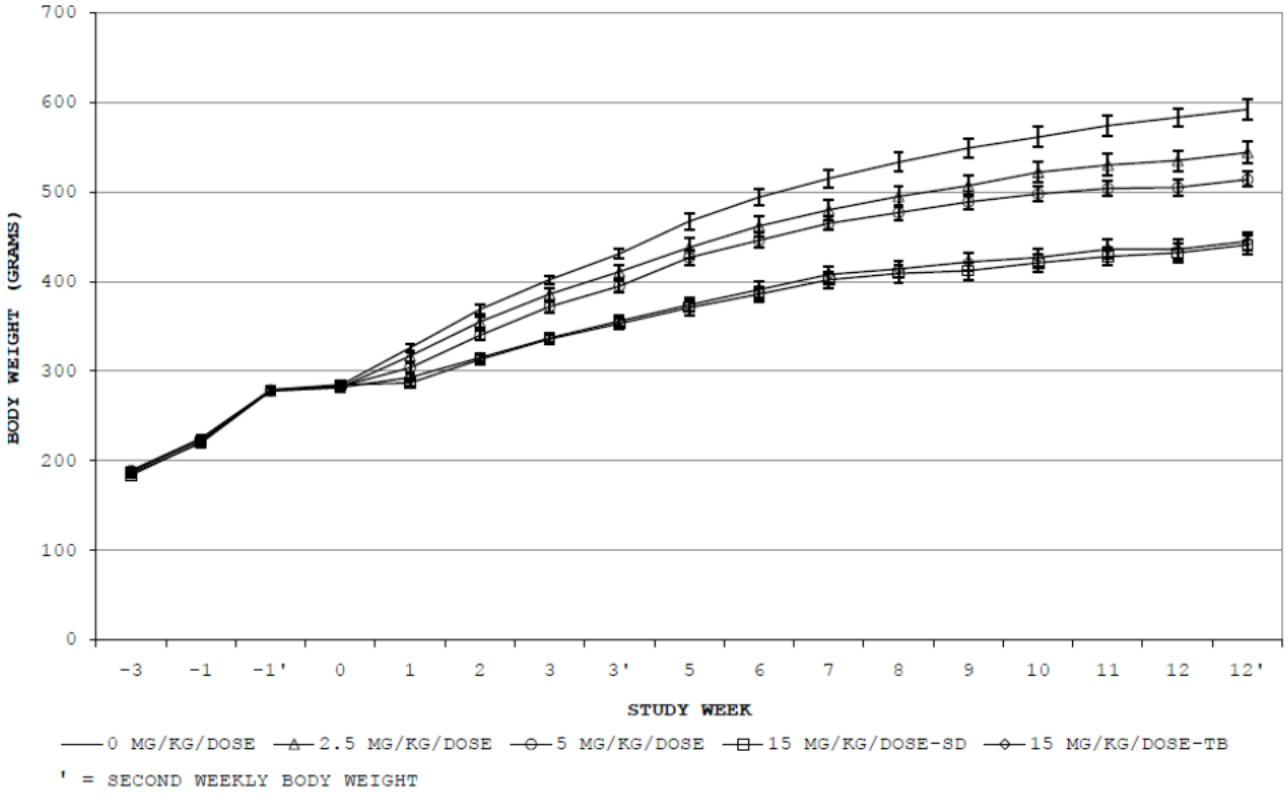
Increased activity occurred in all SD-809 and TBZ dose groups. Ear twitching increased in a dose-dependent manner in all males in the SD-809 and TBZ dose groups as well as in MDF, HDF, and TBZF. The incidence of intermittent tremors was increased in a dose-dependent manner in MDM, HDM and TBZM. Handling-induced convulsions occurred in 1 HDM and 1 TBZM. Partial closure of the eyes occurred in animals dosed with > 2.5 mg/kg SD-809 or TBZ. The type and incidence of clinical signs were similar between rats dosed with the HD of SD-809 and TBZ.

Body Weights: By the end of the dosing period, absolute BW was decreased in a dose-dependent manner in all males dosed with SD-809 or TBZ (-9%, -14%, -25%, and -25% at LD, MD, HD, and TBZ respectively), relative to control (sponsor's figures, below). There was no dose-dependent effect observed in females.

(b) (4)

PROJECT NO. -847005M
SPONSOR:AUSPEX PHARM, INC.
SPONSOR NO.:SD-809-NC-025

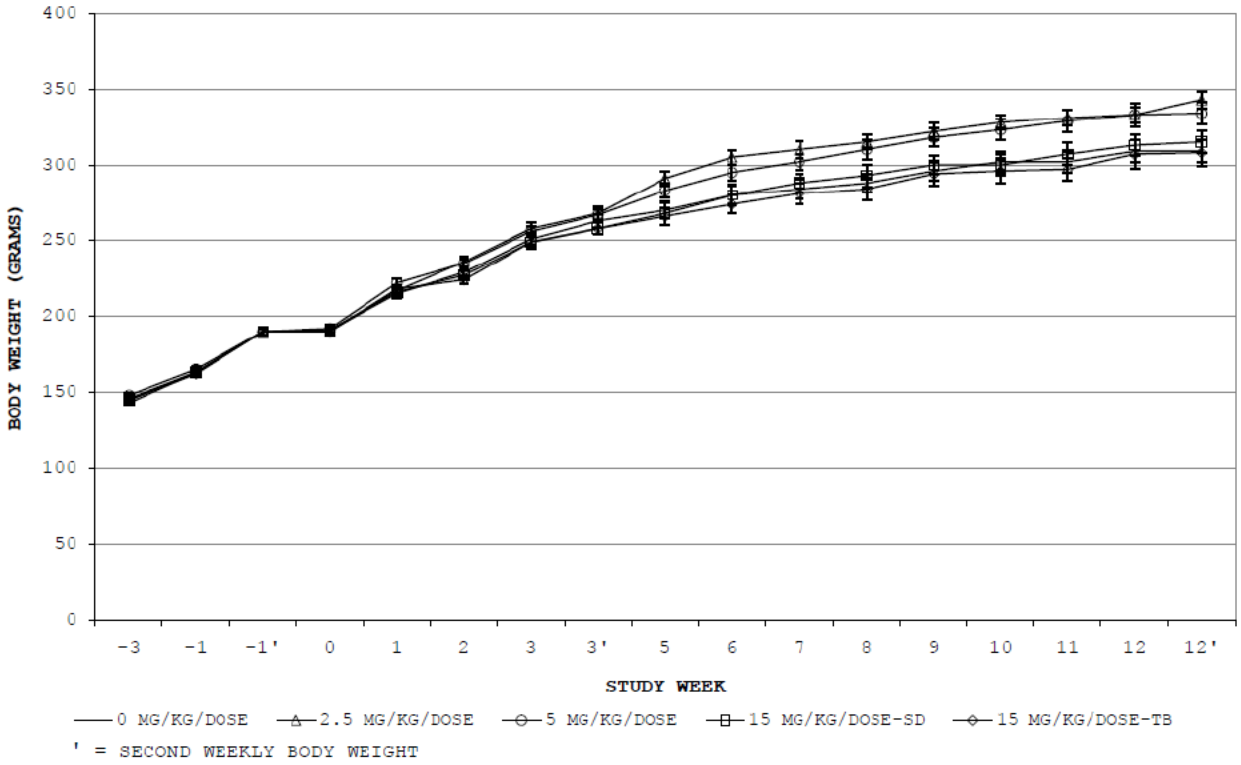
FIGURE 1 (MALES)
SUMMARY OF BODY WEIGHTS [G]
DATA PRESENTED AS MEAN ± SE



APPEARS THIS WAY ON ORIGINAL

PROJECT NO.: (b) (4)847005F
SPONSOR:AUSPEX PHARM, INC.
SPONSOR NO.:SD-809-NC-025

FIGURE 2 (FEMALES)
SUMMARY OF BODY WEIGHTS [G]
DATA PRESENTED AS MEAN ± SE



Feed Consumption: There was no SD-809- or TBZ-related effect on food consumption.

Ophthalmoscopy: When conducted prior to the dosing period and during study weeks 3 and 12, there were no test article-related findings observed with indirect ophthalmoscope or slit-lamp biomicroscope.

Functional Observation Battery (FOB): An FOB was conducted on six males per dose group during week 12. MD, HD and TBZ animals had an increase in grooming, relative to controls. Rotarod performance was decreased markedly in HD (2.7 s) and TBZ (10.8 s) animals, relative to controls (18.5 s). Catalepsy was increased in MD (2.5 s), HD (10.6 s), and TBZ (21.8 s) animals, relative to controls.

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Hematology: Lymphocytes and eosinophils were decreased in HDM and TBZM, relative to control, when assessed during weeks 4 and 13 (sponsor's table, below). Neutrophils were markedly increased in HDM and TBZM, relative to control, when assessed during week 13. There were no test article-related findings in females when assessed during weeks 4 and 13.

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MALES

ANALYSIS	GROUP:	0 MG/KG/DOSE	2.5 MG/KG/DOSE	5 MG/KG/DOSE	15 MG/KG/DOSE-SD	15 MG/KG/DOSE-TB
LYMPH ABSOLUTE (thous/uL)						
WEEK 4	MEAN	8.62	7.17	7.41	5.78	7.07
	% DIFFERENCE		-16.8	-14.0	-32.9	-18.0
	S.D.	1.995	1.893	3.827	1.660	1.851
	S.E.	0.631	0.599	1.210	0.525	0.585
	N	10	10	10	10	10
WEEK 13	MEAN	7.64c	7.48c	6.32	5.42b	5.69a
	% DIFFERENCE		-2.1	-17.3	-29.1	-25.5
	S.D.	2.287	1.855	2.008	1.439	0.814
	S.E.	0.590	0.479	0.518	0.372	0.210
	N	15	15	15	15	15
EOS ABSOLUTE (thous/uL)						
WEEK 4	MEAN	0.09c	0.08	0.08	0.05	0.04a
	% DIFFERENCE		-11.1	-11.1	-44.4	-55.6
	S.D.	0.035	0.031	0.066	0.025	0.009
	S.E.	0.011	0.010	0.021	0.008	0.003
	N	10	10	10	10	10
WEEK 13	MEAN	0.12d	0.14d	0.10	0.05b	0.05b
	% DIFFERENCE		16.7	-16.7	-58.3	-58.3
	S.D.	0.076	0.054	0.044	0.058	0.042
	S.E.	0.020	0.014	0.011	0.015	0.011
	N	15	15	15	15	15
NEU ABSOLUTE (thous/uL)						
WEEK 4	MEAN	1.04	1.01	1.07	1.23	1.25
	% DIFFERENCE		-2.9	2.9	18.3	20.2
	S.D.	0.498	0.232	0.478	0.237	0.505
	S.E.	0.157	0.073	0.151	0.075	0.160
	N	10	10	10	10	10
WEEK 13	MEAN	1.26d	1.28d	1.60	2.63b	2.44b
	% DIFFERENCE		1.6	27.0	108.7	93.7
	S.D.	0.343	0.423	0.775	1.569	1.235
	S.E.	0.089	0.109	0.200	0.405	0.319
	N	15	15	15	15	15

LYMPH ABSOLUTE (thous/uL)
For statistical analyses, control group 1 was compared to groups 2, 3, 4 and 5;
control group 5 was compared to groups 1, 2, 3 and 4.
b - Significantly different from control group 1 at 0.01 using Dunnett's test
d - Significantly different from control group 5 at 0.01 using Dunnett's test

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Clinical Chemistry: Urea nitrogen was increased in HDM and TBZM during weeks 4 and 13 (sponsor's table, below). Liver enzymes (ALP, ALT, AST, GGT) were increased in MDM, HDM and TBZM from week 4 to week 13, relative to control.

		MALES				
ANALYSIS	GROUP:	0 MG/KG/DOSE	2.5 MG/KG/DOSE	5 MG/KG/DOSE	15 MG/KG/DOSE-SD	15 MG/KG/DOSE-TB
UREA NITROGEN (mg/dL)						
WEEK 4	MEAN	14.7d	14.4d	15.9d	20.9b	20.0b
	% DIFFERENCE		-2.0	8.2	42.2	36.1
	S.D.	0.93	1.95	2.33	1.65	2.95
	S.E.	0.29	0.62	0.74	0.52	0.93
	N	10	10	10	10	10
WEEK 13	MEAN	15.3d	17.7d	18.5bd	23.1b	22.9b
	% DIFFERENCE		15.7	20.9	51.0	49.7
	S.D.	1.87	3.01	2.84	2.75	2.75
	S.E.	0.48	0.78	0.73	0.71	0.71
	N	15	15	15	15	15
ALP (U/L)						
WEEK 4	MEAN	155.c	140.d	148.d	186.	195.a
	% DIFFERENCE		-9.7	-4.5	20.0	25.8
	S.D.	21.9	22.0	20.5	35.7	36.4
	S.E.	6.9	6.9	6.5	11.3	11.5
	N	10	10	10	10	10
WEEK 13	MEAN	69.d	84.d	90.b	98.b	104.b
	% DIFFERENCE		21.7	30.4	42.0	50.7
	S.D.	10.5	17.8	21.6	21.6	12.8
	S.E.	2.7	4.6	5.6	5.6	3.3
	N	15	15	15	15	15
ALT (U/L)						
WEEK 4	MEAN	39.d	40.d	43.d	57.b	54.b
	% DIFFERENCE		2.6	10.3	46.2	38.5
	S.D.	4.3	3.6	6.5	12.5	8.5
	S.E.	1.4	1.1	2.1	3.9	2.7
	N	10	10	10	10	10
WEEK 13	MEAN	36.d	45.c	48.	69.b	64.b
	% DIFFERENCE		25.0	33.3	91.7	77.8
	S.D.	5.6	5.1	9.8	40.1	18.6
	S.E.	1.4	1.3	2.5	10.3	4.8
	N	15	15	15	15	15
AST (U/L)						
WEEK 4	MEAN	96.d	93.d	114.d	161.b	163.b
	% DIFFERENCE		-3.1	18.8	67.7	69.8
	S.D.	15.6	9.7	13.5	34.8	29.9
	S.E.	4.9	3.1	4.3	11.0	9.4
	N	10	10	10	10	10
WEEK 13	MEAN	83.d	104.d	127.	190.b	168.b
	% DIFFERENCE		25.3	53.0	128.9	102.4
	S.D.	13.3	16.5	58.7	86.3	38.6
	S.E.	3.4	4.3	15.1	22.3	10.0
	N	15	15	15	15	15
GGT (U/L)						
WEEK 4	MEAN	0.1	0.1	0.2	0.2	0.2
	% DIFFERENCE		0.0	100.0	100.0	100.0
	S.D.	0.03	0.06	0.20	0.25	0.14
	S.E.	0.01	0.02	0.06	0.08	0.04
	N	10	10	10	10	10
WEEK 13	MEAN	0.1c	0.1c	0.3	0.4	0.5a
	% DIFFERENCE		0.0	200.0	300.0	400.0
	S.D.	0.04	0.03	0.44	0.35	0.49
	S.E.	0.01	0.01	0.11	0.09	0.13
	N	15	15	15	15	15

For statistical analyses, control group 1 was compared to groups 2, 3, 4 and 5;
control group 5 was compared to groups 1, 2, 3 and 4.
a - Significantly different from control group 1 at 0.05 using Dunnett's test
b - Significantly different from control group 1 at 0.01 using Dunnett's test
c - Significantly different from control group 5 at 0.05 using Dunnett's test
d - Significantly different from control group 5 at 0.01 using Dunnett's test

Urinalysis: There was no test article-related effect observed when assessed during weeks 4 and 13.

Gross Pathology: There were no SD-809- or TBZ-related findings at the necropsies conducted at week 4 or 13.

Organ Weights: Adrenal, liver, pituitary, spleen, and uterus weights were affected by SD-809 and TBZ (sponsor's tables below).

Interim Sacrifice Week 4- Males

GROUP:	0 MG/KG/DOSE	2.5 MG/KG/DOSE	5 MG/KG/DOSE	15 MG/KG/DOSE-SD	15 MG/KG/DOSE-TB
		MALES			
ADRENAL GLANDS (G/100 G FINAL BODY WEIGHT)					
MEAN	0.016d	0.017d	0.019d	0.020b	0.023b
% DIFFERENCE		6.3	18.8	25.0	43.8
S.D.	0.0022	0.0022	0.0030	0.0025	0.0048
S.E.	0.0007	0.0007	0.0009	0.0008	0.0015
N	10	10	10	10	10
LIVER (G)					
MEAN	12.40d	12.20d	10.82a	10.18b	9.65b
% DIFFERENCE		-1.6	-12.7	-17.9	-22.2
S.D.	0.682	1.552	1.288	1.139	1.130
S.E.	0.216	0.491	0.407	0.360	0.357
N	10	10	10	10	10
PITUITARY (G)					
MEAN	0.0149d	0.0142d	0.0138d	0.0127a	0.0110b
% DIFFERENCE		-4.7	-7.4	-14.8	-26.2
S.D.	0.00231	0.00225	0.00205	0.00133	0.00158
S.E.	0.00073	0.00071	0.00065	0.00042	0.00050
N	10	10	10	10	10
SPLEEN (G)					
MEAN	0.74	0.75	0.65	0.58a	0.63
% DIFFERENCE		1.4	-12.2	-21.6	-14.9
S.D.	0.093	0.132	0.139	0.090	0.094
S.E.	0.029	0.042	0.044	0.028	0.030
N	10	10	10	10	10
THYMUS (G)					
MEAN	0.5000c	0.4311	0.3955	0.3227b	0.3789a
% DIFFERENCE		-13.8	-20.9	-35.5	-24.2
S.D.	0.08451	0.08707	0.13932	0.04562	0.09332
S.E.	0.02672	0.02753	0.04406	0.01443	0.02951
N	10	10	10	10	10

Terminal Sacrifice Week 13- Males

GROUP:	0 MG/KG/DOSE	2.5 MG/KG/DOSE	5 MG/KG/DOSE	15 MG/KG/DOSE-SD	15 MG/KG/DOSE-TB
		MALES			
ADRENAL GLANDS (G)					
MEAN	0.0642d	0.0699	0.0737	0.0815b	0.0801b
% DIFFERENCE		8.9	14.8	26.9	24.8
S.D.	0.00782	0.01039	0.01258	0.01689	0.01593
S.E.	0.00202	0.00268	0.00325	0.00436	0.00411
N	15	15	15	15	15
LIVER (G)					
MEAN	15.69d	13.47bd	12.89bd	11.47b	11.31b
% DIFFERENCE		-14.1	-17.8	-26.9	-27.9
S.D.	1.814	1.438	1.175	1.373	0.997
S.E.	0.468	0.371	0.303	0.355	0.257
N	15	15	15	15	15
SPLEEN (G)					
MEAN	0.90d	0.85d	0.80ad	0.66b	0.64b
% DIFFERENCE		-5.6	-11.1	-26.7	-28.9
S.D.	0.114	0.152	0.087	0.090	0.082
S.E.	0.029	0.039	0.022	0.023	0.021
N	15	15	15	15	15
THYMUS (G)					
MEAN	0.2979d	0.2530	0.2610	0.2282a	0.2031b
% DIFFERENCE		-15.1	-12.4	-23.4	-31.8
S.D.	0.09279	0.05497	0.08104	0.06604	0.05066
S.E.	0.02396	0.01419	0.02092	0.01705	0.01308
N	15	15	15	15	15

Interim Sacrifice Week 4- Females

GROUP:	0 MG/KG/DOSE	2.5 MG/KG/DOSE	5 MG/KG/DOSE	15 MG/KG/DOSE-SD	15 MG/KG/DOSE-TB
		FEMALES			
UTERUS (G)					
MEAN	0.59	0.41	0.38a	0.35b	0.45
% DIFFERENCE		-30.5	-35.6	-40.7	-23.7
S.D.	0.194	0.107	0.101	0.057	0.279
S.E.	0.061	0.034	0.032	0.018	0.088
N	10	10	10	10	10

Interim Sacrifice Week 13- Females

GROUP:	0 MG/KG/DOSE	2.5 MG/KG/DOSE	5 MG/KG/DOSE	15 MG/KG/DOSE-SD	15 MG/KG/DOSE-TB
		FEMALES			
UTERUS (G)					
MEAN	0.77d	0.51bc	0.42b	0.44b	0.38b
% DIFFERENCE		-33.8	-45.5	-42.9	-50.6
S.D.	0.261	0.096	0.067	0.075	0.056
S.E.	0.067	0.025	0.017	0.019	0.015
N	15	15	15	15	15

Adrenal gland weight was increased in a dose-dependent manner in males in all SD-809 and TBZ dose groups at the 4-week and 13-week sacrifice. Liver and spleen weights were decreased in a dose-dependent manner in MD, HD, and TBZM at the 4-week interim sacrifice and in males in all dose groups at the 13-week sacrifice. Thymus weight was decreased males in all SD-809 and TBZ dose groups at both the 4-week and 13-week sacrifices; however, the decrease was not dose-related at the 13-week sacrifice. Uterus weight was decreased in females in all SD-809 and TBZ dose groups at the 4-week and 13-week sacrifices.

Histopathology: Adequate Battery: No, nasal cavity/turbinates, lachrymal gland, Zymbal's gland, and Harderian gland were not assessed; Peer Review: No; Signed and Dated Report: Yes

Mammary gland hyperplasia was observed in females at both the 4-week interim and 13-week terminal sacrifices (sponsor's table, below). The incidence and severity of the finding increased in a dose-dependent manner in all females in the SD-809 dose groups. The severity and incidence of this finding were similar between HDF and TBZF. There were no test article-related findings in males.

Interim Sacrifice Week 4- Females

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES				
Removal Reason: Interim Sacrifice	Group 1 0 mkg/dose	Group 2 2.5mkg/dos	Group 3 5 mkg/dose	Group 4 15 mkg/dos	Group 5 15 mkg/dos
Number of Animals on Study :	10	10	10	10	10
Number of Animals Completed:	(10)	(10)	(10)	(10)	(10)
MAMMARY GLAND; (continued)					
HYPERPLASIA; Alveolar epithelium	(0)	(1)	(3)	(5)	(7)
Minimal	0	1	3	4	5
Mild	0	0	0	1	2

Interim Sacrifice Week 13- Females

Observations: Neo-Plastic and Non Neo-Plastic	FEMALES				
Removal Reasons: All of those SELECTED	Group 1 0 mkg/dose	Group 2 2.5mkg/dos	Group 3 5 mkg/dose	Group 4 15 mkg/dos	Group 5 15 mkg/dos
Number of Animals on Study :	15	15	15	15	15
Number of Animals Completed:	(15)	(15)	(15)	(15)	(15)
MAMMARY GLAND;					
Examined	(15)	(15)	(15)	(15)	(15)
Within Normal Limits	14	7	5	2	2
HYPERPLASIA; Alveolar epithelium	(1)	(8)	(10)	(13)	(13)
Minimal	1	7	10	5	7
Mild	0	1	0	8	6

Estrous Cycle Staging: Estrous cycle arrest occurred in females dosed with SD-809 or TBZ, with the majority remaining in proestrus by Week 13 (sponsor's table, below).

Text Table 4. Incidence of Estrous Cycle Staging by Group

		Estrous Cycle Stage			
Group	Dosage Level	Diestrus	Proestrus	Estrus	Metestrus
	Study Week 4 Interim Necropsy				
1	Vehicle	1	4	4	1
2	2.5 mg/kg/dose SD-809	3	3	2	2
3	5 mg/kg/doseSD-809	1	5	0	4
4	15 mg/kg/doseSD-809	1	8	0	1
5	15 mg/kg/dose Comparator Tetrabenazine	0	9	0	1
	Study Week 13 Primary Necropsy				
1	Vehicle	2	7	4	2
2	2.5 mg/kg/dose SD-809	0	11	2	2
3	5 mg/kg/doseSD-809	0	11	1	3
4	15 mg/kg/doseSD-809	2	11	0	2
5	15 mg/kg/dose Comparator Tetrabenazine	1	10	0	4

Toxicokinetics: Steady state exposure to the alpha and beta metabolites of TBZ were similar at the end of the study in rats dosed with the HD of 15 mg/kg SD-809 or 15 mg/kg TBZ (sponsor's table's, below). Systemic exposure to the alpha metabolite was markedly higher in males, relative to females in rats dosed with SD-809 or TBZ.

Text Table 5. Summary of Toxicokinetic Parameters for the SD-809-Treated Groups

Dosage	AUC_{all} (hr•ng/mL)			C_{max} (ng/mL)			T_{max} (hr)		
	Day 0	Day 34	Day 91	Day 0	Day 34	Day 91	Day 0	Day 34	Day 91
SD-809									
Males									
2.5 mg/kg/dose	2.24	1.12	1.67	1.41	0.72	0.99	1.00	0.50	1.00
5 mg/kg/dose	3.44	2.14	3.00	2.61	1.84	2.25	0.50	0.50	0.50
15 mg/kg/dose	21.6	13.6	17.5	8.10	7.20	10.1	0.50	0.50	0.50
Females									
2.5 mg/kg/dose	1.18	2.06	1.93	1.10	1.33	1.60	0.50	0.50	0.50
5 mg/kg/dose	4.09	9.59	15.7	2.77	6.52	9.79	0.50	0.50	0.50
15 mg/kg/dose	42.8	35.3	53.8	18.5	16.3	18.9	0.50	0.50	0.50
d6-α-dihydrotetrabenazine (SD-948)									
Males									
2.5 mg/kg/dose	315	298	375	107	91.1	100	1.00	1.00	1.00
5 mg/kg/dose	473	392	498	132	102	139	1.00	0.50	0.50
15 mg/kg/dose	1800	1360	1300	479	387	367	1.00	1.00	1.00
Females									
2.5 mg/kg/dose	33.6	27.1	23.8	7.74	6.61	6.82	1.00	1.00	0.50
5 mg/kg/dose	65.8	68.9	62.1	17.6	18.8	17.7	1.00	0.50	0.50
15 mg/kg/dose	370	219	202	104	54.2	49.2	1.00	0.50	0.50
d6-β-dihydrotetrabenazine (SD-949)									
Males									
2.5 mg/kg/dose	1.51	1.45	3.40	1.07	0.92	1.53	1.00	1.00	1.00
5 mg/kg/dose	3.82	4.48	6.64	1.97	2.05	2.81	0.50	0.50	0.50
15 mg/kg/dose	30.1	31.6	42.7	10.3	9.37	12.5	0.50	0.50	0.50
Females									
2.5 mg/kg/dose	1.51	2.58	3.00	0.89	1.27	1.66	0.50	0.50	0.50
5 mg/kg/dose	5.27	10.4	12.3	2.40	4.36	5.37	0.50	0.50	0.50
15 mg/kg/dose	39.5	37.1	44.6	15.6	12.0	14.2	1.00	0.50	0.50

Text Table 6. Summary of Toxicokinetic Parameters for the Comparator Tetrabenazine-Treated Group

Dosage	AUC_{all} (hr•ng/mL)			C_{max} (ng/mL)			T_{max} (hr)		
	Day 0	Day 34	Day 91	Day 0	Day 34	Day 91	Day 0	Day 34	Day 91
Tetrabenazine (SD-808)									
Males									
15 mg/kg/dose	14.0	11.4	14.5	5.55	5.49	6.42	1.00	0.50	0.50
Females									
15 mg/kg/dose	38.7	38.6	55.4	18.3	17.4	18.8	0.50	0.50	0.50
α-dihydrotetrabenazine (SD-946)									
Males									
15 mg/kg/dose	1470	1070	1280	397	330	345	1.00	0.50	0.50
Females									
15 mg/kg/dose	357	245	249	116	64.5	72.4	1.00	1.00	1.00
β-dihydrotetrabenazine (SD-947)									
Males									
15 mg/kg/dose	13.8	14.8	28.2	4.76	6.20	8.83	0.50	0.50	1.00
Females									
15 mg/kg/dose	23.0	29.1	43.2	9.04	10.6	16.5	1.00	0.50	1.00

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: SD-946: Salmonella-E.coli/ Mammalian Microsome Reverse Mutation Assay

Study no.:	SD-809-NC-028
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/5/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-946 (α-dihydrotetrabenazine); Batch CCS-1209d0/B476/MB(Alfa)/03; 99.4%

Key Study Findings

- **SD-946 (α-dihydrotetrabenazine) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation and pre-incubation methods were used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plated. In the pre-incubation method, the bacteria, test article, and metabolic activation mixture were mixed together and incubated for 20 minutes at 37°C. In both cases, the plates were incubated for 2 days at 37°C.

Results: The methods used were consistent with current regulatory guidance. SD-946 was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

Study title: SD-947: Salmonella-E.coli/ Mammalian Microsome Reverse Mutation Assay

Study no.:	SD-809-NC-030
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/5/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-947(β-dihydrotetrabenazine), Batch CCS-1209d0/B476/MB(Beta)/03, 99.7%

Key Study Findings

- **SD-947 (β-dihydrotetrabenazine) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation and pre-incubation methods were used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plated. In the pre-incubation method, the bacteria, test article, and metabolic activation mixture were mixed together and incubated for 20 minutes at 37°C. In both cases, the plates were incubated for 2 days at 37°C.

Results: The methods used were consistent with current regulatory guidance. SD-947 was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

Study title: SD-948: Salmonella-E.coli/ Mammalian Microsome Reverse Mutation Assay

Study no.:	SD-809-NC-032
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/5/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-948(d6-α-dihydrotetrabenazine), Batch CCS-1209d6/B495/MB(Alfa)/01, 99.5%

Key Study Findings

- **SD-948 (d6-α-dihydrotetrabenazine) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation and pre-incubation methods were used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plated. In the pre-incubation method, the bacteria, test article, and metabolic activation mixture were mixed together and incubated for 20 minutes at 37°C. In both cases, the plates were incubated for 2 days at 37°C.

Results: The methods used were consistent with current regulatory guidance. SD-948 was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

Study title: SD-949: Salmonella-E.coli/ Mammalian Microsome Reverse Mutation Assay

Study no.:	SD-809-NC-034
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/5/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-949 (d6-β-dihydrotetrabenazine), Batch CCS-1209d6/B495/MB(Beta)/01, 99.5%

Key Study Findings

- **SD-949 (d6-β-dihydrotetrabenazine) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation and pre-incubation methods were used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plated. In the pre-incubation method, the bacteria, test article, and metabolic activation mixture were mixed together and incubated for 20 minutes at 37°C. In both cases, the plates were incubated for 2 days at 37°C.

Results: The methods used were consistent with current regulatory guidance. SD-949 was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

Study title: SD-1021 Salmonella-E.coli/ Mammalian Microsome Reverse Mutation Assay

Study no.:	SD-809-NC-066
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/15/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-1021(Metabolite M1), Lot 54238-032P1, 98%

Key Study Findings

- **Metabolite M1 (SD-1021) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation and pre-incubation methods were used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plated. In the pre-incubation method, the bacteria, test article, and metabolic activation mixture were mixed together and incubated for 20 minutes at 37^{o}C. In both cases, the plates were incubated for 2 days at 37^{o}C.

Results: The methods used were consistent with current regulatory guidance. SD-1021 (metabolite M1) was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

Study title: SD-809 with [redacted] Bacterial Reverse Mutation Assay

Study no.:	SD-809-NC-056
Study report location:	EDR
Conducting laboratory and location:	[redacted]
Date of study initiation:	10/8/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-809, Batch DT21213001, 99.8% [redacted] (impurity), Batch 30138-054A1, 98.6%

Key Study Findings

- **SD-809 spiked with [redacted] (an impurity/ degradant present in SD-809) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate, spiked with [redacted]
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation method was used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plates were incubated for 2 days at 37ºC.

Results: The methods used were consistent with current regulatory guidance. SD-809 spiked with [redacted] was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

Study title: [redacted] **Salmonella-E.coli/ Mammalian Microsome Reverse Mutation Assay**

Study no.:	SD-809-NC-058
Study report location:	EDR
Conducting laboratory and location:	[redacted]
Date of study initiation:	9/30/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	[redacted] (impurity), Batch 30138-047C1, 99.5%

Key Study Findings

- [redacted] **(an impurity present in SD-809) was negative for mutagenicity.**

Strains:	*Salmonella typhimurium* TA1537, TA98, TA100, TA1535 & *E. coli* WP2 *uvrA*
Concentrations in definitive study:	0, 100, 250, 500, 1000, 2500, 5000 µg/plate
Basis of concentration selection:	5000 µg/plate is the highest concentration currently recommended by regulatory guidance.
Negative control:	DMSO
Positive control:	ICR-191 acridine (0.5 µg/plate) for TA1537 2-nitrofluorene (2.5 µg/plate) for TA98 4-nitroquinoline-N-oxide (2.0 µg/plate) for WP2 *uvrA* Sodium azide (1.0 µg/plate) for TA100 & TA1535 2-aminoanthracene for metabolic activation (2.5 to 10 µg/plate).
Formulation/Vehicle:	DMSO
Incubation & sampling time:	The plate incorporation and pre-incubation methods were used. Human liver S9 fraction was used for metabolic activation. For the plate incorporation method, bacteria, test article, and the metabolic activation mixture (or saline) were mixed together and plated. In the pre-incubation method, the bacteria, test article, and metabolic activation mixture were mixed together and incubated for 20 minutes at 37°C. In both cases, the plates were incubated for 2 days at 37°C.

Results: The methods used were consistent with current regulatory guidance. [redacted] (an impurity present in SD-809) was negative for mutagenicity in all strains in the presence and absence of metabolic activation. The positive controls increased the number of revertant colonies, as expected.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: SD-946 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Study no.:	SD-809-NC-029
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/22/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-946 (α-dihydrotetrabenazine), Batch CCS-1209d0/B476/MB(alfa)/03, 99.4%

Key Study Findings

- **SD-946 was negative for clastogenicity.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	325 µg/mL is equal to 1 mM, the highest concentration recommended by ICH S2(R1)
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 200 to 300 µg/mL) Mitomycin C (0.3 to 0.8 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation or for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

Table 1. SD-946 Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations		
	3 h without S9	3 h with S9	22 h without S9
DMSO (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.60	--	0.30
Cyclophosphamide (µg/mL)	--	300	--
SD-946 (µg/mL)	43.6 106 325	43.6 85.2 325	43.6 85.2 325

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. SD-946 did not cause chromosomal aberrations in hPBL. The positive controls did increase the number of chromosomal aberrations, as expected.

Study title: SD-947 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Study no.:	SD-809-NC-031
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/22/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-947 (β-dihydrotetrabenazine), Batch CCS-1209d0/B476/MB(beta)/03, 99.7%

Key Study Findings

- **SD-947 was negative for clastogenicity.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	325 µg/mL is equal to 1 mM, the highest concentration recommended by ICH S2(R1). In the 22 hour study, mitotic reduction was ~50% at the highest concentration.
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 200 to 300 µg/mL) Mitomycin C (0.3 to 0.8 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation or for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

Table 1. SD-947 Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations		
	3 h without S9	3 h with S9	22 h without S9
DMSO (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.60	--	0.40
Cyclophosphamide (µg/mL)	--	300	--
SD-947 (µg/mL)	34.9 106 325	34.9 106 260 325	22.3 85.2 208

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. SD-947 did not cause chromosomal aberrations in hPBL. The positive controls did increase the number of chromosomal aberrations, as expected.

Study title: SD-948 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Study no.:	SD-809-NC-033
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/17/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-948 (d6-α-dihydrotetrabenazine), Batch CCS-1209d6/B495/MB(alfa)/01, 99.5%

Key Study Findings

- **SD-948 was negative for clastogenicity.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	325 µg/mL is equal to 1 mM, the highest concentration recommended by ICH S2(R1).
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 200 to 300 µg/mL) Mitomycin C (0.3 to 0.8 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation and for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

Table 1. SD-948 Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations		
	3 h without S9 [1]	3 h with S9 [2]	22 h without S9 [3]
DMSO (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.60	--	0.30
Cyclophosphamide (µg/mL)	--	300	--
SD-948 (µg/mL)	43.6 106 325	43.6 106 325	68.2 133 325

[1] Analyzed from aberration assay (dosing date 17-May-2012)
[2] Analyzed from both aberration assay (dosing date 17-May-2012 and repeat aberration assay (dosing date 06-Sep-2012)
[3] Analyzed from repeat aberration assay (dosing date 06-Sep-2012)

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. SD-948 did not cause chromosomal aberrations in hPBL. The positive controls did increase the number of chromosomal aberrations, as expected.

Study title: SD-949 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Study no.:	SD-809-NC-035
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/17/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-949 (d6-β-dihydrotetrabenazine), Batch CCS-1209d6/B495/MB(beta)/01, 99.5%

Key Study Findings

- **SD-949 was negative for clastogenicity.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	325 µg/mL is equal to 1 mM, the highest concentration recommended by ICH S2(R1).
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 300 µg/mL) Mitomycin C (0.4 to 0.8 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation or for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

Table 1. SD-949 Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations		
	3 h without S9	3 h with S9	22 h without S9
DMSO (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.80	--	0.40
Cyclophosphamide (µg/mL)	--	300	--
SD-949 (µg/mL)	27.9 85.2 325	27.9 85.2 325	27.9 85.2 325

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. SD-949 did not cause chromosomal aberrations in hPBL. The positive controls did increase the number of chromosomal aberrations, as expected.

Study title: SD-1021 In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Study no.:	SD-809-NC-067
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/15/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-1021 (metabolite M1), Lot 54238-032P1, 98%

Key Study Findings

- **SD-1021 (metabolite M1) was negative for clastogenicity.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	The study was conducted with up to 1 mM SD-1021, the highest concentration recommended by ICH S2(R1).
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 500 µg/mL) Mitomycin C (0.4 to 0.8 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation or for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

Table T1. SD-1021 Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations		
	3 Hour without S9	22 Hour without S9	3 Hour with S9
Vehicle (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.8	0.4	--
Cyclophosphamide (µg/mL)	--	--	500
SD-1021 (µg/mL)	90 180 360	90 180 360	90 180 360

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. SD-1021 did not cause chromosomal aberrations in hPBL. The positive controls did increase the number of chromosomal aberrations, as expected.

Study title: SD-809 with (b) (4) In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes

Study no.:	SD-809-NC-057
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/8/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-809, Batch DT21213001, 99.8% (b) (4) Batch 30138-054A1, 98.6%

Key Study Findings

- **SD-809 with (b) (4) (impurity/degradant) was negative for clastogenicity.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	The three-hour incubation without S9 was conducted with up to 1 mM SD-809, the highest concentration (HC) recommended by ICH S2(R1). The HC in the other study conditions was chosen based on the formation of precipitates at doses higher than the chosen HC.
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 500 µg/mL) Mitomycin C (0.4 to 0.8 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation or for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

Table T1. SD-809 with (b) (4) Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations		
	3 Hour without S9	22 Hour without S9	3 Hour with S9
Vehicle (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.8	0.4	--
Cyclophosphamide (µg/mL)	--	--	500
SD-809 with (b) (4) (µg/mL)	100 175 325	50 75 125	50 100 175

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. SD-809 with (b) (4) did not cause chromosomal aberrations in hPBL. The positive controls did increase the number of chromosomal aberrations, as expected.

Study title: [redacted] **In Vitro Chromosome Aberration Test in Cultured Human Peripheral Blood Lymphocytes**

Study no.:	SD-809-NC-059
Study report location:	EDR
Conducting laboratory and location:	[redacted]
Date of study initiation:	10/8/2014
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	[redacted] (impurity), Lot 30138-047C1, 99.5%

Key Study Findings

- **When incubated with human liver S9 fraction for 3 hours or at 22 hours in the absence of S9 fraction, [redacted] markedly increased the number of cells with chromosomal aberrations or polyploidy, respectively, at a cytotoxic concentration (> 50% suppression of growth).**
- **[redacted] was negative for clastogenicity in the absence of human liver S9 fraction.**

Cell line:	Human peripheral blood lymphocytes; human liver S9 fraction used for metabolic activation.
Concentrations in definitive study:	See sponsor's table, below.
Basis of concentration selection:	The study was conducted with up to 1 mM [redacted], the highest concentration recommended by ICH S2(R1) in the 3 hour incubation without S9. Mitosis was reduced by approximately 50% at the high dose for the other two incubation conditions.
Negative control:	DMSO
Positive control:	Cyclophosphamide (in presence of S9; 500 µg/mL) Mitomycin C (0.4 to 0.6 µg/mL)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Cells were incubated with the test article, positive control, or vehicle for 3 hours in the presence or absence of metabolic activation or for 22 hours in the absence of metabolic activation. Cells were harvested 22 hours after incubation and slides were prepared.

[redacted] APPEARS THIS WAY ON ORIGINAL

Table T1. [(b) (4)] Concentrations Evaluated for Chromosome Aberrations

Treatment	Treatment Conditions and Concentrations: 3 Hour without S9	22 Hour without S9	3 Hour with S9 [a]
Vehicle (%)	1.0	1.0	1.0
Mitomycin C (µg/mL)	0.6	0.4	--
Cyclophosphamide (µg/mL)	--	--	500
[(b) (4)] (µg/mL)	100	25	150
	175	50	225
	325	75	300

[a] Scored from repeat aberration assay

Study Validity & Results: The study was conducted in accordance with current regulatory guidance and is, therefore, valid. [(b) (4)] did not cause chromosomal aberrations in hPBL in the absence of S9. However, in the presence of S9, the number of cells with chromosomal aberrations increased markedly at the highest concentration tested (300 µg/mL; see sponsor's table, below). This occurred at a dose which caused a >50% decrease in mitotic index. The positive controls did increase the number of chromosomal aberrations, as expected.

Table 1. Cytotoxicity and Aberration Summary: 3-Hour Incubation without Metabolic Activation

Treatment	% Mitotic Reduction	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
DMSO (1%)	0	2.0	0.0	0.0	0.3
MMC 0.6 µg/mL	57	90.9 *	51.5 *	0.0	0.0
[(b) (4)]					
100 µg/mL	16	1.0	0.0	0.0	0.8
175 µg/mL	22	0.5	0.0	0.3	0.3
325 µg/mL	33	2.0	0.0	0.0	1.0

Endo = Endoreduplicated cells DMSO = Dimethylsulfoxide
Abs = Aberrations MMC = Mitomycin C
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test

Table 2. Cytotoxicity and Aberration Summary: 22-Hour Incubation without Metabolic Activation

Treatment	% Mitotic Reduction	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
DMSO (1%)	0	2.0	0.5	0.0	0.5
MMC 0.4 µg/mL	50	93.8 *	62.5 *	0.0	0.3
(b) (4)					
25 µg/mL	23	1.0	0.0	0.0	0.3
50 µg/mL	13	1.5	0.5	0.0	1.0
75 µg/mL	59	1.0	0.0	0.0	8.3 *

Endo = Endoreduplicated cells
Abs = Aberrations
DMSO = Dimethylsulfoxide
MMC = Mitomycin C
Percent Aberrant cells: * $p \leq 0.01$ using Fisher's Exact Test

Table 3. Cytotoxicity and Aberration Summary: 3-Hour Incubation with Human Liver S9 Metabolic Activation (Repeat Aberration Assay)

Treatment	% Mitotic Reduction	% Cells w/Abs	% Cells w/>1 Abs	% Endo Cells	% Polyploid Cells
DMSO (1%)	0	3.5	0.0	0.0	0.3
CP 500 µg/mL	9	9.0 **	0.5	0.0	2.0 **
(b) (4)					
150 µg/mL	0	1.0	0.0	0.0	0.3
225 µg/mL	31	4.0	0.0	0.0	0.5
300 µg/mL	55	27.0 *	9.9 *	0.0	0.0

Endo = Endoreduplicated cells
Abs = Aberrations
DMSO = Dimethylsulfoxide
CP = Cyclophosphamide
Percent Aberrant cells: * $p \leq 0.01$, ** $p \leq 0.05$ using Fisher's Exact Test

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: A Mouse Bone Marrow Micronucleus Assay of SD-809 and SD-808

Study no:	SD-809-NC-044
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/25/2012
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-808 (TBZ), Batch CCS-1209d0/STG-05/00111, 99.2% SD-809 (d6-TBZ), Batch CCS-1209d6/STG-05/00111, 99.3%

Key Study Findings

- **SD-808 and SD-809 were negative in the bone marrow micronucleus assay.**

Doses in definitive study:	See sponsor's tables, below
Frequency of dosing:	Once daily for 3 days
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% Tween 80
Species/Strain:	Crl:CD-1 (ICR)BR mice
Number/Sex/Group:	See sponsor's tables, below
Basis of dose selection:	The HD in the dose range-finding study resulted in premature sacrifice. Therefore, the HD in the definitive study was set at 80 mg/kg/day.
Negative control:	0.5% carboxymethylcellulose with 0.1% Tween 80
Positive control:	Cyclophosphamide, single dose of 60 mg/kg/day

Study Design

Range-Finding Phase (b) (4)-847020)

Group Number	Treatment [a]	Dosage Level (mg/kg/day)	Dose Volume (mL/kg)	Number of Animals [b] Males	Females
1	Vehicle control [c]	0	10	3	3
2	SD-809	25	10	3	3
3	SD-809	50	10	3	3
4	SD-809	100	10	3	3
5	SD-808	25	10	3	3
6	SD-808	50	10	3	3
7	SD-808	100	10	3	3

[a] = For discussion and data reporting purposes, dose group levels of 25, 50, and 100 mg/kg/day SD-809 or SD-808 are referred to as 25, 50, and 100 mg/kg/day-09 or -08, respectively.

[b] = All surviving animals were euthanized without bone marrow collection and discarded approximately 24 hours following the last dose administration (study day 3).

[c] = 0.5% carboxymethylcellulose with 0.1% (weight/volume) Tween® 80 in deionized water.

Definitive Phase (b) (4)-847020D)

Group Number	Treatment [a]	Dosage Level (mg/kg/day)	Dose Volume (mL/kg)	Number of Animals [b] Males	Females
1	Vehicle control [c]	0	10	6	6
2	SD-809	20	10	6	6
3	SD-809	40	10	6	6
4	SD-809	80	10	6	6
5	SD-808	20	10	6	6
6	SD-808	40	10	6	6
7	SD-808	80	10	6	6
8	Positive control [d]	60	10	6	6

[a] = For discussion and data reporting purposes, dose group levels of 20, 40, and 80 mg/kg/day SD-809 or SD-808 are referred to as 20, 40, and 80 mg/kg/day-09 or-08, respectively.

[b] = All animals were euthanized following 3 days of dose administration, at approximately 18 to 24 hours following the final dose administration (study day 3); 5 animals/sex/group were utilized for bone marrow collection.

[c] = 0.5% carboxymethylcellulose with 0.1% (weight/volume) Tween® 80 in deionized water.

[d] = A single dose of CPS was administered to the positive control group on study day 2; animals were euthanized at approximately 18 to 24 hours following dosing (study day 3).

Study Validity & Results:

Dose Range-Finding Study: Based on the occurrence of intermittent tremors, decreased activity, hypothermia, and decreased respiration rate in animals dosed with 100 mg/kg/day SD-809 or SD-808, 1 HDM and 1 HDF dosed with SD-809 and 1 HDM and 2 HDF dosed with SD-808 were sacrificed prematurely on the second day of dose administration. The NOAELs were 50 mg/kg/day SD-809 and 25 mg/kg/day SD-808.

Definitive Study: All animals survived to scheduled euthanasia. Intermittent tremors occurred in all SD-808 dose groups and in the MD and HD SD-809 groups (sponsor's tables, below). Decreased activity and partial eye closure occurred in MD and HD animals dosed with SD-808 or SD-809 (sponsor's tables, below). Other clinical signs, such as hypothermia, occurred sporadically and only in some HD animals dosed with SD-808 or SD-809. There were no test article-related clinical signs observed in LD animals, SD-808 or SD-809.

Text Table 7. Summary of Test Article-Related Post-Dosing Clinical Observations (Definitive Phase, Males) Total occurrences/No. of animals

Observation	Vehicle	SD-809			SD-808			CPS
Dose Group (mg/kg/day)	0	20	40	80	20	40	80	60
1 Hour Post-Dosing								
Tremors, intermittent	0/0	0/0	1/1	11/6	3/3	6/6	14/6	0/0
Partial closure of the eye(s)	0/0	0/0	2/1	34/6	0/0	4/2	36/6	0/0
Body cool to touch	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Decreased activity	0/0	0/0	1/1	15/6	0/0	1/1	18/6	0/0
Yellow material, urogenital area	0/0	0/0	0/0	1/1	3/3	2/2	3/2	0/0
Yellow material, forelimb(s)	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Yellow material, dorsal trunk	0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0
Unscheduled Observations (>75 minutes)								
Hypoactivity	0/0	0/0	0/0	0/0	0/0	0/0	3/3	0/0
Tremors, intermittent	0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0
Partial closure of the eye(s)	0/0	0/0	0/0	4/2	0/0	0/0	6/3	0/0
Body cool to touch	0/0	0/0	0/0	0/0	0/0	0/0	3/3	0/0
Decreased activity	0/0	0/0	0/0	2/2	0/0	0/0	0/0	0/0

Text Table 8. Summary of Test Article-Related Post-Dosing Clinical Observations (Definitive Phase, Females) Total occurrences/No. of animals

Observation	Vehicle	SD-809			SD-808			CPS
Dose Group (mg/kg/day)	0	20	40	80	20	40	80	60
1 Hour Post-Dosing								
Tremors, intermittent	0/0	0/0	3/3	16/6	0/0	4/3	17/6	0/0
Partial closure of the eye(s)	0/0	0/0	2/1	30/6	0/0	8/3	34/6	0/0
Decreased activity	0/0	0/0	0/0	18/6	0/0	4/3	18/6	0/0
Unscheduled Observations (>75 minutes)								
Hypoactivity	0/0	0/0	0/0	2/2	0/0	1/1	7/4	0/0
Tremors, intermittent	0/0	0/0	0/0	1/1	0/0	0/0	1/1	0/0
Partial closure of the eye(s)	0/0	0/0	0/0	6/2	0/0	2/1	14/4	0/0
Pale extremities	0/0	0/0	0/0	0/0	0/0	1/1	1/1	0/0
Extremities cool to touch	0/0	0/0	0/0	0/0	0/0	1/1	1/1	0/0
Body cool to touch	0/0	0/0	0/0	1/1	0/0	0/0	6/4	0/0
Decreased activity	0/0	0/0	0/0	1/1	0/0	0/0	0/0	0/0

SD-808 and SD-809 did not increase the number of micronucleated polychromatic erythrocytes in the bone marrow. Cyclophosphamide, the positive control, did increase the number of micronucleated PCEs, as expected.

7.4 Computational Toxicology

A MultiCASE (SD-809-NC-063) and DEREK structure analysis (SD-809-NC064) of metabolite M1 was negative for mutagenicity. A DEREK Nexus and Sarah Nexus assessment of SD-809, (b) (4) were negative for mutagenicity (DRK157-0724). (b) (4) was negative for mutagenicity when analyzed by MultiCASE (SD-809-NC-075) and DEREK Nexus (SD-809-NC-074).

9 Reproductive and Developmental Toxicology

9.2 Embryonic Fetal Development

Study title: A Twice-Daily Oral (Gavage) Dose Range-Finding Study of the Effects of Deuterated Tetrabenazine on Embryo/Fetal Development in Rats

Study no.:	SD-809-NC-051
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7/23/2013
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	SD-809, Lot CCS-1209d6/STG-05/00111, 99.3%

Key Study Findings

- **The NOAEL was 10 mg/kg/day.**
- **BW gain was markedly lower at > 10 mg/kg/day.**
- **Resorptions and postimplantation losses were increased at > 10 mg/kg/day.**

Methods

Doses:	0, 10, 30, 50 mg/kg/day
Frequency of dosing:	Twice daily from GD 6 through 17; euthanized on GD 20.
Dose volume:	10 mL/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% polysorbate 80
Species/Strain:	Crl:CD(SD) rats
Number/Group:	8 females/group

Mortality & Clinical Signs: There were no early deaths. Slight tremors and drooping eyelids occurred at the MD and HD throughout the dosing period. Hypoactivity occurred at the HD.

Body Weight & Food Consumption: BW gain was lower in MD (25%) and HD (43%) groups, relative to control, during the dosing period. Food consumption was also decreased at the MD (12%) and HD (20%), relative to controls.

Necropsy: There were no test article-related findings in dams.

Cesarean Section and Offspring Data: Resorptions (early and late) and postimplantation loss were increased at the MD and HD (sponsor's table, below). There was a single finding of unilateral microphthalmia at the HD (fetus # 88902-10).

PROJECT NO. (b) (4) 847024 TABLE S10
SPONSOR:AUSPEX PHARM, INC. ORAL R-F STUDY OF D6-TETRABENAZINE ON EMBRYO/FETAL DEV IN RATS
SPONSOR NO.:SD-809-NC-051 SUMMARY OF FETAL DATA AT SCHEDULED NECROPSY

GROUP		SEX M	SEX F	VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS
1	TOTAL	49	44	93	0	4	0	4	97	114	17
	MEAN	7.0	6.3	13.3	0.0	0.6	0.0	0.6	13.9	16.3	2.4
	S.D.	3.06	3.25	3.73	0.00	0.79	0.00	0.79	3.93	2.43	2.37
	S.E.	1.15	1.23	1.41	0.00	0.30	0.00	0.30	1.49	0.92	0.90
2	TOTAL	63	65	128	0	2	0	2	130	142	12
	MEAN	7.9	8.1	16.0	0.0	0.3	0.0	0.3	16.3	17.8	1.5
	S.D.	1.55	1.36	1.41	0.00	0.46	0.00	0.46	1.28	1.58	1.07
	S.E.	0.55	0.48	0.50	0.00	0.16	0.00	0.16	0.45	0.56	0.38
3	TOTAL	59	60	119	0	6	1	7	126	129	3
	MEAN	7.4	7.5	14.9	0.0	0.8	0.1	0.9	15.8	16.1	0.4
	S.D.	2.50	2.98	2.64	0.00	1.39	0.35	1.36	2.49	2.42	0.52
	S.E.	0.89	1.05	0.93	0.00	0.49	0.13	0.48	0.88	0.85	0.18
4	TOTAL	41	53	94	0	11	3	14	108	126	18
	MEAN	5.9	7.6	13.4	0.0	1.6	0.4	2.0	15.4	18.0	2.6
	S.D.	2.67	3.69	5.09	0.00	2.64	1.13	2.77	3.10	2.08	3.15
	S.E.	1.01	1.39	1.93	0.00	1.00	0.43	1.05	1.17	0.79	1.19

None significantly different from control group
NA = NOT APPLICABLE
MEAN NUMBER OF VIABLE FETUSES, MEAN NUMBER OF IMPLANTATION SITES, MEAN NUMBER OF CORPORA LUTEA,
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 50 MG/KG/DAY

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

Study no.:	SD-809-ND-052
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/21/2013
GLP compliance:	Yes, US FDA GLP
QA statement:	Yes
Drug, lot #, and % purity:	SD-809, Lot CCS-1209d6/STG-05/00111, 99.3% SD-808 (TBZ), Lot CCS-1209d0/STG-05/00111, 99.2%

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 TBZ.**
- **Exposure to TBZ 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).**

Methods

Doses:	SD-809: 5, 10, 30 mg/kg/day administered BID SD-808: 30 mg/kg/day administered BID
Frequency of dosing:	Twice daily from GD 6 to GD 17; euthanized on GD 20
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% carboxymethylcellulose with 0.1% polysorbate 80
Species/Strain:	Crl:CD(SD) rats
Number/Group:	Main: 25 females/group; TK: 6 females/group
Deviation from study protocol:	Deviations were minor and did not impact the validity of the study.

Dosing Solution Analysis: The formulations used to dose animals were within +/- 15% of the nominal concentration.

Mortality & Clinical Signs: All animals survived until planned sacrifice. Lacrimation was increased at the HD of SD-809 and SD-808.

Body Weight & Food Consumption: Mean BW gain was lower in the HD SD-809 group (35%) and the SD-808 group (25%), relative to controls, during the dosing period. Food consumption was decreased slightly in the HD SD-809 group (8%), relative to control.

Necropsy & Cesarean Section Data: There were no test article-related findings in the SD-809 or SD-808 dose groups.

Offspring: There were no test article-related external or visceral malformations and variations. There were no test article-related skeletal malformations. However, 7th

cervical rib, a skeletal variation, occurred in a dose-related manner in SD-809 dose groups (1, 2, 3, 5; control, LD, MD, HD SD-809, respectively); two fetuses in the SD-808 group had 7th cervical rib. 7th cervical rib occurred only once in each litter in which it was observed (reviewer's table, below).

Test Article & Dose (mg/kg/d)	Dam ID #	Fetus ID #
0 (SD-809)	96210	16
5 (SD-809)	96104	9
	96171	12
10 (SD-809)	96081	9
	96191	15
	96213	1
30 (SD-809)	96088	9
	96112	16
	96149	15
	96202	5
	96221	10
30 (TBZ)	96093	14
	96232	5

Reviewer's Table: Fetuses with 7th Cervical Rib.

The proportion of animals/litter with 7th cervical rib was increased in a dose-dependent manner in animals dosed with SD-809 (see sponsor's table, below).

				Dosage Level (mg/kg/day)				
					Test Article			Reference Article
Sex	Variable	Type	Statistic	0	5	10	30	30
	7TH CERVICAL RIB(S)	SKE	Mean	0.3	0.5	0.8	1.3	0.5
			SD	1.25	1.82	2.27	2.64	1.85
			SE	0.25	0.37	0.45	0.54	0.37
			N	25	24	25	24	25
			Median	0.0	0.0	0.0	0.0	0.0
			Dunn p-value	-	1.000	1.000	0.947	NT
			Pairwise p-value	NT	NT	NT	-	0.462

Toxicokinetics: Systemic exposure to SD-809 and its respective alpha and beta metabolites (SD-948 and SD-949) was higher at 30 mg/kg/day SD-809 than exposure to the TBZ and its metabolites (SD-946 and SD-947; sponsor's tables, below) at 30 mg/kg/day TBZ.

Text Table 2. Toxicokinetic Parameters for SD-809 after Oral Administration of SD-809 in Pregnant Rats

SD-809 Dosage (mg/kg/day):	5	10	30
Parameter (Units)		Gestation Day 6	
AUC_{last} (ng·h/mL)	1.76	19.2	68.8
SE AUC_{last} (ng·h/mL)	0.352	12.5	7.55
Dose-Normalized AUC_{last}	0.352	1.92	2.29
C_{max} (ng/mL)	1.52	3.64	36.9
SE C_{max} (ng/mL)	0.331	0.225	3.11
Dose-Normalized C_{max}	0.304	0.364	1.23
T_{max} (h)	1	1	1
$T_{1/2}$ (h)	NC	NC	1.5
		Gestation Day 17	
AUC_{last} (ng·h/mL)	16.7	50.5	274
SE AUC_{last} (ng·h/mL)	2.74	2.88	23.2
Dose-Normalized AUC_{last}	3.34	5.05	9.13
C_{max} (ng/mL)	9.09	21.7	104
SE C_{max} (ng/mL)	2.16	0.608	11.5
Dose-Normalized C_{max}	1.82	2.17	3.47
T_{max} (h)	1	1	1
$T_{1/2}$ (h)	NC	1.7	1.5
Accumulation Ratio	9.5	2.6	4.0

Note= Units for dose-normalized AUC_{last} are (ng·h/mL)/(mg/kg/day); units for dose-normalized C_{max} are (ng/mL)/(mg/kg/day).
NC = Not calculable
SE = Standard error

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Text Table 3. Toxicokinetic Parameters for SD-948 after Oral Administration of SD-809 in Pregnant Rats

SD-809 Dosage (mg/kg/day):	5	10	30
Parameter (Units)		Gestation Day 6	
AUC_{last} (ng·h/mL)	20.7	89.1	332
SE AUC_{last} (ng·h/mL)	3.59	18.0	33.6
C_{max} (ng/mL)	5.61	15.4	89.4
SE C_{max} (ng/mL)	1.22	0.581	7.89
T_{max} (h)	1	1	1
$T_{1/2}$ (h)	2.6†	2.7†	2.1†
Metabolite/Parent Ratio	12	4.6	4.8
		Gestation Day 17	
AUC_{last} (ng·h/mL)	72.5	155	572
SE AUC_{last} (ng·h/mL)	13.5	11.8	74.6
C_{max} (ng/mL)	11.8	26.2	107
SE C_{max} (ng/mL)	3.01	1.01	27.5
T_{max} (h)	1	1	1
$T_{1/2}$ (h)	2.8†	2.8†	2.6†
Accumulation Ratio	3.5	1.7	1.7
Metabolite/Parent Ratio	4.3	3.1	2.1

† = Value is considered to be an approximation; failed to meet acceptance criteria.
SE = Standard error

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Text Table 4. Toxicokinetic Parameters for SD-949 after Oral Administration of SD-809 in Pregnant Rats

SD-809 Dosage (mg/kg/day):	5	10	30
Parameter (Units)		Gestation Day 6	
AUC_{last} (ng·h/mL)	1.50	19.2	41.1
SE AUC_{last} (ng·h/mL)	0.321	14.1	6.96
C_{max} (ng/mL)	1.19	3.09	17.7
SE C_{max} (ng/mL)	0.321	0.193	0.889
T_{max} (h)	1	1	1
$T_{1/2}$ (h)	NC	NC	1.2
Metabolite/Parent Ratio	0.85	1.0	0.60
		Gestation Day 17	
AUC_{last} (ng·h/mL)	4.69	12.9	66.1
SE AUC_{last} (ng·h/mL)	0.832	1.56	7.89
C_{max} (ng/mL)	2.41	6.48	21.7
SE C_{max} (ng/mL)	0.536	1.47	3.72
T_{max} (h)	1	1	1
$T_{1/2}$ (h)	NC	NC	1.7
Accumulation Ratio	3.1	0.67	1.6
Metabolite/Parent Ratio	0.28	0.26	0.24

NC = Not calculable
SE = Standard error

Text Table 5. Toxicokinetic Parameters for SD-808 after Oral Administration of SD-808 in Pregnant Rats

SD-808 Dosage (mg/kg/day):	30
Parameter (Units)	Gestation Day 6
AUC_{last} (ng·h/mL)	41.6
SE AUC_{last} (ng·h/mL)	2.84
C_{max} (ng/mL)	21.3
SE C_{max} (ng/mL)	1.58
T_{max} (h)	1
$T_{1/2}$ (h)	1.2
	Gestation Day 17
AUC_{last} (ng·h/mL)	196
SE AUC_{last} (ng·h/mL)	17.1
C_{max} (ng/mL)	65.1
SE C_{max} (ng/mL)	13.3
T_{max} (h)	1
$T_{1/2}$ (h)	1.6
Accumulation Ratio	4.7

SE = Standard error

Text Table 6. Toxicokinetic Parameters for SD-946 after Oral Administration of SD-808 in Pregnant Rats

SD-808 Dosage (mg/kg/day):	**30**
Parameter (Units)	Gestation Day 6
AUC_{last} (ng·h/mL)	237
SE AUC_{last} (ng·h/mL)	14.0
C_{max} (ng/mL)	63.5
SE C_{max} (ng/mL)	7.92
T_{max} (h)	1
$T_{1/2}$ (h)	1.9
Metabolite/Parent Ratio	5.7
	Gestation Day 17
AUC_{last} (ng·h/mL)	404
SE AUC_{last} (ng·h/mL)	44.1
C_{max} (ng/mL)	69.1
SE C_{max} (ng/mL)	20.4
T_{max} (h)	1
$T_{1/2}$ (h)	2.6†
Accumulation Ratio	1.7
Metabolite/Parent Ratio	2.1

†= Value is considered to be an approximation; failed to meet acceptance criteria.
SE=Standard error

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Text Table 7. Toxicokinetic Parameters for SD-947 after Oral Administration of SD-808 in Pregnant Rats

SD-808 Dosage (mg/kg/day):	**30**
Parameter (Units)	Gestation Day 6
AUC_{last} (ng·h/mL)	17.3
SE AUC_{last} (ng·h/mL)	0.784
C_{max} (ng/mL)	9.18
SE C_{max} (ng/mL)	0.420
T_{max} (h)	1
$T_{1/2}$ (h)	NC
Metabolite/Parent Ratio	0.42
	Gestation Day 17
AUC_{last} (ng·h/mL)	38.0
SE AUC_{last} (ng·h/mL)	5.59
C_{max} (ng/mL)	12.5
SE C_{max} (ng/mL)	4.46
T_{max} (h)	1
$T_{1/2}$ (h)	1.7
Accumulation Ratio	2.2
Metabolite/Parent Ratio	0.19

NC =Not calculable
SE =Standard error

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11 Integrated Summary and Safety Evaluation

SD-809 (deutetrabenazine) is a deuterated form of tetrabenazine (TBZ) that has been developed for treatment of chorea associated with Huntington's disease. Deuterium has been substituted for the hydrogen atoms at the 9 and 10 positions of TBZ in order to take advantage of the kinetic isotope effect (KIE) of deuterium and its ability to alter the kinetics of drug metabolism (Shao L and Hewitt MC, Drug News Perspect. 2010 Jul-Aug;23(6):398-404). In the case of SD-809, deuterium has been added in an attempt to slow the rate of demethylation of the two primary metabolites of TBZ, α- and β-dihydrotetrabenazine, which are also the active metabolites of TBZ. The sponsor has submitted the NDA under 505(b)(2) for the approval of SD-809 under the proprietary name, Austedo. Xenazine (TBZ) is the reference listed drug (RLD). Xenazine was approved on August 15, 2008 under NDA 21-894 for the treatment of chorea associated with Huntington's disease. During the End of Phase 2 (EOP2) meeting regarding SD-809, the sponsor was informed that the abbreviated nonclinical program described in the meeting package, which included a 3-month repeat dose study in rat, an embryofetal development (EFD) study in rat, and a genetic toxicology assessment of SD-809, were adequate to support the NDA for SD-809 "*provided that the clinical exposures to the parent compound and any major circulating metabolites fall within the range of those for the RLD*" (Meeting minutes, IND 112975, 12/26/2012). These nonclinical studies were submitted to support the approval of NDA 208-082.

The primary metabolites of TBZ, α- and β-dihydrotetrabenazine, are high affinity antagonists of the vesicular monoamine transporter 2 (VMAT2), a protein involved in the transport of neurotransmitters into synaptic vesicles. Deuteration of TBZ at the 9 and 10 positions did not markedly impact the binding of these metabolites to VMAT2, suggesting that SD-809 acts at the same biological target as TBZ. Therefore, the established pharmacologic class (EPC) for TBZ (i.e., vesicular monoamine transporter 2 (VMAT2) inhibitor) is also appropriate for SD-809 and should be included in the Highlights of Prescribing Information section of the Austedo labeling.

The pivotal toxicology studies conducted to support the approval of SD-809 consisted of a complete genetic toxicology battery, an EFD study conducted in rat with TBZ as a comparator, and 3-month repeat dose study in rat with TBZ as a comparator. Overall, there were no adverse findings unique to SD-809, relative to TBZ, in any of the pivotal studies.

A complete genetic toxicology battery was conducted with SD-809 and TBZ. Additionally, in vitro bacterial reverse mutation studies and in vitro chromosomal aberration studies were conducted with the primary metabolites of SD-809 and TBZ, α- and β-dihydrotetrabenazine. None of the test articles were positive for mutagenicity or clastogenicity. SD-809 and TBZ were assessed in an in vivo micronucleus assay conducted in mouse, the same species used to conduct the micronucleus assay for the RLD. Both SD-809 and TBZ were negative in the in vivo micronucleus assay.

In the EFD study, exposure to SD-809 and its deuterated primary metabolites, α- and β-dihydrotetrabenazine, was higher (40-70%) in pregnant rats at the HD of 30 mg/kg/day, relative to pregnant rats dosed with TBZ; a similar finding was not observed in the 3-month study conducted with non-pregnant female rats (discussed below). Pregnant rats in the EFD study were dosed with up to 30 mg/kg/day SD-809 (180 mg/m^2/day) which is approximately 6 times the MRHD for SD-809 based on body

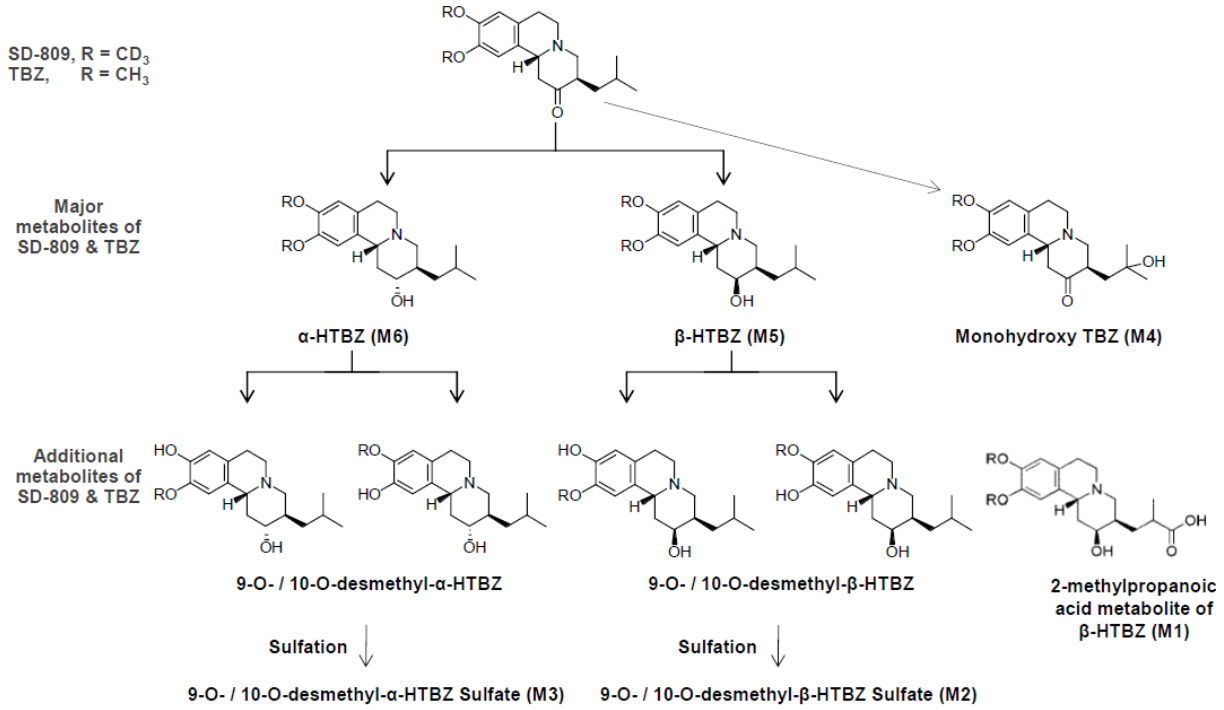
surface area (BSA). Although there was a dose-dependent increase in the incidence of 7th cervical rib at all doses of SD-809 in the pivotal study, this finding also occurred in animals dosed with TBZ; this skeletal variation is not mentioned in the Xenazine labeling. The lowest dose at which this finding occurred was 5 mg/kg/day (30 mg/m^2/day), which is equal to the MRHD based on BSA. Overall, there were no developmental effects that were unique to SD-809, relative to TBZ.

Estrus cycle disruption occurred in rats dosed with SD-809 in the 3-month repeat dose study; a NOEL was not established. The label for Xenazine describes this effect occurring in female rats at doses of TBZ greater than 5 mg/kg; the lowest dose of SD-809 tested in the 3-month study was 5 mg/kg/day (30 mg/m^2). Therefore, although not unique to SD-809, estrus cycle disruption appears to occur at lower doses of SD-809, relative to TBZ. The lowest dose of SD-809 tested in the 3-month repeat dose study (30 mg/m^2) is similar to the maximum recommended human dose (MRHD) of SD-809 based on body surface area (48 mg/day or 29.6 mg/m^2/day based on a 60 kg human). Nervous system effects of SD-809, such as intermittent tremors and catalepsy occurred in rats in the 3-month study at doses greater than 5 mg/kg/day (30 mg/m^2/day), which is similar to the MRHD based on BSA.

In the 3-month repeat dose study, exposure to the primary metabolites of SD-809 and TBZ, α- and β-dihydrotetrabenazine, was similar in rats dosed with comparable doses of either of the test articles; exposure to the alpha metabolite was higher in males dosed with either SD-809 or TBZ. The 3-month study conducted in rat has demonstrated that, at similar exposure to the primary metabolites of SD-809 and TBZ at the HD tested, the adverse test article-related effects are similar. This finding allows the sponsor to bridge to the existing nonclinical safety information for the RLD regarding the primary metabolites of TBZ, α- and β-dihydrotetrabenazine. However, it is important to note that there was no quantitation at steady state of other metabolites of SD-809 or TBZ in the 3-month study conducted in rat.

Both in vitro and in vivo metabolism of SD-809 has been demonstrated to differ from TBZ. For example, when incubated with human liver microsomes, the stability of α- and β-dihydrotetrabenazine was markedly increased by deuteration (SD-809), relative to non-deuterated TBZ (SD-809-NC-001); the impact of deuteration on metabolism of SD-809 in monkey, dog, and rat microsomes was not as consistent or marked which suggests that there is interspecies variability. There is evidence that this increase in stability was mainly due to a slowing of metabolism by CYP2D6 (SD-809-NC-003 & SD-809-NC-41). Although there were no novel metabolites of SD-809, relative to TBZ, when incubated in vitro with human or rat liver S9 fraction (SD-809-NC-049), there is in vivo evidence, mainly in humans, that the level of circulating metabolites of SD-809 are altered, relative to TBZ. A schematic of the metabolism of SD-809 is provided below (sponsor's figure).

Figure 1. Human Metabolism of SD-809



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

While it is outside the scope of the nonclinical review to provide a detailed analysis of the human metabolism of SD-809 (see the Office of Clinical Pharmacology Review), it is important to provide a basic description of the available human metabolism data, mainly because the sponsor was informed during the End-of-Phase 2 (EOP2) meeting that the completed and planned nonclinical studies listed in the meeting packet were adequate to support an NDA for SD-809, with the caveat that clinical exposures to the parent compound and circulating metabolites are within range of the exposure observed in patients dosed with the RLD (Meeting Minutes, IND 112975, 12/26/2012). Therefore, it is important to determine if the sponsor was able to successfully bridge to the PK information available for the RLD. Based on the available information provided by the sponsor for circulating metabolites in humans dosed with SD-809, there is concern regarding the variability in reported levels of SD-809 metabolites and that the level of circulating metabolites may have been underestimated. The sponsor was informed of this concern during the Mid-Cycle Communication Meeting (11/3/15).

The sponsor provided data to the IND during clinical development and in the NDA submission that shows metabolite 1 (M1 or 2-methylpropanoic acid metabolite of β-dihydrotetrabenazine) both as a major human metabolite (MHM) and a minor human metabolite, depending on the submission. Specifically, in the EOP2 meeting packet the level of M1 in humans given a single dose of SD-809 was 12.7% of total circulating drug-related material; a level at which this metabolite would be considered a MHM (sponsor's table, below).

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					

At the time of the EOP2 meeting, an updated table was provided, which demonstrated that the level of M1 was less than 10% (sponsor's table, below).

Table 1: Comparison of Metabolites M1-M6 of SD-809 and Tetrabenazine, updated results

Percentage of total sample radioactivity in time proportional pools (2-12 hours) in study SD-809-C-12, Average (SD)		
	Cohort	
Metabolite Number and Identification	**SD-809, n = 6***	**Tetrabenazine, n = 6***
M1, Acid Metabolite of HTBZ	8.6 (4.5)	4.2 (2.0)
M2, Sulphate of O-desmethyl HTBZ	2.5 (1.1)	6.4 (2.9)
M3, Sulphate of O-desmethyl HTBZ	4.0 (1.5)	16.4 (5.6)
M4, + 16 amu Metabolite	12.9 (3.2)	15.6 (4.9)
M5, β-HTBZ	8.3 (4.2)	1.8 (1.5)
M6, α-HTBZ	13.0 (4.6)	4.0 (1.4)
*: For individual subject data, see Tables 2 and 3		

In the current NDA submission, the sponsor provided a third table which demonstrated that the level of M1 was just slightly below 10% and different from the previous two numbers (sponsor's table, below).

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Table 10. Exposure to Metabolites Following Administration of a Single Dose of [^{14}C]-SD-809[a] or [^{14}C]-Tetrabenazine[a] (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] [^{14}C]-SD-809 and [^{14}C]-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.

The variability among the three tables raises concern that there is some uncertainty regarding the status of metabolite M1 as a major or minor human metabolite. Metabolite M4, a MHM in humans dosed with SD-809 or TBZ (see sponsor's tables above), is not mentioned in the labeling of Xenazine, the RLD.

Further adding to the concern about the metabolism data is the possibility that the method used by the sponsor may underestimate the level of circulating metabolites. A known MHM of TBZ, 9-O-desmethyl-β-dihydrotetrabenazine, was characterized by the sponsor as being a minor human metabolite in humans dosed with TBZ (see footnote "e" in sponsor's table, above). 9-O-desmethyl-β-dihydrotetrabenazine was identified in Xenazine after initial approval of the NDA and required the conduct of multiple nonclinical PMRs to characterize its safety (NDA 21-894; Supplement Approval Letter, 7/6/2011). Based on a quantitative assessment conducted by the sponsor on some of the circulating metabolites of TBZ and SD-809 in humans, it appears that 9-O-desmethyl-dihydrotetrabenazine is present at higher levels than would have been expected from the results previously referenced above (compare sponsor's Table 10 above and Table 11, below). Unfortunately, the levels of M1 and M4 were not assessed in this quantitative assay.

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Table 11. Pharmacokinetic Parameters From the LC-MS/MS Assay and Semi-quantitative Assay (Study SD-809-C-12)

Test article	Metabolite	PK parameters from LC-MS/MS assay from (b) (4) (b) (4) geometric mean (%CV) [a]				Semi-quantitative analysis of radioactivity in plasma samples from (b) (4) mean (SD) [b]	
		C_{max} (ng/mL)	AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	$t_{1/2}$ (h)	DPM/g Plasma (25 mg dose)	% Total Plasma Radioactivity (% total drug related material)
SD-809	SD-809 (n=4)	0.241 (22.4)	0.273 (199)	Not calculated	Not calculated	Not calculated	Not calculated
	α-HTBZ (M6) (n=6)	27.5 (26.3)	454 (45.3)	432 (43.9) (n=5)	12.177 (27.6) (n=5)	82 (36)	13.0 (4.6)
	β-HTBZ (M5) (n=6)	16.8 (48.9)	177 (112)	189 (109)	9.201 (50.2)	52 (31)	8.3 (4.2)
	9-ODM α-HTBZ (n=6)	0.849 (16.7)	12.6 (29.0)	Not calculated	Not calculated	Not calculated	Not calculated
	9-ODM β-HTBZ (n=6)	2.48 (19.6)	83.1 (16.2)	Not calculated	Not calculated	Not calculated	Between 1% to 10%
	10-ODM α-HTBZ	BLQ	BLQ	BLQ	BLQ	Not calculated	Not calculated
	10-ODM β-HTBZ	BLQ	BLQ	BLQ	BLQ	Not calculated	Not calculated
	sulfate of ODM-α-HTBZ (M3) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	24 (9)	4.0 (1.5)
	sulfate of ODM-β-HTBZ (M2) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	15 (5)	2.5 (1.1)
	M1 (2-methylpropanoic acid-β-HTBZ) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	54 (19)	9.2 (3.6)
	M4 (mono-hydroxy SD-809) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	77 (14)	12.9 (3.2)

Test article	Metabolite	PK parameters from LC-MS/MS assay from (b) (4) (b) (4) geometric mean (%CV) [a]				Semi-quantitative analysis of radioactivity in plasma samples from (b) (4) mean (SD) [b]	
		C_{max} (ng/mL)	AUC_{last} (ng*h/mL)	AUC_{inf} (ng*h/mL)	$t_{1/2}$ (h)	DPM/g Plasma (25 mg dose)	% Total Plasma Radioactivity (% total drug related material)
Tetrabenazine	Tetrabenazine (n=3)	0.946 (251)	0.683 (273)	Not calculated	Not calculated	Not calculated	Not calculated
	α-HTBZ (M6) (n=6)	17.6 (52)	109 (28.3)	121 (34.5) (n=4)	5.682 (44.0) (n=4)	22 (8)	4.0 (1.4)
	β-HTBZ (M5) (n=6)	6.62 (77.4)	24.2 (50.1)	45.7 (26.5) (n=2)	3.198 (15.6) (n=2)	10 (9)	1.8 (1.5)
	9-ODM a-HTBZ (n=6)	2.73 (44.65)	32.5 (32.7)	Not calculated	Not calculated	Not calculated	Not calculated
	9-ODM β-HTBZ (n=6)	8.03 (51.9)	160 (16.1)	189 (17.1) (n=3)	18.474 (20.6) (n=3)	Not calculated	Between 1% to 10%
	10-ODM a-HTBZ	BLQ	BLQ	BLQ	BLQ	Not calculated	Not calculated
	10-ODM β-HTBZ (n=5)	0.997 (46.6)	1.2 (168.0)	Not calculated	Not calculated	Not calculated	Not calculated
	sulfate of ODM-α-HTBZ (M3) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	94 (45)	16.4 (5.6)
	sulfate of ODM-β-HTBZ (M2) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	40 (21)	6.4 (2.9)
	M1 (2-methylpropanoic acid-β-HTBZ) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	25 (14)	4.1 (2.0)
	M4 (mono-hydroxy tetrabenazine) (n=6)	Not part of method	Not part of method	Not part of method	Not part of method	86 (31)	15.6 (4.9)

a: References: SD-809-C-12, Tables 14.2.8.4.1 and Table 14.2.8.4.3.
b: References: SD-809-C-12, Section 16.1.13.4.
Abbreviations: AUC_{inf}, area under the concentration vs time curve from time 0 extrapolated to infinity; AUC_{last}, area under the concentration vs time curve from time 0 to the last quantifiable time point; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DPM, disintegrations per minute; HTBZ, dihydrotetrabenazine; LC-MS/MS, liquid chromatography with tandem mass spectrometry; ODM, O-desmethyl; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, apparent first order elimination half-life.

Overall, it appears that the sponsor's initial semi-quantitative assay may underestimate the circulating level of SD-809- and TBZ-related metabolites in humans; further adding to the uncertainty regarding the data on human metabolism of SD-809. Therefore, if certain metabolites of SD-809, such as M1 and M4, are determined to be MHMs, as defined in ICH M3(R2) (i.e., > 10% of total drug-related exposure), then the safety of these metabolites would need to be assessed in the pivotal nonclinical studies. Currently, it is not possible to perform this assessment because of the lack of adequate quantitation of metabolites, other than α- and β-dihydrotetrabenazine, in the nonclinical studies. Specifically, as discussed on page 25 of the Toxicology Written Summary, M1 was "observed to be a trace metabolite in male and female rat plasma extracts" and

metabolite M4, based on normalized peak height, “was present in the rat at a peak intensity that was approximately 10-fold greater than that from human samples,” according to the sponsor. This method of assessment is not acceptable for comparison of exposure in animals and humans. 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 EFD study conducted in rat. 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, a critical element for the approval of Austedo under 505(b)(2). The Sponsor has attempted to address the Division’s concern by providing a response to the Mid-Cycle Communication Minutes (12/22/15), mostly by referring to the information on TBZ metabolism contained in the Summary Basis of Approval for NDA 21-894; this information does not belong to the sponsor and cannot be considered in the process of determining the adequacy of the nonclinical support for SD-809.

To summarize, it is not possible to determine if the nonclinical studies submitted in the current application support bridging to the available nonclinical information on the RLD without a definitive determination on the status of SD-809 metabolites as major or minor, as defined by ICH M3(R2). If it is determined that the metabolite profile for SD-809 is similar to the RLD and there are no new 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 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 of SD-809 was qualified in the pivotal nonclinical studies. Given that the TK assessment performed in the pivotal nonclinical studies was limited to an assessment of the steady state levels of deuterated α- and β-dihydrotetrabenazine, it would not be possible to determine if MHM other than these were qualified without the sponsor providing additional nonclinical data. Furthermore, if MHMs are identified in humans dosed with SD-809 that are not described in the labeling of the RLD, a full nonclinical assessment, including a chronic study in a single species (up to 6 months in rodents and 9 months in nonrodent), reproductive and developmental toxicity studies (e.g., EFD and pre- and postnatal development), and a carcinogenicity assessment may be required to demonstrate the safety of these SD-809-specific MHMs.

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/s/

CHRISTOPHER D TOSCANO
02/03/2016

LOIS M FREED
02/04/2016