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APPLICATION NUMBER:

208082Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA Number:	208082
Submission Type:	Complete Response Resubmission
Resubmission Date:	Oct 3, 2016
Generic Name:	Deutetrabenazine (SD-809)
Brand Name:	Austedo®
Dosage form:	Oral Tablets
Dosage strength:	6 mg, 9 mg and 12 mg
Proposed Indication:	Treatment of Chorea Associated with Huntington's Disease
Applicant:	Teva Pharmaceuticals, Inc.
Reviewer:	Hristina Dimova, Ph.D.
Team Leader:	Sreedharan Sabarinath, Ph.D.
OCP Division:	DCP1
OND Division:	Division of Neurology Products (DNP)

1.0 EXECUTIVE SUMMARY

New Drug Application (NDA) 208082, for SD-809 (deutetrabenazine) for chorea associated with Huntington's Disease (HD), was submitted on 29 May 2015 as a 505(b)(2) application. Xenazine® (NDA 021894) was referenced as the listed drug. This NDA submission received a **Complete Response (CR) Letter** on May 27, 2016 mainly due to Clinical Pharmacology and Nonclinical issues listed below[1]. Please refer to the Clinical Pharmacology review in DARRTS (Apr 8, 2016) for further details.

CLINICAL PHARMACOLOGY

Your clinical pharmacology studies were not adequate to determine whether all major human metabolites of deutetrabenazine have been identified. This information is needed to assess whether the bridge to the listed drug on which you are relying (Xenazine®) is scientifically justified to address the toxicity of all major metabolites of deutetrabenazine.

Please note that the method you proposed in your April 8, 2016, amendment to this NDA to assess potential major metabolites is acceptable, on face, and pending demonstration of suitable stability.

NONCLINICAL

The toxicokinetic analyses of metabolites in the pivotal nonclinical studies of deutetrabenazine are limited to quantitation of the primary metabolites of deutetrabenazine (i.e., alpha and beta-DHTBZ). 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 or that plasma exposure to each does not exceed that in humans with Xenazine.

The Applicant submitted a Complete Response to NDA 208082 on Oct 3, 2016, which included the following sections:

- Updated draft labeling, Update of nonclinical written and tabulated summaries (Section 2.6)
- Update of the Summary of Clinical Pharmacology (Section 2.7.2) reflecting additional data for SD-809 metabolites

No new clinical study reports were submitted in this NDA resubmission. In the CR letter, FDA indicated that the original analyses of the human [^{14}C]-ADME and mass-balance study SD-809-C-12 was not adequate to determine whether SD-809 metabolites M1 and M4 were major or minor. The sponsor validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) bioanalytical methods for M1 and M4 metabolites and analyzed the retained clinical plasma samples from the mass-balance study SD-809-C-12 for these metabolites to provide definitive human plasma exposure data in this resubmission.

[1] Complete Response Letter for NDA 208082 dated 05/27/2017

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP)/ Division of Clinical Pharmacology-1 has reviewed the Clinical Pharmacology information submitted to NDA 208082 and finds it acceptable. The NDA can be approved from a clinical pharmacology perspective.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The clinical pharmacology findings are as follows:

- Based on the reanalysis of M1 and M4 metabolites in retained clinical samples of subjects treated with SD-809, M4 was determined to be a minor metabolite (about 6% of total drug related material (TDRM).
- The mean ratio of M1 as a percentage of TDRM was about 10%. Therefore, M1 is not a major human metabolite as defined by ICH M3(R2) as it does not circulate at levels greater than 10% of the total drug-related exposure.
- The Clinical Pharmacology information reviewed during the resubmission is adequate to support the approval of NDA 208082.

2.0 NDA RESUBMISSION REVIEW

2.1 Background

Deutetrabenazine (SD-809), like tetrabenazine (TBZ), is rapidly converted by carbonyl reductase to the active metabolites α-HTBZ and β-HTBZ, which are O-dealkylated by CYP450 enzymes, principally CYP2D6 (with minor contribution of CYP1A2), to form 9- and 10-desmethyl-α- and β-DHTBZ. Subsequently, they are metabolized to sulfate or glucuronide conjugates (See Figure below).

Metabolic Pathway of SD-809 and Tetrabenazine in Humans

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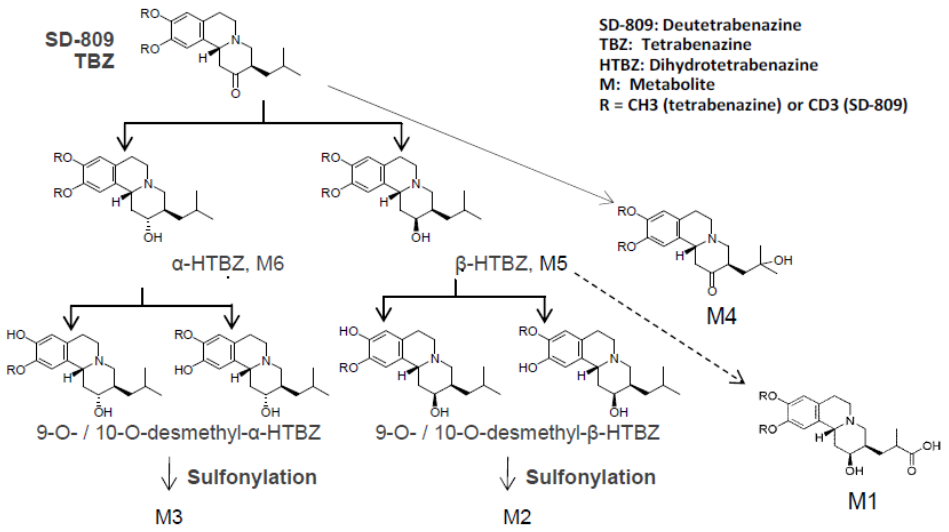

Source: Section 2.7.2 Summary of Clinical Pharmacology Studies, Figure 7

The metabolite profiling and identification results of the human [^{14}C]-ADME and mass-balance study presented in the original NDA submission were inconclusive to determine whether the SD-809 metabolites 2-methylpropanoic acid metabolite of β-HTBZ (M1) and monohydroxy tetrabenazine (M4), are major or minor human metabolites.

2.2 Clinical Pharmacology Information Submitted with the Complete Response

No new clinical study reports were submitted in this NDA resubmission. The sponsor has validated LC-MS/MS bioanalytical methods for M1 and M4 and analyzed the retained clinical plasma samples from the human [^{14}C]-ADME and mass-balance study SD-809-C-12 for these metabolites to provide definitive human plasma exposure data.

The Applicant has also analyzed retained clinical plasma samples from the multiple-dose Study AUS-SD-809-CTP-07, Part 2 to provide human exposure of M1 and M4 at steady state in order to assess whether these metabolites are adequately represented in nonclinical species in the toxicology studies.

In addition, the sponsor has submitted the results of several nonclinical pharmacology studies (off-target binding and genetic toxicology studies of metabolites M1 and M4) and the following Analytical Methods and Validation Reports:

- Validation Report DP-2016-068 (b) (4) Project Code: VAL194)
- Validation Report DP-2016-069 (b) (4) Project Code: VAL195)

Stability of the analytes M1 and M4 was assumed based on re-analyses of SD-809, α-HTBZ, and β-HTBZ in retained plasma samples. According to the Applicant, the stability of SD-809 and the HTBZ metabolites can be reasonably expected to reflect stability of

M1 and M4 based on the structural similarities of M1 to β-HTBZ and M4 to SD-809 in the same samples.

The Applicant assessed stability/reproducibility of SD-809, α-HTBZ and β-HTBZ concentrations in retained plasma samples stored at -80°C from the human [^{14}C]-ADME and mass-balance study SD-809-C-12 and from the multiple-dose portion of Study AUS-SD-809-CTP-07, Part 2. Audited concentrations for SD-809, α-HTBZ and β-HTBZ obtained from reanalysis using the validated LC-MS/MS method were compared to the original results listed in their respective clinical study reports (Study SD-809-C-12 completion date 25 August 2012; Study AUS-SD-809-CTP-07 completion date 22 June 2012). More than 67% of the re-analyzed samples passed the ISR acceptance criteria for SD-809 and for the HTBZ metabolites.

2.3 Metabolite Characterization

The following changes have been made to the sampling approach, bioanalytical methodology and the calculations for the metabolites M1 and M4 with respect to total drug-related material from Study SD-809-C-12:

Plasma samples

- In the original study results submitted to NDA 208082, only 4 plasma samples per subject (2, 2.5, 6 and 12 hours post-dose) were pooled (per protocol) in a time proportional manner, from each of the subjects treated with SD-809 (n = 6) or tetrabenazine (n = 6), for radio-chromatographic analysis of metabolites.
- In the new analysis presented in this document, all 11 plasma samples drawn over the first 12 hours post-dose were assessed individually for each subject. In addition, the remaining plasma samples in the 216-hour study period were included in the analysis, for a total of 23 samples per subject, allowing for evaluation over the full plasma time course of total drug-related material.

Reviewer's Comment: This is acceptable.

Evaluation of metabolites with respect to total drug related material (TDRM)

- In the original study results submitted to NDA 208082, the plasma pool for each subject (as described above) was used to estimate the percentage of metabolites with respect to total drug-related material in the same pool.
- In the new analysis presented in the NDA resubmission, the plasma concentrations for M1 and M4, obtained using validated bioanalytical methods, were used to calculate their respective area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}) values and were subsequently expressed as a percentage of the AUC_{inf} for total drug-related material, which had

been previously quantified from samples throughout the same 216-hour post-dose time course (Study Report SD-809-C-12, Listing 16.2.6.2).

Reviewer's Comments: According to SD-809-C-12 study report (see below), elimination half-life for the total plasma radioactivity could only be calculated in 1 subject. Therefore, according to this report, the AUC_{inf} for total plasma radioactivity could not be adequately estimated for 5 out of the 6 subjects.

From Original NDA 208082 Submission, Clinical Study Report SD-809-C-12 Amendment 01 ((b) (4) 113049) Version 2.0 (06 March 2015), Page 66 of 287:

Pharmacokinetic parameter estimates for whole blood and plasma total radioactivity are presented in Data Listings 16.2.6.1 and 16.2.6.2, and summarized in Tables 14.2.8.1 and 14.2.8.2, respectively. Following oral administration of 25 mg [^{14}C]-SD-809, concentrations of total radioactivity in plasma were detected at 0.67 h (i.e., 40 min) after dosing in all subjects. Maximum concentrations occurred between 0.67 and 6.00 h post-dose in individual subjects; thereafter, concentrations declined in a biphasic manner. Maximal concentrations for each subject ranged from 90.7 to 148.5 ng equivalents/mL in plasma. Radioactivity in plasma was less than 2 x background for the majority of subjects by 96 h and was below the limit of detection by 144 h post-dose for all subjects. An elimination half-life could only be calculated in 1 subject and is therefore not included in Table 7. The geometric mean MRT for total radioactivity was 22.9 h.

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Protocol: SD-809-C-12

TABLE 14.2.8.2
Plasma Pharmacokinetic Parameters: Total Radioactivity
Summary Statistics: PK Population

Treatment		Tlag (h)	Tmax (h)	Cmax (ng equiv/mL)	AUC(0-last) (h*ng equiv/mL)	AUC(0-inf) (h*ng equiv/mL)	AUC%extrap (%)
SD-809	Mean	0.330	3.028	128	3290	NC	NC
(N=6)	Median	0.330	3.000	132	3530	NC	NC
	SD	0.000	1.984	21.2	809	NC	NC
	CV%	0.0	65.5	16.5	24.6	NC	NC
	Geo Mean	0.330	2.404	126	3190	NC	NC
	Geo CV%	0.0	95.6	18.3	28.3	NC	NC
	Min	0.33	0.67	90.7	1980	4370	8.40
	Max	0.33	6.00	149	4000	4370	8.40
	n	6	6	6	6	1	1
	n*	6	6	6	6	1	1
TETRABENAZINE	Mean	0.333	2.117	164	2230	NC	NC
(N=6)	Median	0.330	2.000	164	2210	NC	NC
	SD	0.300	1.225	54.4	217	NC	NC
	CV%	89.9	57.9	33.2	9.7	NC	NC
	Geo Mean	0.470	1.844	154	2220	NC	NC
	Geo CV%	42.7	62.6	44.5	9.7	NC	NC
	Min	0.00	1.00	68	1950	2500	7.74
	Max	0.67	4.20	230	2550	2500	7.74
	n	6	6	6	6	1	1
	n*	4	6	6	6	1	1

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DATA LISTING 16.2.6.2
Plasma Pharmacokinetic Parameters: Total Radioactivity
Individual Values: All Subjects

Treatment	Parameter	Subject Number 001	002	003	004	005	006
SD-809	Tlag (h)	0.33	0.33	0.33	0.33	0.33	0.33
	Tmax (h)	4.00	1.50	6.00	0.67	4.00	2.00
	Cmax (ng equiv/mL)	137	145	127	120	90.7	149
	AUC(0-last) (h*ng equiv/mL)	3310	2700	4000	1980	3980	3760
	AUC(0-inf) (h*ng equiv/mL)	3750 b	3220 ab	4370	3740 ab	5290 ab	4450 ab
	AUC%extrap (%)	11.80 b	16.33 ab	8.40	47.02 ab	24.85 ab	15.41 ab
	Lambda-z (1/h)	0.0260 b	0.0196 ab	0.0346	0.0097 ab	0.0077 ab	0.0125 ab
	Tl/2el (h)	26.66 b	35.42 ab	20.03	71.25 ab	90.28 ab	55.23 ab
	MRT(0-inf) (h)	32.20 b	37.07 ab	29.98	79.15 ab	88.10 ab	53.05 ab
	MRT(0-t) (h)	21.71	20.26	23.47	15.55	34.49	26.33
	Data points	3	4	7	3	3	3
	Elimination Phase Start (h)	36.00	24.00	8.00	24.00	72.02	48.00
	Elimination Phase End (h)	72.10	72.08	72.05	48.02	120.00	120.00
	Rsq	0.9945	0.7883	0.9939	0.7356	0.3550	0.8404

Note: Treatment definition: SD-809 = 25 mg [14C]-SD-809 TETRABENAZINE = 25 mg [14C]-tetrabenazine
a=Rsq of regression <0.9000. Estimate reported but not included in summary stats
b=Period used for regression analysis < 2-fold the calculated T-half. Est reported but not included in summary stats
NC=Not calculated
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Source: Clinical Study Report SD-809-C-12 Amendment 01 ([(b) (4)]113049) Version 2.0 (06 March 2015)

This issue was discussed with the sponsor at the End of Review (Type A Meeting) on Sept 20, 2016. The clinical pharmacology team recommended calculating the percentage of total drug-related material based on AUC_{0-t} (for total plasma radioactivity and for M1/M4) instead of the AUC_{inf}.

The discussion at the Type A meeting focused mainly on M1 since (according to the nonclinical reviewer) M4 was adequately bridged to Xenazine.

Applicant's justification for using AUC_{inf} instead of AUC_{0-t}:

The Applicant focused on presenting M1 and M4 with respect to total drug related material (TDRM) using $AUC_{0-\infty}$ as AUC_{0-t} clearly underestimates overall exposure to TDRM but not to these metabolites (2.7.2 Summary of Clinical Pharmacology Studies, page 63).

Reviewer's Comments: I agree with the sponsor that AUC_{0-t} seem to underestimate the total radioactivity but not so much that the systemic exposure to M1/M4 due to the differences in bioanalytical methods for metabolites and for TDRM: the lowest value reported for TDRM was 7.9 ng eq/mL at 96 h post-dose (Report SD-809-C-12), while for M1 the lowest value reported was 0.22 ng/mL (also at 96 h post-dose). The extrapolated areas under the curve ($AUC_{\%extrap}$) were <2% for M1 and M4 for all subjects. Extrapolation was <25% for 5 of the 6 subjects for TDRM due to the slower terminal decline of total drug-related material than for M1 and M4.

However, according to the sponsor (Table 1 below), elimination rate constant can be reliably estimated for 4 out of 6 subjects in the mass-balance study.

Table 1: Evaluation of Elimination Rate Constants, AUC_{inf} of Total Drug-Related Material, and M1 Percentage of Total Drug-Related Material in Study SD-809-C-12, SD-809-Treated Subjects

Subject	r^2 (elimination rate constant of TDRM)[a]	Duration of time used for regression constant/ derived half-life[b]	$AUC\%_{extrap}$	M1	Acceptance Based on Teva Criteria
S001	0.9945	1.35	11.8%	9.2%	Acceptable
S002	0.7883	1.36	16.3%	10.0%	Acceptable
S003	0.9939	3.20	8.4%	10.2%	Acceptable
S004	0.7356	0.34	47.0%	Did not calculate	Not included in briefing document analysis (AUC_{extrap} >25%)
S005	0.3550	0.53	24.9%	8.6%	Could consider excluding from analysis (r^2<0.75)
S006	0.8404	1.30	15.4%	7.3%	Acceptable
Average (S001, 002, 003, 005, 006)				**9.1%**	--
Average (S001, 002, 003, 006)				**9.2%**	--

Abbreviations: AUC, area under concentration-time curve; TDRM, total drug-related material.
Teva acceptance criteria applied to total drug-related material: r^2 >0.75, duration of time used for regression constant/ derived half-life > 1; AUC_{extrap} <25%
Vendor acceptance criteria: r^2 >0.90, Duration of time used for regression constant/ derived half-life > 2; AUC_{extrap} not described
a: Source: Study SD-809-C-12 Clinical Study Report, Listing 16.2.6.2.
b: Derived from the elimination beginning and end and half-life, both provided in Study SD-809-C-12 Clinical Study Report, Listing 16.2.6.2.

Source: NDA 208082, Sequence No. 0024, 1.6.2 Meeting Background Materials (July 22, 2016)

In the Type A Meeting Briefing document, the sponsor had accepted AUC_{inf} for 5 of the 6 subjects. One subject was excluded due to $AUC_{\%extrap}$ >45%.

In light of FDA's comments, the sponsor revisited the criteria for accepting elimination rate constants in the original mass balance study report and believes that $r^2 > 0.75$ and $\%AUC_{extrap}$ less than 25% are the most relevant to the current analysis of total drug-related material.

Upon this re-evaluation, the sponsor considers 4 out of the 6 subjects in the mass-balance study as acceptable, as their r^2 for elimination rate constants were greater than 0.75, and AUC_{extrap} values ranged from 8.4% to 16.3% (See Table 1 above). In a single subject (S005; See Table 1 above), the r^2 for elimination rate constant was less than 0.75; this AUC_{inf} could be considered not evaluable.

The sponsor further argues that, based on AUC_{inf}, assessment of the systemic exposures to M1 and M4 at steady state indicate that, across the dose range (7.5 mg to 22.5 mg BID), M1 corresponds to on average 6.5% (range across 3 doses: 4.5% to 8.8%) and M4

on average 3.4% (range across 3 doses: 1.7% to 5.5%) of total drug-related material, indicating that systemic exposures to M1 and M4 are below 10%.

Reviewer's Comments: The metabolite/ TDRM ratio described above was calculated using results from different studies, different formulations and single vs. multiple dosing: the metabolite M1/M4 plasma steady state values are from Study AUS-SD-809-CTP-07, Part 2, while the total radioactivity (single dose) values are from the mass-balance study SD-809-C-12. Assessing metabolite/ TDRM ratio using results from different studies, different formulations and single vs. multiple dosing may not be appropriate for the reasons discussed below.

The sponsor claims that using AUC_{inf} of total drug-related material from SD-809-C-12 as a surrogate for AUC_{tau} of total drug-related material at steady state in AUS-SD-809-CTP-07, is justified based on two assumptions:

First, the pharmacokinetics of parent and metabolites should be dose and time independent.

Reviewer's Comment: While linearity was demonstrated for the primary metabolites α-HTBZ and β-HTBZ, this cannot be confirmed for all metabolites that comprise the remaining total drug-related material. Therefore, the single-dose AUC_{inf} for total drug-related material cannot be assumed to reliably predict the corresponding AUC_{tau} at steady state.

The second assumption is that subjects in the single-dose human [^{14}C]-ADME and mass-balance study are representative of those in Study AUS-SD-809-CTP-0.

Reviewer's Comments: The second assumption is not justified due to the high variability in the metabolism of SD-809.

In addition, two different formulations were used in these 2 studies.

Therefore, assessing metabolite/ TDRM ratio using results from different studies, different formulations and single vs. multiple dosing may not be appropriate.

Notes:

The steady state M1/M4 human exposure information was requested by the Agency (Late-Cycle Meeting Minutes, March 21, 2016) in order to assess whether these metabolites are adequately represented in nonclinical species in the toxicology studies. M1/M4 plasma steady state values were not meant to be used to calculate metabolite/TDRM ratio as no data for TDRM is available from study AUS-SD-809-CTP-07.

While the steady-state exposures to M4 after SD-809 administration are less compared to the M4 exposures after tetrabenazine, exposures to M1 after SD-809 administration are about 5x higher than those after tetrabenazine (2.8x higher after extrapolating to equipotent dose).

Plasma Metabolites of SD-809 and Tetrabenazine: AUC_{0-24} Values for M1 and M4 at Steady State from AUS-SD-809-CTP-07, Part 2

	Observed Data				Extrapolated to Equipotent Dose[a]			
Metabolite	**AUC_{0-24}[b]**		**C_{max}**		**AUC_{0-24}**		**C_{max}**	
BID Dose	**SD-809 22.5 mg**	**TBZ 25 mg**	**SD-809 22.5 mg**	**TBZ 25 mg**	**SD-809 24 mg**	**TBZ 50 mg**	**SD-809 24 mg**	**TBZ 50 mg**
M1	498	95	26.8	5.74	531	190	28.6	11.5
M4	257	491	23.8	54.3	274	981	25.4	109

[a] Equipotent Dose=Observed AUC/C_{max} for M1/M4* (24 mg/22.5 mg for SD-809) or (50 mg/25 mg for TBZ)
[b] AUCτ•2=AUC_{0-24}
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; AUCτ, area under the concentration-time curve over the dosing interval; BID, twice daily; C_{max}, maximum concentration AUC=ng•h/mL, C_{max}=ng/mL
To compare their exposures at the maximum recommended daily dose for each treatment, steady-state areas under the concentration-time curve from time 0 to 24 hours post-dose (AUC_{0-24}) were normalized to 24 mg BID SD-809 from the 22.5 mg treatment group or 50 mg BID for tetrabenazine.

Source: NDA 208082, 2.7.2 Summary of Clinical Pharmacology Studies, Table 16

The results from the single-dose mass-balance study show the same trend for M1 exposures.

2.4 Results of the Evaluation of M1 and M4 with Respect to Total Drug Related Material (TDRM)

The systemic exposures to M1 and M4, expressed as a % of TDRM **using $AUC_{0-\infty}$** for both metabolites and TDRM, are shown below. (Note: The applicant has included subject S005 in the analysis even though initially considered excluding this subject).

Applicant's Analysis Using AUC_{inf}

$AUC_{0-\infty}$ (h•ng/mL)	**SD-809 Individual Exposure ($AUC_{0-\infty}$) Parameters and TDRM for M1 and M4 in Subjects S001 through S006 (Cohort 1)**						
	S001	**S002**	**S003**	**S004**	**S005**	**S006**	**Mean (SD)**
M1	346	322	447	223	457	326	353 (87.4)
M4	185	158	294	194	213	243	214 (48)
TDRM	3750	3220	4370	NC[a]	5290	4450	4220 (781)
Metabolite	**SD-809: Percentage of TDRM Ratio in Subjects S001 through S006 (Cohort 1) [b]**						
	S001	**S002**	**S003**	**S004**	**S005**	**S006**	**Mean (SD)**
M1	9.2	10.0	10.2	NC[a]	8.6	7.3	9.1 (1.2)
M4	4.9	4.9	6.7	NC[a]	4.0	5.5	5.2 (1.0)

Data calculated from following equation: $AUC_{0-\infty}$ of M1 or M4/$AUC_{0-\infty}$ of total plasma sample radioactivity
[a] NC = not used for group mean of $AUC_{0-\infty}$ total radioactivity, as %AUC_{extrap} ~45%.

[b] ng equiv were calculated from each plasma sample: ng eq/mL= ((DPM/sample- background dpm)/mL)•% efficiency)) / specific activity for each individual's SD-809 dose (dpm/mg). The ng eq/mL, or total radioactivity, represents the TDRM in each sample.
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinity; DPM, disintegrations per minute; NC, Not calculated; SD, standard deviation; TDRM, total drug-related material

Reviewer's Comments: The applicant used the following criteria for calculating the PK parameters for M1 and M4 (Report DP-2016-065, Section 3.4. Pharmacokinetic Analysis):

For calculating pharmacokinetic parameters, a BLQ value at time 0, at a sampling time before the first quantifiable plasma concentration, or at a sampling time between 2 quantifiable concentrations was treated as zero. All other BLQ values were treated as missing.

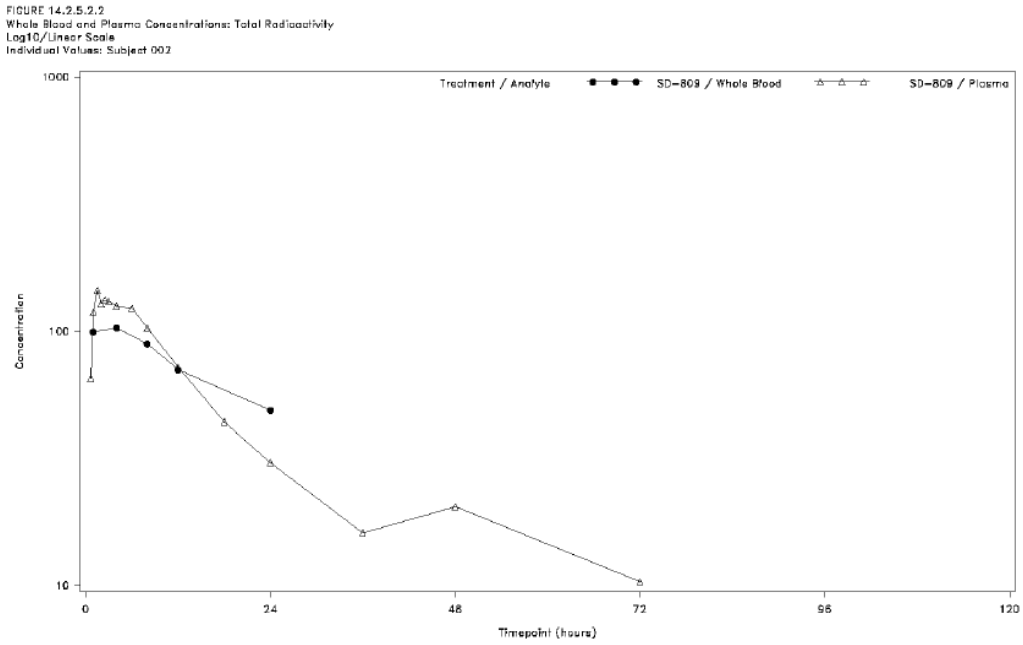
However, the same criteria were not applied to calculating the PK parameters for TDRM. For example, for Subject 006, the BLQ value at 96 h was excluded (instead of setting to 0).

DATA LISTING 16.2.5.5.2
Whole Blood and Plasma Concentrations: Total Radioactivity
Individual Values: All Subjects

Subject Number	Treatment	Time point	Date of Sample	Time of Sample	Total Rad Plasma (ng equiv/mL)
006	SD-809	PREDOSE	03AUG2012	08:10	ND
		20 MIN	03AUG2012	08:50	ND
		40 MIN	03AUG2012	09:10	89.4
		1 H	03AUG2012	09:30	136.5
		1.5 H	03AUG2012	10:00	140.7
		2 H	03AUG2012	10:30	148.5
		2.5 H	03AUG2012	11:00	142.9
		3 H	03AUG2012	11:30	138.9
		4 H	03AUG2012	12:30	138.7
		6 H	03AUG2012	14:30	122.5
		8 H	03AUG2012	16:30	110.2
		12 H	03AUG2012	20:30	86.5
		18 H	04AUG2012	02:30	58.9
		24 H	04AUG2012	08:30	57.1
		36 H	04AUG2012	20:30	39.8
		48 H	05AUG2012	08:30	22.9
		72 H	06AUG2012	08:30	11.6
		96 H	07AUG2012	08:30	ND
		120 H	08AUG2012	08:30	8.6
		144 H	09AUG2012	08:31	ND
		168 H	10AUG2012	08:30	ND
		192 H	11AUG2012	08:30	ND

Source: Clinical Study Report SD-809-C-12 Amendment 01 (b) (4) 113049) Version 2.0 06 March 2015

The reviewer re-analyzed the PK parameters for M1, M4 and TDRM for all subjects using non-compartmental analysis (NCA); the results of this analysis are presented below. Of note, for subjects 002, 004 and 005, the slope (and therefore $AUC_{0-\infty}$ of TDRM) could not be reliably estimated. An example is shown below.



Source: Clinical Study Report SD-809-C-12 Amendment 01 (b) (4) 113049) Version 2.0 06 March 2015

Reviewer's Analysis Using AUC_{inf}

$AUC_{0-\infty}$ (h•ng/mL)	**SD-809 Individual Exposure ($AUC_{0-\infty}$) Parameters and TDRM for M1 and M4 in Subjects S001 through S006 (Cohort 1)**						
	S001	**S002**	**S003**	**S004**	**S005**	**S006**	**Mean (SD)** (SD)
M1	346	322	447	223	457	326	353
M4	185	158	294	194	213	243	214
TDRM	3744	3221	4379	NC[a]	4553	4511	4082
Metabolite	**SD-809: Percentage of TDRM Ratio in Subjects S001 through S006 (Cohort 1)**						
	S001	**S002**	**S003**	**S004**	**S005**	**S006**	**Mean (SD)**
M1	9.2	10.0	10.2	NC[a]	10.0	8.0	9.5
M4	4.9	4.9	6.7	NC[a]	4.7	5.9	5.4

Source: Reviewer's analysis

The systemic exposures to M1 and M4, expressed as a % of TDRM **using AUC_{0-t}** for M1/M4 metabolites and TDRM, are presented below:

AUC_{0-t} (h•ng/mL)	**SD-809 Individual Exposure (AUC_{0-t}) Parameters and TDRM for M1 and M4 in Subjects S001 through S006 (Cohort 1)**						
	S001	S002	S003	S004	S005	S006	**Mean** (SD)
M1	339	319	440	217	448	319	347 (86.5)
M4	181	156	292	191	209	238	211 (48.2)
TDRM	3310	2700	4000	1980	3980	3760	3290 (809)
Metabolite	**SD-809: Percentage of TDRM Ratio in Subjects S001 through S006 (Cohort 1) [a]**						
	S001	**S002**	**S003**	**S004**	**S005**	**S006**	**Mean (SD)**
M1	10.2	11.8	11.0	11.0	11.3	8.5	10.6 (1.2)
M4	5.5	5.8	7.3	9.7	5.3	6.3	6.6 (1.7)

Data calculated from following equation: AUC_{0-t} of M1 or M4/AUC_{0-t} of total plasma sample radioactivity
[a] ng equiv were calculated from each plasma sample: ng eq/mL= ((DPM/sample- background dpm)/mL)•% efficiency)) / specific activity for each individual's SD-809 dose (dpm/mg). The ng eq/mL, or total radioactivity, represents the TDRM in each sample.
Abbreviations: AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; DPM, disintegrations per minute; NC, Not calculated; SD, standard deviation; TDRM, total drug-related material
Source: Reviewer's analysis

2.5 Discussion of the Results of the Evaluation of M1 and M4 with Respect to TDRM

The applicant has validated sensitive assays for M1 and M4 and reanalyzed M1 and M4 in retained clinical samples of subject treated with SD-809 as requested in the Complete Response Letter (May 27, 2016).

The sponsor has re-evaluated the criteria for acceptance of the elimination rate constants (from the original SD-809-C-12 report) and $\%AUC_{extrap}$ to determine which subjects were suitable for calculation of the percentage of total drug-related material for M1. The sponsor has used the following criteria (see Table 1): $r^2 > 0.75$ and $\%AUC_{extrap}$ less than 25% and ratio of the duration of time used to derive the regression constant/half-life >1.

Reviewer's Comments: *The sponsor did not provide a convincing justification for using these acceptance criteria. In addition, the sponsor acknowledges that the elimination rate constant of TDRM cannot be reliably estimated from 2 of the 6 subjects (using the above criteria). in fact, the elimination rate constant of TDRM could not be reliably estimated for 3 of the 6 subjects. It is arguable whether or not excluding half of the subjects dosed with SD-809 in the mass balance study from the estimation of the metabolite/ TDRM ratio is appropriate.*

However, even in the case when the percentage of systemic exposures to M1 and M4 are expressed as a % of TDRM using AUC_{0-t} for M1/M4 metabolites and TDRM (a method which underestimates the total radioactivity but not so much the systemic exposure to M1/M4 due to differences in bioanalytical ranges applied to metabolites and to TDRM), M4 is clearly a minor metabolite (mean 6.6% of TDRM) and M1 is about 10% (mean 10.6% of TDRM).

In addition, the nonclinical studies provided to support the resubmission (pharmacology, pharmacokinetic, and genetic toxicology studies of metabolites M1 and M4) do not show any findings of concern. Therefore, we believe the concerns raised during the original NDA review about M1/M4 are addressed in this resubmission.

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Appendix

Updates to the Biopharmaceutic Studies and Associated Analytical Methods

Liquid chromatography with tandem mass spectrometry (LC-MS/MS) bioanalytical methods for M1 (2-methylpropanoic acid-β HTBZ) and M4 (monohydroxy SD-809) have been validated and used for the analysis of retained clinical plasma samples from studies SD-809-C-12 and AUS-SD-809-CTP-07, Part 2 for these metabolites.

Note: Separate validated LC-MS/MS methods were used to measure plasma concentrations of SD-809, its deuterated α-HTBZ and β-HTBZ metabolites (SD-809-CLN-12) and ODM (SD-809-CLN-051) and tetrabenazine, its nondeuterated α-HTBZ and β-HTBZ metabolites (SD-809-CLN-11) and ODM metabolites (SD-809-CLN-50) in all clinical studies. The results from these analyses and the validation reports were discussed in the original NDA submission (see Clinical Pharmacology review Apr 8, 2016).

Summary of Method Validation for M1 and M4 Metabolites of SD-809 and Tetrabenazine by LC-MS/MS in Human Plasma Containing Lithium Heparin as Anticoagulant

Document Control Number: Report Type	Analyte	Standard Curve Range (ng/mL)	Precision[a] (%CV)		Accuracy[b] over Assay Range (%)		Stability
			Intra	Inter	Intra	Inter	
DP-2016-069: method validation report	Nondeuterated M1 (SD-1027)	0.2 to 200	1.0 to 8.9	2.3 to 7.7	-5.8 to 9.0	-2.7 to 1.3	Room temperature: 25 h Freeze/thaw: 5 cycles Long-term stability: 145 days @ -80°C
	Nondeuterated M4 (SD-1026)		1.2 to 6.7	2.1 to 4.5	-4.7 to 5.3	-3.3 to 2.8	
DP-2016-068: method validation report	Deuterated M1 (SD-1021)	0.2 to 200	0.9 to 5.1	1.9 to 4.9	-3.3 to 5.7	-2.7 to 3.2	Room temperature: 24 h Freeze/thaw: 5 cycles Long-term stability: 145 days @ -80°C
	Deuterated M4 (SD-1018)		1.5 to 7.7	2.2 to 5.1	-2.7 to 6.5	-2.0 to 4.3	
DP-2016-127: fit for purpose method validation report	Nondeuterated M1 (SD-1027)	0.2 to 200	1.0 to 9.1	3.8 to 6.6	0.0 to 3.7	-3.5 to 2.7	Room temperate: 24 h Long term stability: 449 days @ -80°C
DP-2016-126: fit for purpose method validation report	Deuterated M1 (SD-1021)	0.2 to 200	1.7 to 6.9	2.3 to 10.4	-3.7 to 4.5	-5.3 to -0.5	Room temperate: 24 h Long term stability: 449 days @ -80°C

[a] Precision: (SD/Mean Measured Concentration) x 100
[b] Accuracy: [(Mean Measured Concentration – Nominal Concentration) x 100]/ Nominal Concentration
Abbreviations: CV, coefficient of variation; HTBZ, dihydrotetrabenazine; SD, standard deviation.

The validated methods used to quantify deuterated and non-deuterated M1 and M4 metabolites in human plasma demonstrated stability of all analytes for at least 140 days in samples stored at -80ºC. Prior to availability of the validated methods, qualified (fit for purpose) methods for deuterated and non-deuterated M1 in human plasma demonstrated

stability for at least 449 days in samples stored at -80ºC (DP-2016-126 and DP-2016-127). The "qualified methods" were not validated.

In all validation reports, the following analyte ID numbers were used:

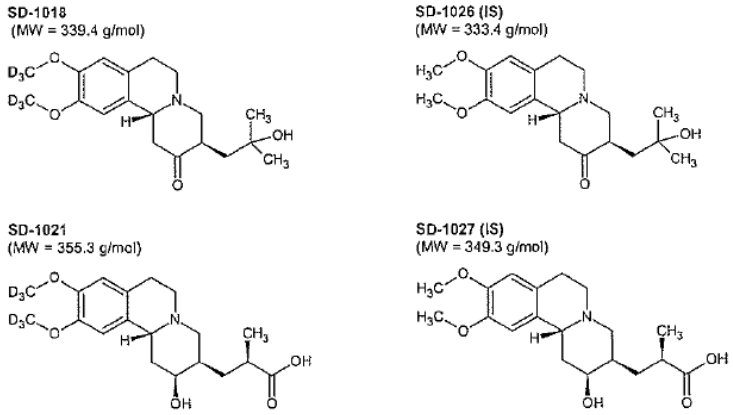
Table A1: Analyte Identification Numbers

Analyte	SD #	TEV #	Metabolite ID
Deuterated (d6-) tetrabenazine	809	50717	NA
Deuterated 2-methylpropanoic acid-β-HTBZ	1021	NA	M1
Deuterated monohydroxy tetrabenazine	1018	NA	M4
Tetrabenazine	808	48923	NA
2-methylpropanoic acid-β-HTBZ	1027	NA	M1
monohydroxy tetrabenazine	1026	NA	M4

Validation Report DP-2016-068 (b) (4) Project Code: VAL194)

The objective of this study was to validate a method for analysis of SD-1021 (d6-M1) metabolite and SD-1018 (d6-M4) metabolite of SD-809 (d6-tetrabenazine) in human plasma containing lithium heparin (LiH) as anticoagulant.

The method extracts SD-1018 and SD-1021 and the Internal Standards (SD-1026 and SD-1027, respectively) from human plasma using a protein precipitation procedure. The analytes are separated by HPLC on a C18 column, and the eluates monitored by an API4000 MS/MS detector in positive MRM mode. The data are acquired and processed by the data acquisition system Analyst® (Sciex) linked directly to the API4000 MS/MS detector and then processed in Watson LIMS™ (Thermo Scientific), where applicable. The method range is from 0.200 to 200 ng/mL for both SD-1018 and SD-1021 using 20 µL of plasma and has a run time of approximately 5.5 minutes per sample.



The method was fully validated to investigate method selectivity*, accuracy & precision (including sensitivity at LLOQ), recovery, linearity, dilution, the effect of haemolysis and lipaemia on quantitation, matrix factor and matrix effects, ruggedness (e.g. system and analyst) and stability (i.e. freeze/thaw, benchtop, processed stability, reinjection, stock solutions**, long term** and whole blood).

*OTC drugs: No interference with the analyte or IS was observed when tested with acetaminophen, amoxicillin, aspirin, caffeine, chlorpheniramine maleate, lidocaine, naproxen, desipramine, ibuprofen, RR(-)-pseudoephedrine, salicylic acid, theobromine, theophylline, tetracycline and xanthine.

**Long term stability in plasma and stock solution stability (145 days) was reported as an addendum (Sept 14, 2016) to the validation report.

Validation Results

Method	**ALM-194**	
Matrix (Anticoagulant)	Human plasma (Lithium Heparin)	
Analyte	SD-1018	SD-1021
Internal Standard	SD-1026	SD-1027
Calibration Range	0.200 to 200 ng/mL	0.200 to 200 ng/mL
Linearity	Coefficient of determination for curves run during validation $r^2 \geq 0.9966$	Coefficient of determination for curves run during validation $r^2 \geq 0.9929$
Inter-Assay Precision (Mean % CV)	Between 2.2% and 5.1% n=18 (PQCL, PQCM, PQCH) PQCLOQ 10.1% n=18	Between 1.9% and 4.9% n=18 (PQCL, PQCM, PQCH) PQCLOQ 10.7% n=18
Inter-Assay Accuracy (% Rel. Error)	Between -2.0% and 4.3% n=18 (PQCL, PQCM, PQCH) PQCLOQ 3.0% n=18	Between -2.7% and 3.2% n=18 (PQCL, PQCM, PQCH) PQCLOQ 1.0% n=18
Intra-Assay Precision (Mean % CV)	Between 1.5% and 7.7% n=6 on 3 occasions (PQCL, PQCM, PQCH) PQCLOQ between 4.4% and 11.3% n=6 on 3 occasions	Between 0.9% and 5.1% n=6 on 3 occasions (PQCL, PQCM, PQCH) PQCLOQ between 7.9% and 10.1% n=6 on 3 occasions
Intra-Assay Accuracy (% Rel. Error)	Between -2.7% and 6.5% n=6 on 3 occasions (PQCL, PQCM, PQCH) PQCLOQ between -5.0% and 10.0% n=6 on 3 occasions	Between -3.3% and 5.7% n=6 on 3 occasions (PQCL, PQCM, PQCL) PQCLOQ between -4.0% and 10.0% n=6 on 3 occasions

Reviewer's Comment: The validation results are acceptable.

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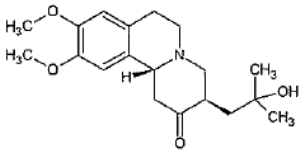
Validation Report DP-2016-069 ((b) (4) Project Code: VAL195)

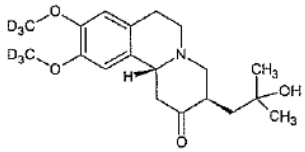
The objective of this study was to fully validate a method for the determination of SD-1027 (d0-M1) metabolite and SD-1026 (d0-M4) metabolite of tetrabenazine in human plasma containing lithium heparin (LiH) as anticoagulant.

The method extracts SD-1026 and SD-1027 and the Internal Standards (SD-1018 and SD-1021, respectively) from human plasma using a protein precipitation procedure. The analytes are separated by HPLC on a C18 column, and the eluates monitored by an API4000 MS/MS detector in positive MRM mode. The data are acquired and processed by the data acquisition system Analyst® (Sciex) linked directly to the API4000 MS/MS detector and then processed in Watson LIMS™ (Thermo Scientific), where applicable. The method range is from 0.200 to 200 ng/mL for both SD-1026 and SD-1027 using 20 µL of plasma and has a run time of approximately 5.5 minutes per sample.

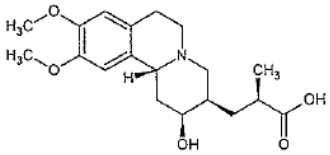
SD-1026
(MW =333.4 g/mol)



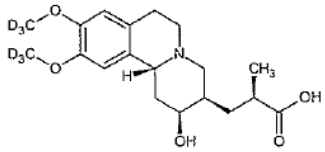
SD-1018 (IS)
(MW = 339.4 g/mol)



SD-1027
(MW =349.3 g/mol)



SD-1021 (IS)
(MW = 355.3 g/mol)



Analyte ID	Q1 Mass (Da)	Q3 Mass (Da)	Dwell (msec)
SD-1018	340.4	198.1	60
SD-1021	356.3	171.1	60
SD-1026	334.3	192.0	80
SD-1027	350.3	165.2	80

The method was fully validated to investigate method selectivity, accuracy & precision (including sensitivity at LLOQ), recovery, linearity, dilution, the effect of haemolysis and lipaemia on quantitation, matrix factor and matrix effects, ruggedness (e.g. system and analyst) and stability (i.e. freeze/thaw, benchtop, processed stability, reinjection, stock solutions, long term and whole blood).

Validation Results

Method	**ALM-195**	
Matrix (Anticoagulant)	Human plasma (Lithium Heparin)	
Analyte	SD-1026	SD-1027
Internal Standard	SD-1018	SD-1021
Calibration Range	0.200 to 200 ng/mL	0.200 to 200 ng/mL

Linearity	Coefficient of determination for curves run during validation $r^2 \geq 0.9942$	Coefficient of determination for curves run during validation $r^2 \geq 0.9929$
Inter-Assay Precision (Mean % CV)	Between 2.1% and 4.5% n= 24 (PQCL, PQCH), n=23 (PQCM) PQCLOQ 14.9% n=24	Between 2.3% and 7.7% n= 18 (PQCL, PQCH), n=23 (PQCM) PQCLOQ 16.8% n=24
Inter-Assay Accuracy (% Rel. Error)	Between -3.3% and 2.8% n= 24 (PQCL, PQCH), n= 23 (PQCM) PQCLOQ 8.0% n=24	Between -2.7% and 1.3% n= 24 (PQCL, PQCH), n=23 (PQCM) PQCLOQ 6.0% n=24
Intra-Assay Precision (Mean % CV)	Between 1.2% and 6.7% n=6 on 4 occasions (PQCL, PQCH) n=6 on 3 occasions and n= 5 on 1 occasion (PQCM) PQCLOQ between 7.8% and 19.3% n= 6 on 4 occasions	Between 1.0% and 8.9% n=6 on 4 occasions (PQCL, PQCH) n=6 on 3 occasions and n= 5 on 1 occasion (PQCM) PQCLOQ between 6.6% and 12.8% n=6 on 4 occasions
Intra-Assay Accuracy (% Rel. Error)	Between -4.7% and 5.3% n=6 on 4 occasions (PQCL, PQCH) n=6 on 3 occasions and n= 5 on 1 occasion (PQCM) PQCLOQ between -1.5% and 19.0% n=6 on 4 occasions	Between -5.8% and 9.0% n=6 on 4 occasions (PQCL, PQCH) n=6 on 3 occasions and n=5 on 1 occasion (PQCM) PQCLOQ between -5.5% and 12.5% n=6 on 3 occasions

Reviewer's Comment: The validation results are acceptable.

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/s/

HRISTINA DIMOVA
02/23/2017

SREEDHARAN N SABARINATH
02/23/2017

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Deutetrabenazine (SD-809)
PRODUCT (Brand Name):	Austedo
NDA:	208082
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	6 mg, 9 mg and 12 mg
INDICATION:	Treatment of chorea associated with Huntington's disease (HD)
NDA TYPE	Standard
SUBMISSION DATE:	May 29, 2015
SPONSOR:	Teva Pharmaceuticals, Inc
PRIMARY REVIEWER:	Hristina Dimova, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
PHARMACOMETRICS REVIEWER:	Xiaofeng Wang, Ph.D.
PHARMACOMETRICS TEAM LEADER:	Kevin Krudys, Ph.D.
GENOMICS REVIEWERS:	Jeffrey Kraft, Ph.D. Christian Grimstein, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

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1.0 EXECUTIVE SUMMARY

This is a 505(b)(2) NDA submission for SD-809 with Xenazine (Tetrabenazine, NDA 021894) as the referenced listed drug (RLD). The proposed indication is to treat chorea associated with Huntington's disease (HD) with individualized dosing regimen for each patient established through titration to achieve optimal chorea control and tolerability (6 mg to 48 mg per day).

Tetrabenazine (TBZ) has been approved in the United States in 2008 as Xenazine for the treatment of chorea associated with HD. Orally administered TBZ is rapidly converted in the liver by carbonyl reductase to its active metabolites alpha-dihydrotetrabenazine (α-HTBZ) and beta-dihydrotetrabenazine (β-HTBZ), which mediate the in vivo efficacy of TBZ. Alpha (α)-HTBZ and β-HTBZ are subsequently metabolized principally by CYP2D6. SD-809 is a selectively deuterated form of TBZ in which the two O-linked methyl groups (CH_3) of the TBZ molecule have been replaced by two trideuteromethyl groups (CD_3). This deuteration is expected to increase the half-life of d6-α-HTBZ and d6-β-HTBZ and reduce the impact of CYP2D6 status due to genotype or concomitant medication usage.

The safety and pharmacokinetics (PK) of SD-809 have been evaluated in six Phase 1 studies in healthy subjects, including a mass balance study to compare the metabolism of SD-809 to that of TBZ, a DDI study with a strong CYP2D6 inhibitor, a food effect study and a QTc study. The primary efficacy data for this application are based on SD-809-C-15 (First-HD), a Phase 3 randomized, double-blind, placebo-controlled trial of SD-809 in patients with chorea associated with HD (N=90). Supportive efficacy data are included from SD-809-C-16 (ARC-HD), an ongoing Phase 3, open-label, long-term safety trial (N=112). ARC-HD included two cohorts of subjects, ARC-Rollover and ARC-Switch. ARC-Switch subjects were previously on a stable regimen of Xenazine, then were switched overnight to an initial SD-809 dosing regimen predicted to provide comparable exposure to total (α+β)-HTBZ relative to their prior Xenazine dose.

1.1 RECOMMENDATION

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

- The proposed dose range of SD-809 (6 mg to 48 mg per day), selected to match the systemic exposure to total (α+β)-HTBZ across the range of approved Xenazine dose, is supported by results of the efficacy trial and is acceptable.
- The sponsor's PK bridging strategy (in ARC-Switch study) to demonstrate comparable bioavailability to justify the reliance on Xenazine for a 505(b)(2) application, for which the primary basis of approval will be a clinical efficacy trial, is acceptable.
- The adequacy of the safety database and the ability to rely on the Agency's determination that TBZ is safe depends, in part, on how similar SD-809 is to

Xenazine with respect to the levels of the active metabolites and on the condition that there are no new significant metabolites that are unique to SD-809. However, the results of the mass balance study (SD-809-C-12) to compare the metabolism of SD-809 to that of TBZ are inconclusive. It is recommended that the sponsor assess the concentration of circulating SD-809-related metabolites for the purpose of determining if there are major metabolites in humans dosed with SD-809. Whether this could be done post approval will be decided by the non-clinical and clinical teams.

- The daily dose of SD-809 should not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.
- The activity (VMAT2 and off-target binding) of the metabolites M1 and M4 should be evaluated. This could be done post approval as a PMR.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Parent compounds SD-809 and TBZ are rapidly and extensively metabolized to α-HTBZ and β-HTBZ, which exhibit considerably greater exposure in plasma than parent. The α-HTBZ and β-HTBZ metabolites of SD-809 and TBZ are potent inhibitors of VMAT2 in the central nervous system and contribute to the therapeutic benefit of both molecules for the reduction of chorea in patients with HD. *In vitro* studies of VMAT2, the primary pharmacological target of SD-809 and TBZ, indicated that the HTBZ metabolites from both compounds inhibited VMAT2 binding.

General Pharmacokinetics (ADME characteristics) of SD-809
Absorption: Following oral administration of SD-809, the extent of absorption is >80%. After oral dosing, plasma concentrations of SD-809 are generally below the limit of detection by 3 hours post-dose because of the rapid and extensive hepatic metabolism of SD-809 by carbonyl reductase to the active metabolites α-HTBZ and β-HTBZ. Peak plasma concentrations (C_{max}) of α-HTBZ and β-HTBZ are reached within 3 to 4 hours post-dosing. Food had no effect on (α+β)-HTBZ AUC, however Cmax was increased by approximately 50% with food. SD-809 was administered with food in all clinical studies and is recommended to be administered with food; this is acceptable.
Distribution: The median volume of distribution (Vc/F) of the α-HTBZ, and the β-HTBZ metabolites are approximately 500 L and 730 L, respectively, in the HD patient population (Population PK report SD-809-CLN-078).
Metabolism: SD-809, like TBZ, is rapidly converted by carbonyl reductase to the active metabolites α-HTBZ and β-HTBZ, which are O-dealkylated by CYP450 enzymes, principally CYP2D6 (with minor contribution of CYP1A2), to form 9- and 10-desmethyl-α- and β-DHTBZ. Subsequently, they are metabolized to sulfate or glucuronide conjugates.
Systemic exposure to total (α+β)-HTBZ following SD-809 administration is approximately 2-fold greater than following TBZ administration.
At least two major circulating metabolites, α-HTBZ and monohydroxy tetrabenazine (M4), have been identified after oral administration of SD-809; however the metabolite profiling and identification results of the mass balance study are inconclusive.

Elimination: SD-809 is primarily renally eliminated in the form of metabolites (83% of the dose recovered in the urine). The half-life of total (α+β)-HTBZ from SD-809 is approximately 9 to 10 hours.
Dose proportionality: A linear dose dependence of C_{max} and AUC was observed for the active metabolites α-HTBZ and β-HTBZ following single or multiple doses of SD-809 (6 mg to 24 mg and 7.5 mg BID to 22.5 mg BID).
Pharmacokinetics in patients:
PK of SD-809 was similar between healthy subjects and HD patients based on comparision between phase 1 study data in healthy subjects and exposure data in HD patients derived from popPK analysis.
Intrinsic Factors:
The pharmacokinetics of SD-809 and its primary metabolites have not been formally studied in specific populations, including pediatric, geriatric subjects and patients with renal or hepatic impairment. There was no apparent effect of gender on the PK of α-HTBZ or β-HTBZ.
Per the Xenazine label, the exposure to α-HTBZ and β-HTBZ was 30-39% greater in patients with hepatic impairment and the mean TBZ C_{max} in hepatically impaired subjects was approximately 7- to 190-fold higher than that in healthy subjects. Similar to Xenazine, SD-809 is contraindicated for patients with hepatic impairment.
CYP2D6 poor metabolizers: please refer to Extrinsic Factors below.
Extrinsic Factors:
SD-809, like TBZ, is rapidly converted in the liver by carbonyl reductase to its active metabolites α-HTBZ and β-HTBZ, which are subsequently metabolized principally by CYP2D6. Strong CYP2D6 inhibitors markedly increase exposure to the active metabolites of TBZ (Xenazine label). The daily dose of Xenazine should not exceed 50 mg per day and the maximum single dose of Xenazine should not exceed 25 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers. The sponsor proposes to remove this restriction for SD-809 as the metabolism of deuterated α-HTBZ and β-HTBZ by CYP2D6 is attenuated relative to non-deuterated α-HTBZ and β-HTBZ. However, the results of an in vivo drug-drug interaction (DDI) study conducted with SD-809 still showed a 3-fold increase in total (α+β)-HTBZ exposures when a strong CYP2D6 inhibitor (paroxetine) was co-administered with SD-809. Because of this, the SD-809 dose was capped at 18 mg BID (36 mg daily) in patients taking strong CYP2D6 inhibitors in the efficacy and safety trials. Therefore, the daily dose of SD-809 should not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.
In Vitro Studies: *In vitro* metabolism studies (conducted with TBZ) indicated that there is no meaningful inhibition or induction of CYP-based enzymes by TBZ and its metabolites α-HTBZ and β-HTBZ at concentrations that are relevant for dosing. In addition, the SD-809 metabolites with exposures >25% of (α+β)-HTBZ, e.g. 2-methylpropanoic acid metabolite of β-HTBZ (M1) and monohydroxy tetrabenazine (M4), have been evaluated in a panel of in vitro DDI studies; the results indicate that M1/M4 are not expected to cause clinically relevant drug interactions.
Biopharmaceutics:
The biopharmaceutics team has identified the presence of (b) (4) excipients in the proposed drug product; in addition, during the clinical development, the sponsor

referred to their product as [redacted] formulation of SD-809. However, an [redacted] claim was not requested for the proposed drug product in the NDA. The biopharmaceutics team will address this issue.

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: tablet (6, 9, or 12 mg)

Indication: treatment of chorea associated with Huntington's disease

Pharmacologic Class: vesicular monoamine transporter 2 (VMAT2) inhibitor

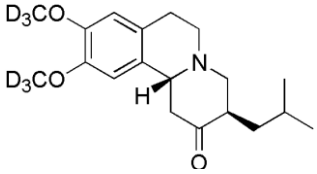
Chemical Name: RR, SS)-1, 3, 4, 6, 7, 11b-hexahydro-9, 10-di(methoxy-d3)-3-(2-methylpropyl)-2Hbenzo[a]quinolizin-2-one.

International Non-Proprietary Name: Deutetrabenazine

Molecular formula: $C_{19}H_{21}D_6NO_3$

Molecular mass: 323.46 g/mol

Chemical structure:



Physical Characteristics: white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol. The pKa is 6.31.

Formulation: AUSTEDO tablets contain deutetrabenazine as the active ingredient and the following inactive ingredients: ammonium hydroxide, black iron oxide, n-butyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyethylene oxide, polysorbate 80, polyvinyl alcohol, povidone, propylene glycol, shellac, talc, titanium dioxide, and FD&C blue #2 lake. The 6 mg tablets also contain FD&C red #40 lake. The 12 mg tablets also contain FD&C yellow #6 lake.
Note: In the assessment of the formulation of the proposed drug product, the biopharmaceutics team has identified the presence of [redacted] excipients; however, an [redacted] claim was not requested for the proposed drug product in the NDA.

2.1.2 Mechanism of action and therapeutic indication:

The precise mechanism by which deutetrabenazine (SD-809) 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-HTBZ and β-HTBZ metabolites of SD-809 are potent inhibitors of VMAT2 in the central nervous system and contribute to the therapeutic benefit of SD-809 for the reduction of chorea in patients with HD.

2.1.3 Proposed dosages and route of administration:

Starting dose (6 mg, QD) should be titrated up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea. Doses of 12 mg per day and higher should be given as two divided doses. (b) (4) (b) (4) (b) (4) The maximum recommended SD-809 daily dose is 48 mg (maximum single dose of 24 mg).

OCP Recommendation: The maximum daily dose in patients who are CYP2D6 poor metabolizers (PMs) or are taking strong CYP2D6 inhibitors is 36 mg with a maximum single dose of 18 mg.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

The studies (clinical pharmacology or clinical) that support dosing or claims/indication, are presented in the table below. In addition, a population PK report (SD-809-CLN-078) described the pharmacokinetics of SD-809 in the HD patient population.

The clinical pharmacology program established that the SD-809 dose range of 6 mg to 48 mg per day provides comparable systemic exposure (AUC) to Xenazine 12.5 to 100 mg per day, but with lower C_{max} values. This dose range is supported by the results of the efficacy tial SD-809-C-15 (First-HD).

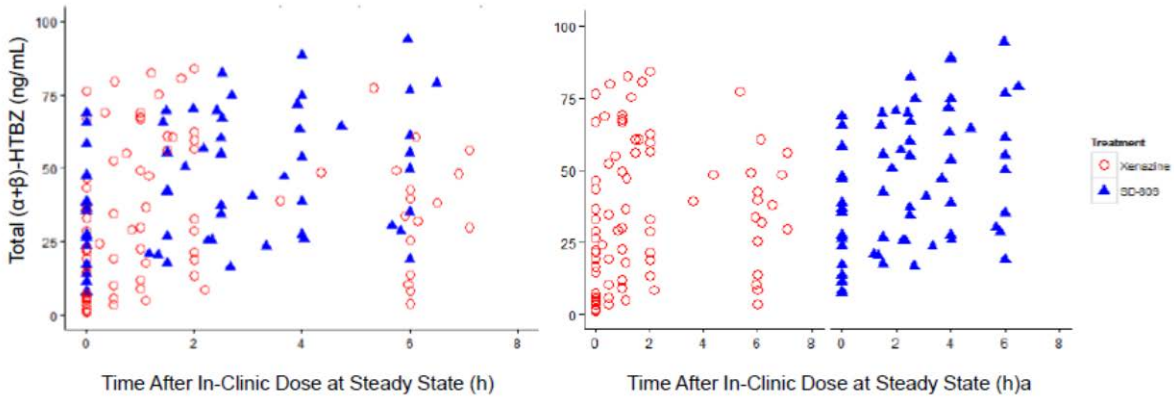
PK Bridging Strategy

A US approved Xenazine tablets was not available for PK bridging (to the listed drug) in the Phase 1 studies. Exposure to the active α-HTBZ and β-HTBZ metabolites of SD-809 and TBZ was evaluated in Phase 1 studies, in which TBZ was administered as unformulated powder-in-capsule and as commercially available tablets sourced from (b) (4). Xenazine was only available as a baseline medication in Study SD-809-C-16, Switch Cohort. Subjects in the Switch Cohort were converted from their existing Xenazine dosing regimen to an SD-809 regimen predicted to provide comparable daily exposure (AUC) of total (α+β)-HTBZ relative to the subject's prior Xenazine dose.

PK data were collected in 12 subjects using a rich sampling scheme (5 samples/subject over 6 hours post-dose) and in 24 subjects using a sparse sampling scheme (2 samples/subject).

To establish a bridge between Xenazine and SD-809 exposure over the intended dose range, two approaches were used.
In the first, non-normalized plasma concentrations of total (α+β)-HTBZ were compared from samples collected pre and post in-clinic visit, allowing comparison of Xenazine (baseline visit) with SD-809 (Week 8 visit).

Non-normalized total (α+β)-HTBZ plasma concentrations at Baseline (Xenazine) and at Week 8 (SD-809)



Note: At Week 8 the SD-809 dose could be different (after 2:1 conversion) from that at Week 0 (Xenazine) for the same subject.

Therefore, in addition to presenting all available concentration data as in the figure above, concentrations and parameters were analyzed (normalized) to enable comparison across a variety of dose levels. The parameters were normalized to the highest recommended single dose for each treatment (24 mg of SD-809 and 37.5 mg of Xenazine).

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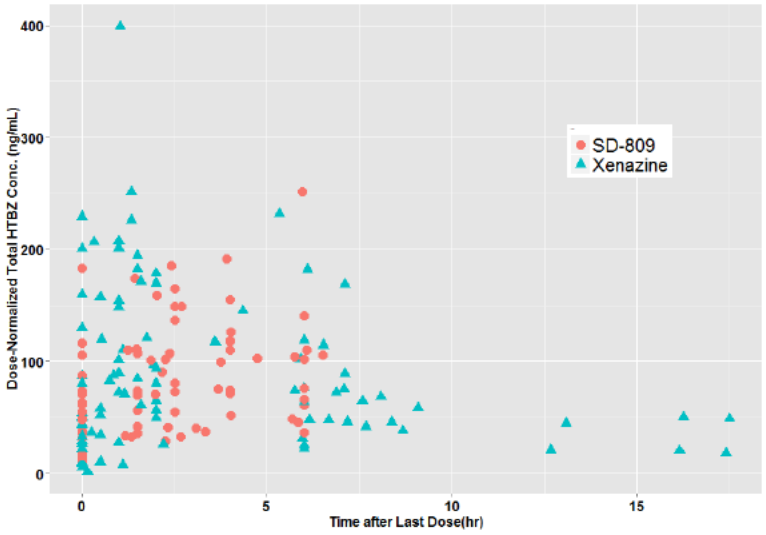
Dose-normalized Plasma Concentrations of Total (α+β)-HTBZ in the Switch Cohort of Study SD-809-C-16 (dose normalized to the maximum single dose for each treatment)



Cmax Comparison between Xenazine and SD-809 in ARC-SWITCH, Dose-normalized (from the pharmacometrics review)

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

Notes: Data came from ARC-SWITCH study (rich sampling subgroup; n=11 for both Xenazine and SD-809).

Due to the approximate 9-hour half-life of total (α+β)-HTBZ for SD-809 at steady state and the approximate 6-hour half-life of total (α+β)-HTBZ for Xenazine, the 6-hour sampling interval in ARC-Switch was not long enough for adequate estimation of AUC values for comparison of Xenazine and SD-809.

Reviewer's Comments: Since the sponsor has conducted an efficacy study using the SD-809 commercial formulation, the goal of the PK bridging was to ensure that total (α+β)-HTBZ plasma concentrations after SD-809 administration are in the range (not higher) than these after Xenazine administration; there is no need to demonstrate bioequivalence (BE). The results of this analysis show that C_{max} of SD-809 at highest proposed dose is not higher than C_{max} of Xenazine at highest approved dose. Further details of the bridging strategy analysis will be provided in the pharmacometrics review.
This strategy is also considered acceptable by OND/ODEI and ORP.
Additional bridging is required to provide evidence that the exposures to TBZ/SD-809 metabolites are similar for both TBZ and SD-809 and that the SD-809 metabolites are not expected to represent an increased safety risk for patients after dose adjustment. This is discussed in Sect. 2.2.8 and the Individual study (SD-809-C-12) review.

Summary of Design Features of Pharmacology and Clinical Studies of SD-809

Study Number	Design	Subject Population	Subject Characteristics	Treatment	Number of subjects exposed to SD-809
Phase 1 Studies with SD-809 Unformulated Powder-in-Capsule and Tetrabenazine Unformulated Powder-in-Capsule[a]					
AUS-SD-809-CTP-06	Randomized, double-blind, single-dose, 2-way crossover study of the PK, safety, and tolerability of SD-809 and tetrabenazine	Healthy adult volunteers	Age range 18-39 years 48% male	SD-809 25 mg (single dose) Tetrabenazine 25 mg (single dose)	21 subjects
SD-809-C-12	Open-label, sequential-group study to evaluate mass balance recovery, metabolite profile, and metabolite identification of SD-809 and tetrabenazine	Healthy adult volunteers	Age range 37-62 years 100% male	Cohort 1: [^{14}C]-SD-809 25 mg (single dose) Cohort 2: [^{14}C]-tetrabenazine 25 mg (single dose)	6 subjects (+6 subjects exposed to tetrabenazine only)
Phase 1 Studies with SD-809 Tablets and Tetrabenazine Commercially Available Tablets					
AUS-SD-809-CTP-07 Part 2	Open-label, sequential-group, single and multiple ascending dose study of the PK, safety, and tolerability of SD-809 and tetrabenazine	Healthy adult volunteers	Age range 18-42 years 71% male	SD-809 7.5 mg, 15 mg, and/or 22.5 mg (single dose; repeated doses) Tetrabenazine[b] 25 mg (single dose; repeated doses)	24 subjects
SD-809-C-21	Randomized, double-blind, placebo- and positive-controlled, 6-period crossover study to evaluate the effects of SD-809 and tetrabenazine on cardiac repolarization	Healthy adult volunteers	Age range 18-49 years 75% male	SD-809 12 or 24 mg Tetrabenazine[c] 25 mg Moxifloxacin 400 mg Placebo equivalents	46 subjects
Phase 1 Drug-Drug Interaction Study with SD-809 Tablets and Paroxetine					
SD-809-C-08	Open-label, drug-drug interaction (DDI) study of single doses of SD-809 and repeated doses of paroxetine in CYP2D6 Extensive Metabolizers and Intermediate Metabolizers	Healthy adult volunteers	Age range 19-49 years 67% male	SD-809 22.5 mg (single dose on Day 1 and Day 11) Paroxetine 20 mg on Days 4 through 12	24 subjects
Phase 3 Studies with SD-809 Tablets					
SD-809-C-15 (First-HD)	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of SD-809 in subjects with chorea associated with HD	Adult subjects with manifest HD and chorea	Age range 23-74 years 56% male	SD-809 or placebo 6 mg/day to 48 mg per day, administered BID, titrated based on chorea control and tolerability	45 subjects
SD-809-C-16 (ARC-HD), ARC-Rollover	Open-label, single-arm, long-term safety study of SD-809	Adult subjects with HD and chorea who completed First-HD	Age range 23-75 years 57% male	SD-809 6 mg/day to 72 mg/day, administered BID, titrated based on chorea control and tolerability	75 subjects[d]

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

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

2.2.2 What are the clinical endpoints and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint in the pivotal, randomized, double-blind, placebo-controlled trial SD-809-C-15 (First-HD) was the change from Baseline to maintenance therapy in Total Maximal Chorea (TMC) score.
Secondary Efficacy Endpoints (tested in hierarchical manner) included Patient Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC), Short Form 36 Health Survey (SF-36) physical functioning scale and Change in Total Motor Score (TMS) from UHDRS from Baseline to maintenance therapy.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

An exposure-effectiveness relationship has not been established for SD-809. In the pivtal efficacy trial SD-809-C-15, the dose was individually tritrated and intended to match the systemic exposure to total (α+β)-HTBZ across the range of approved Xenazine dose levels.

2.2.4 What are the characteristics of exposure-safety relationships?

A statistically significant exposure response relationship has been observed between total (α+ β) –HTBZ and QT prolongation in the TQT study SD-809-C-21.The results show that the maximum time-matched, placebo-adjusted change in QTcF for the SD-809 top dose of 24 mg was 4.5 msec, with an upper bound of the 90% two-sided CI of 6.5 ms. However, there is a limitation of this TQT study that the α- and β-HTBZ concentrations achieved with the highest dose (single dose of 24 mg SD-809), do not cover the expected steady state exposure following the highest therapeutic dose of 24 mg b.i.d. and the worst case clinical scenario (CYP2D6 poor metabolizer or administration of aa strong CYP2D6

inhibitor). Therefore, it was concluded by the QT review team that clinically relevant QT prolongation might be expected in some patients at the highest therapeutic dose of 24 mg b.i.d., especially in CYP2D6 poor metabolizers or patients co-administered a strong CYP2D6 inhibitor. Moreover, these findings are in line with those for Xenazine.

2.2.5 Are the proposed dosage regimens adequately supported by the clinical trials and consistent with the dose-response relationship?

Yes. The SD-809 dose range was selected to match the systemic exposure to total (α+β)-HTBZ across the range of approved Xenazine dose levels (12.5 mg to 100 mg per day). Based on Phase 1 study results and modeling and simulations, the dose range for SD-809 was predicted to be 6 mg to 48 mg per day, e.g. half the milligram dose of TBZ. This dosing is supported by the efficacy results of the pivotal trial SD-809-C-15 (First-HD). In addition, in the second phase 3 trial SD-809-C-16 (ARC-HD), subjects who switched overnight from a stable dosing regimen of Xenazine to a predicted AUC-matched dosing regimen of SD-809 experienced no loss in control of chorea, as assessed by the UHDRS TMC and Total Motor Scores, at Week 1.
Dose adjustment was permitted after Week 1; the mean weekly dose was increased from 20.3 at Week 1 to 33.5 mg at Week 8, indicating potential improvement in chorea control and/or improvement in tolerability following SD-809 dose adjustment.
Please refer to the review by Dr Kenneth Bergmann (Medical Officer, DNP) for more details.

2.2.6 Does SD-809 prolong QT or QTc interval?

A randomized, double-blind, placebo- and positive-controlled, six-period, crossover study was conducted to evaluate the effects of SD-809 and TBZ on the corrected QT (QTc) interval (study SD-809-C-21).
However, according to the Interdisciplinary Review Team, the design of this study is not adequate to evaluate the effect of study drugs on the QT interval:
There is a clear limitation of this TQT study that the plasma alpha- and beta-HTBZ concentrations achieved with the single dose of 24 mg SD-809 do not cover the expected steady state exposure (Cmax) following the highest therapeutic dose of 24 mg b.i.d. and the worst case clinical scenario (CYP2D6 poor metabolizer or administered a strong CYP2D6 inhibitor). Similar to Xenazine, a statistically significant exposure response relationship between the sum concentration of the active metabolites (α+β) and QT has been observed. Clinically relevant QT prolongation might be expected in some patients at the highest therapeutic dose of 24 mg b.i.d., especially in CYP2D6 poor metabolizers or patients co-administered a strong CYP2D6 inhibitor.

2.2.7 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Two validated assays were used: ALM.TBZ.1 for measuring the concentrations of TBZ and its α- and β-HTBZ metabolites in human plasma and ALM.SD809.1 for SD-809

and its deuterated α- and β-HTBZ metabolites with ranges 0.100 ng/mL to 10.0 ng/mL for SD-809 or TBZ and 0.500 ng/mL to 100 ng/mL for HTBZ metabolites.
Separate validated assays were used to measure the 9-O- and 10-O-desmethyl metabolites of deuterated and non-deuterated α-HTBZ and β-HTBZ (SD-809-CLN-050 and SD-809-CLN-051) with ranges 0.500 to 50.0 ng/mL for O-desmethyl-metabolites.
Details pertaining to assay methodology, assay validation, acceptance criteria, and stability are provided in Section 2.6 and the individual study reviews.

2.2.8 What are the general ADME characterstics of SD-809?

Absorption:

After oral dosing, plasma concentrations of SD-809 were very low because of the rapid and extensive hepatic metabolism of SD-809 to the active metabolites α-HTBZ and β-HTBZ.

	Mean (CV%) N=30 (Per-Protocol PK Analysis Set)				
	A: 6 mg SD-809 Standard Meal	B: 12 mg SD-809 Standard Meal	C: 18 mg SD-809 Standard Meal	D: 24 mg SD-809 Standard Meal	E: 18 mg SD-809 High-Fat Meal
Parent Drug (SD-809)					
C_{max} (ng/mL)	0.054 (186)	0.167 (81)	0.272 (73)	0.351 (67)	0.358 (44)
t_{max} (hr)	3.25[a] (22)	3.76[b] (35)	3.26[c] (31)	3.42 (37)	3.62 (34)
t_{lag} (hr)	2.56[a] (32)	2.46[b] (49)	2.16[c] (44)	1.88 (52)	2.07 (55)
AUC_{0-t} (ng·hr/mL)	0.030 (223)	0.215 (104)	0.391 (80)	0.706 (73)	0.653 (50)
$t_{1/2}$ (hr)	N.C.	N.C.	0.819[d] (7.2)	1.20[e] (36)	0.855[d] (6.1)
Total d_6-(α+β)-HTBZ					
C_{max} (ng/mL)	15.5 (22)	32.1 (25)	47.8 (25)	60.9 (23)	49.0 (17)
t_{max} (hr)	3.74 (26)	3.90 (33)	3.63 (23)	3.92 (30)	4.09 (30)
t_{lag} (hr)	1.20 (47)	1.07 (62)	0.87 (68)	0.88 (75)	0.92 (59)
AUC_{inf} (ng·hr/mL)	132 (35)	289 (40)	419 (39)	580 (39)	436 (30)
$t_{1/2}$ (hr)	8.64 (21)	9.79 (25)	10.2 (33)	10.4 (23)	10.2 (24)
d_6-α-HTBZ					
C_{max} (ng/mL)	10.0 (21)	20.2 (22)	30.1 (22)	37.6 (18)	30.4 (18)
t_{max} (hr)	3.65 (26)	3.90 (33)	3.60 (24)	3.82 (29)	4.09 (30)
t_{lag} (hr)	1.20 (47)	1.07 (62)	0.87 (68)	0.88 (75)	0.92 (59)
AUC_{inf} (ng·hr/mL)	102 (28)	213 (31)	307 (31)	419 (31)	316 (24)
$t_{1/2}$ (hr)	9.97 (26)	10.4 (25)	10.7 (24)	10.8 (23)	10.7 (20)
d_6-β-HTBZ					
C_{max} (ng/mL)	5.57 (31)	11.9 (35)	17.9 (35)	23.4 (32)	18.8 (20)
t_{max} (hr)	3.85 (26)	3.92 (34)	3.69 (23)	3.90 (31)	4.09 (33)
t_{lag} (hr)	1.63 (37)	1.35 (50)	1.10 (54)	1.10 (61)	1.13 (49)
AUC_{inf} (ng hr/mL)	33.9 (63)	79.1 (65)	114 (63)	164 (63)	122 (47)
$t_{1/2}$ (hr)	4.01 (53)	4.74 (40)	4.87 (36)	5.19 (38)	4.76 (34)

CV=coefficient of variation; C_{max}=maximum observed plasma concentration; T_{max}=time of the maximum observed plasma concentration; T_{lag}=time prior to first measurable (non-zero) plasma concentration; AUC=area under the concentration time curve; $t_{1/2}$=half-life; N.C.=not calculable.
Key: [a] n=8; [b] n=23; [c] n=29; [d] n=3; [e] n=5.

Two initial ER formulations were evaluated (study AUS-SD-809-CTP-07). The C_{max} values for total (α+β)-HTBZ were lower for both SD-809 formulations in the fed and

fasted states at a dose level of 15 mg than for TBZ at a dose level of 25 mg. The T_{max} values were significantly later for total (α+β)-HTBZ for both SD-809 formulations in the fed and fasted states compared with TBZ (2.5 to 6 hours compared with 1 hour). The apparent half-life was significantly longer for total (α+β)-HTBZ following SD-809 in the fed and fasted states compared with TBZ.
Food had no effect on (α+β)-HTBZ AUC, however C_{max} was increased by approximately 50% with food for Formulation A.

d_6-Total (α+β)-HTBZ or Total (α+β)-HTBZ / Mean (CV%) (N=24) (Per-Protocol Pharmacokinetic Analysis Set)					
	SD-809 ER-A 15 mg Fed	SD-809 ER-B 15 mg Fed	SD-809 ER-A 15 mg Fasted	SD-809 ER-B 15 mg Fasted	Tetrabenazine 25 mg
C_{max} (ng/mL)	33.3 (33)	28.7 (39)	22.5 (36)	14.5 (42)	65.1 (33)
t_{max} (hr)	4.80 (35)	6.28 (31)	2.65 (70)	4.22 (67)	1.13 (33)
t_{lag} (hr)	0.81 (99)	1.02 (97)	0.23 (128)	0.29 (123)	0.06 (270)
AUC_{inf} (ng·hr/mL)	305 (46)	315 (46)	273 (45)	259 (47)	257 (69)
$t_{1/2}$ (hr)	6.99 (23)	7.02 (20)	9.35 (25)	9.95 (16)	4.46 (57)

Notes: SD-809 Formulation A was selected for use in the future clinical trials.
SD-809 was administered with food in all subsequent clinical studies.

In addition, the results of another phase 1 study (SD-809-C-11) demonstrated that the SD-809 formulation (A) was not sensitive to meal composition: The relative bioavailability of d6-HTBZ metabolites for administration of SD-809 18 mg with a high-fat meal compared with administration with a standard meal met the criteria for BE for C_{max}, AUC_{0-t}, and AUC_{inf}.

		Treatment E vs Treatment C High-Fat Meal vs Standard Meal (SD-809 18 mg) N=30 (Per-Protocol PK Analysis Set)	
		% Ratio of LS Means Test/Reference	90% Confidence Interval
Total d_6-HTBZ	C_{max} (ng/mL)	104.2	(97.3-111.6)
	AUC_{0-t} (hr•ng/mL)	107.0	(101.4-112.9)
	AUC_{inf} (ng•hr/mL)	106.4	(100.9-112.2)
d_6-α-HTBZ	C_{max} (ng/mL)	101.6	(95.5-108.0)
	AUC_{0-t} (hr•ng/mL)	105.1	(100.2-110.2)
	AUC_{inf} (ng•hr/mL)	104.3	(99.6-109.3)
d_6-β-HTBZ	C_{max} (ng/mL)	109.2	(99.7-119.7)
	AUC_{0-t} (hr•ng/mL)	113.3	(104.6-122.8)
	AUC_{inf} (ng•hr/mL)	113.1	(104.7-122.1)

Following oral administration of SD-809, the extent of absorption is at least 80% based on the results of the mass balance study: After administration of single oral doses of [^{14}C]-SD-809 to six healthy subjects, 74.78 – 86.48 % of the SD-809 dose was excreted in the urine.

Distribution:

The median volume of distribution (Vc/F) of the α-HTBZ, and the β-HTBZ metabolites are approximately 500 L and 730 L, respectively, in the HD patient population (Population PK report SD-809-CLN-078).
The deuterium substitution should not alter the distribution of SD-809 or its metabolites, therefore SD-809 distribution profile will be referenced from the Xenazine prescribing information. The sponsor proposes the following in the labeling:
Results of PET-scan studies in humans show that following intravenous injection of ^{11}C-labeled tetrabenazine or α-HTBZ, radioactivity is rapidly distributed to the brain, with the highest binding in the striatum and lowest binding in the cortex.
The in vitro protein binding of TBZ, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. TBZ binding ranged from 82% to 85%, α-HTBZ binding ranged from 60% to 68%, and β-HTBZ binding ranged from 59% to 63%.

Metabolism:

SD-809 is rapidly converted by carbonyl reductase to the active metabolites α-HTBZ and β-HTBZ, which are O-dealkylated by CYP450 enzymes, principally CYP2D6 (with minor contribution of CYP1A2), to form 9- and 10-desmethyl-α- and β-DHTBZ. Subsequently, they are metabolized to sulfate or glucuronide conjugates.
Systemic exposure to total (α+β)-HTBZ following SD-809 administration is approximately 2-fold greater than following TBZ administration.

Metabolic Pathway of SD-809 and Tetrabenazine in Humans

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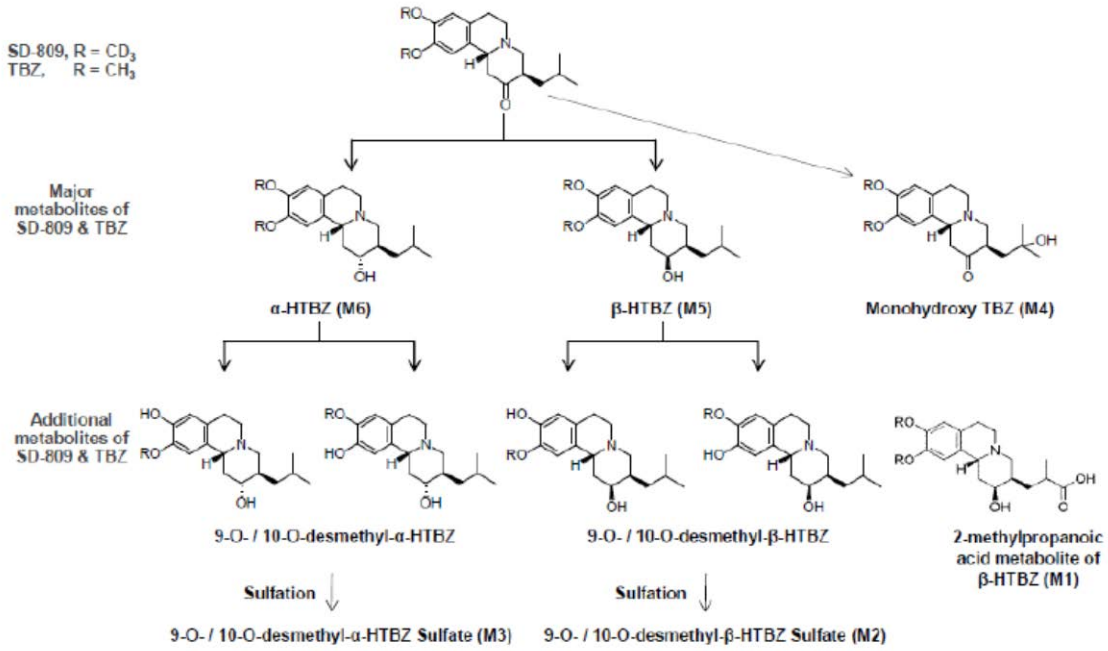


SD-809: Deutetrabenazine
TBZ: Tetrabenazine
HTBZ: Dihydro metabolite of SD-809 or of tetrabenazine
R = CH_3 for tetrabenazine and metabolites
R = CD_3 for SD-809 and metabolites
M = Metabolite M1 through M6 assigned in clinical Study SD-809-C-12 based on Xenazine label and / or prevalence in Study SD-809-C-12

At least two major circulating metabolites, defined as >10% of total circulating SD-809-related radioactivity, α-HTBZ and monohydroxy tetrabenazine (M4), have been identified after oral administration of SD-809 (Mass balance study SD-809-C-12). According to the sponsor, the estimated exposure to metabolites M1, M2, M3, and M4 following administration of SD-809 12.5 mg is similar to or less than that of these same metabolites following administration of tetrabenazine 25 mg, however several discrepancies were noted in the Metabolite Profiling and Identification Report of Study SD-809-C-12. Note: M1 is not present in rats and would represent an uncharacterized safety issue for SD-809 according to the nonclinical reviewer.

The clinical pharmacology reviewer's main concerns are as follows:

1. Bioanalytical Methods:

- Based on the semi-quantitative methods of analysis (b) (4) (b) (4) Study no ASX/04), the Sponsor has changed positions on the status of M1 as a major human metabolite (MHM; >10% total drug-related exposure);
- Has not been able to demonstrate, with the semi-quantitative methods, that a known MHM of TBZ (per the Xenazine label), 9-O-desmethyl-β-DHTBZ, is a MHM in the patients dosed with TBZ in the mass balance study;
- Using the semi-quantitative methods, the exposure to the active metabolites (α+ β)-HTBZ (metabolites M5 + M6) after administration of 25 mg SD-809 was estimated to be 4x higher (instead of the expected 2x higher) than that following administration of 25 mg TBZ (see Table 10 below). The remaining studies in the clinical pharmacology program for SD-809 (using validated quantitative methods of analysis) show that an SD-809 dose that is half that of TBZ results in similar exposure to the respective (α+ β)-HTBZ.

2. Plasma pooling strategy

The plasma pooling for metabolite identification and profiling is questionable. Plasma samples from only 4 time points (2, 2.5, 6, and 12 h) were selected for pooling for metabolite profiling. Although the max concentration of radioactivity in plasma was observed at 3-4 h post- dose, these time points were not included in the pooling. This pooling strategy has the potential to change the percent of total plasma radioactivity for each metabolite and could be responsible for the discrepancy between the original data for Xenazine (NDA 21894) and the SD-809-C-12 study results related to the status of 9-O-desmethyl-β-DHTBZ as a MHM.

Please refer to the SD-809-C-12 Individual study review for details.

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

In addition, as the sponsor is unable to reference the activity of the metabolites M1 and M4 from past experience with Xenazine, M1 and M4 need to be evaluated in *in vitro* studies (VMAT2 and off-target binding). This could be done post approval as a PMR.

Elimination:

SD-809 is primarily renally eliminated in the form of metabolites (83% of the dose recovered in the urine, SD-809-C-12 mass balance study report). The half-life of total (α+β)-HTBZ from SD-809 is approximately 9 to 10 hours.

The median clearance values (CL/F) of the α-HTBZ, and the β-HTBZ metabolites of SD-809 are approximately 47 L/hour and 70 L/hour, respectively, in the HD patient population without impaired CYPD2D6 function or CYP2D6 inhibition (Population PK report SD-809-CLN-078).

2.2.9 What are the basic pharmacokinetic parameters of SD-809 after single and multiple doses?

Pharmacokinetic parameters of SD-809 and its active metabolites after single and multiple doses are shown in the tables below.

Mean Pharmacokinetic Parameters (%CV) for SD-809 following Single and Multiple Oral Doses of SD-809

		SD-809 Single-Dose Data					
Study	Dose/Formulation/ Conditions	C_{max} (ng/mL)	t_{max} (h)	T_{lag} (h)	AUC_t (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{½}$ (h)
AUS-SD-809-CTP-07 Part 2 (N=12)	7.5mg SD/A/Std Meal	0.064 (107)	2.75 (2.50-3.50)	2.25 (1.00-3.00)	0.039 (121)	nc	nc
	15mg SD/A/Std Meal	0.196 (24)	3.00 (2.00-3.50)	2.00 (1.00-3.00)	0.219 (53)	nc	nc
	22.5mg SD/A/Std Meal	0.303 (49)	3.00 (2.50-4.00)	2.00 (1.00-3.00)	0.428 (51)	nc	nc

SD-809-C-11 (N=30)	6mg SD/Tablet/Std Meal	0.054 (186)	3.50 (2.00-4.00) (N=8)	2.75 (1.50-3.50) (N=8)	0.030 (223)	nc	nc
	12mg SD/Tablet/Std Meal	0.167 (81)	4.00 (1.50-5.00) (N=23)	2.50 (0.50-4.00) N=23	0.215 (104)	nc	nc
	18mg SD/Tablet/Std Meal	0.272 (73)	3.00 (1.50-5.01) (N=29)	2.00 (0.50-4.00) (N=29)	0.391 (80)	1.16 (21) (N=3)	0.819 (7.2) (N=3)
	24mg SD/Tablet/Std Meal	0.351 (67)	3.25 (1.00-6.00)	1.50 (0.50-4.00)	0.706 (73)	1.57 (35) (N=5)	1.20 (36) (N=5)
	18mg SD/Tablet/High Fat	0.358 (44)	3.26 (1.50 - 5.02)	2.25 (0.50-4.01)	0.653 (50)	1.29 (12) (N=3)	0.855 (6.1) (N=3)

		SD-809 Multiple-Dose Data						
Study	Dose/Formulation/ Conditions	C_{max} (ng/mL)	t_{max} (h)	C_{max}/C_{min}	C_{min} (ng/mL)	$AUC_{(0-12)}$ (ng•h/mL)	$t_{½}$ (h)	Rac
AUS-SD-809-CTP-07 Part 2 (N=12)	7.5mg BID/Tablet/ Std Meal	0.105 (64)	2.50 (2.00-3.50) (N=9)	nc	0	0.125 (91)	nc	nc
	15mg BID/Tablet/ Std Meal (N=11)	0.257 (33)	2.50 (2.00-3.02)	nc	0.00 (0)	0.475 (50)	nc	nc
	22.5mg BID/Tablet/Std Meal	0.414 (56)	3.25 (2.50-5.00)	nc	0.012 (346)	1.46 (53)	nc	nc

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

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

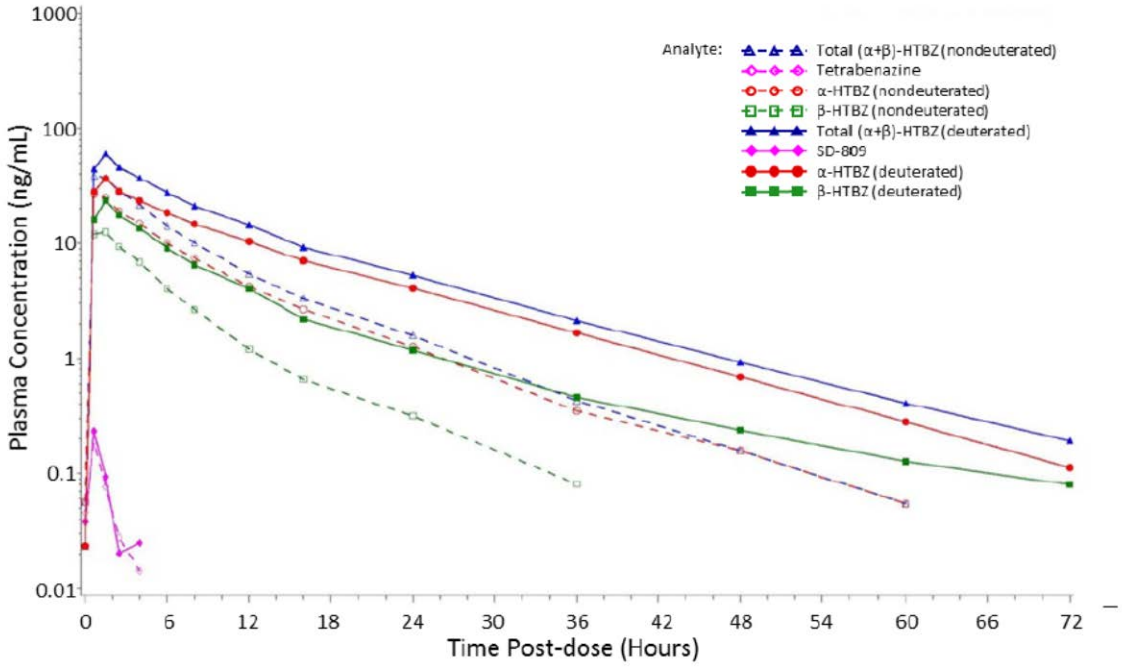
		Total-(α+β)-HTBZ Single-Dose Data					
Study	Dose/Formulation/ Conditions	C_{max} (ng/mL)	t_{max} (h)	T_{lag} (h)	AUC_t (ng•h/mL)	AUC_{inf} (ng•h/mL)	$t_{½}$ (h)
AUS-SD-809-CTP-06 (N=19)	25mg SD/PIC/Fasted	74.6 (37)	1.50 (0.67-2.00)	na	530 (54)	542 (54)	8.62 (38.2)
AUS-SD-809-CTP-07 Part 1 (N=24)	15mg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

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

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

There was no observable difference between the mean profiles of SD-809 and TBZ following equal 25 mg doses (see figure and table below), however the plasma concentrations of α-HTBZ and β-HTBZ were higher following administration of SD-809 25 mg than following TBZ 25 mg. The deuterium substitution had an equal impact on α-HTBZ and β-HTBZ. Overall, systemic exposure to total (α+β)-HTBZ from SD-809 was approximately double that from TBZ following administration of equal doses of SD-809 and TBZ. Plasma concentrations of 9-ODM-α-HTBZ and 9-ODM-β-HTBZ after SD-809 dosing were approximately one-half those of 9-ODM-α-HTBZ and 9-ODM-β-HTBZ after TBZ dosing.

Mean Plasma Concentration-Time Curves for SD-809, TBZ, and Their Dihydro Metabolites Following Single-Dose Administration of SD-809 25 mg or TBZ 25 mg (Study AUS-SD-809-CTP-06; PK Population, N=19)



Pharmacokinetic Parameters for SD-809, TBZ, and Their Dihydro Metabolites Following Single-Dose Administration of SD-809 25 mg or TBZ 25 mg (Study AUS-SD-809-CTP-06)

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

Pharmacokinetic Parameters for O-Desmethyl Metabolites Following Single-Dose Administration of SD-809 25 mg or TBZ 25 mg (Study AUS-SD-809-CTP-06; N=14)

Analyte	9-ODM-α-HTBZ		9-ODM-β-HTBZ		10-ODM-β-HTBZ	
Parameter	**SD-809**	**Tetrabenazine**	**SD-809**	**Tetrabenazine**	**SD-809**	**Tetrabenazine**
C_{max} (ng/mL)	2.15 (52.5)	5.05 (38.6)	6.29 (31.7)	15.7 (27.3)	0.59 (73.9)	1.62 (37.2)
t_{max} (h)	3.02 (1.50-16.00)	2.00 (0.67-4.00)	1.75 (0.67-8.02)	1.75 (0.67-4.00	1.50 (1.00-2.00)	1.25 (0.67-2.50)
AUC_{last} (ng•h/mL)	21.0 (37.2)	42.5 (47.1)	92.4 (29.6)	205 (32.6)	0.68 (111)	2.97 (46.3)
AUC_{inf} (ng•h/mL)	35.4 (34) (n=4)	49.8 (59.8) (n=8)	107 (27)	220 (31)	NC	NC
$t_{½}$ (h)	11.0 (34)	6.95 (47.1) (n=8)	15.5 (30)	16.2 (22.9)	NC	NC

2.2.10 Do the pharmacokinetic parameters change with time following chronic dosing?

No.

Individual Cmax and systemic exposure (AUC) values at steady-state for total (α+β)-HTBZ were generated and normalized to dose levels intended for labeling. Dose-normalized PK parameters did not differ comparing Weeks 9 and 12 (SD-809-CLN-078: Population PK Analysis of SD-809 in Subjects with Chorea with HD).

2.2.11 What is the variability in the PK data?

The inter-individual variability in CL/F, estimated via population pharmacokinetics, was 38.2 % for α-HTBZ CL/F and 67.3% for β-HTBZ. The inter-individual variability of Vd/F was 12.8 % for α-HTBZ and 23.9% for β-HTBZ.

2.2.12 How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients?

Population PK models previously constructed for α-HTBZ and β-HTBZ in Phase 1 studies were updated with PK concentration-time data collected in a Phase 3 trial (SD-809-C-15 [First-HD]).

To compare exposure to total (α+β)-HTBZ from SD-809 in the HD subject population with healthy volunteers, PK parameters from Study SD-809-C-15 were estimated for subjects with HD with functional CYP2D6 (defined as not receiving a concomitant CYP2D6 inhibitor and not a PM phenotype). The parameters were normalized to a dose of 15 mg BID and compared to results from healthy subjects administered 15 mg BID in Study AUS-SD-809-CTP-07 Part 2. Peak and systemic exposure (AUC) values in subjects with HD were similar to the exposure in healthy volunteers receiving equivalent doses.

Comparison of Steady-State Exposure of Total (α+β)-HTBZ in Healthy Volunteers and Simulations from Subjects with HD Following 15 mg BID Dosing

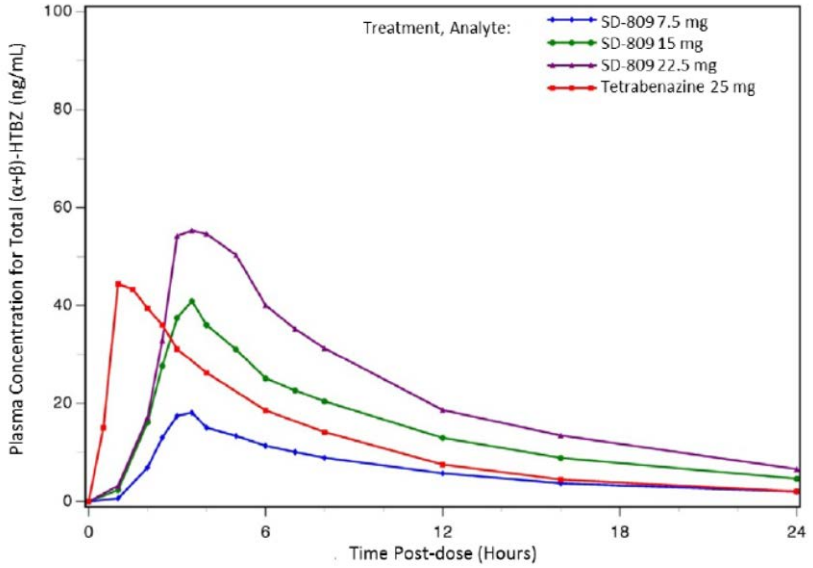
Parameter	SD-809-CTP-07 Part 2 (N=11)	SD-809-C-15 Population PK [a] Week 9
C_{max} (ng/mL)	72 (15)	70 (31)
AUC_{0-24} (ng•h/mL)	886 (252)[b]	1149 (733)
C_{min} (ng/mL)	21 (9)	32 (29)

Reference: AUS-SD-809-CTP-07 Part 2, Appendix 16.1.12.2, Table 14.2.5.4; Source SD-809-CLN-078 Appendix 1, Table 5.11.
Note: Data are mean (SD) in subjects with functional CYP2D6.
[a] Week 9 from SD-809-CLN-078 Appendix 1, Table 5.11 was chosen for comparison; there was no effect of visit (Week 9 or Week 12) on population PK parameters.
[b] AUC_{0-24} for SD-809-CTP-07 was calculated as AUC_{0-12} * 2.

2.2.13 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

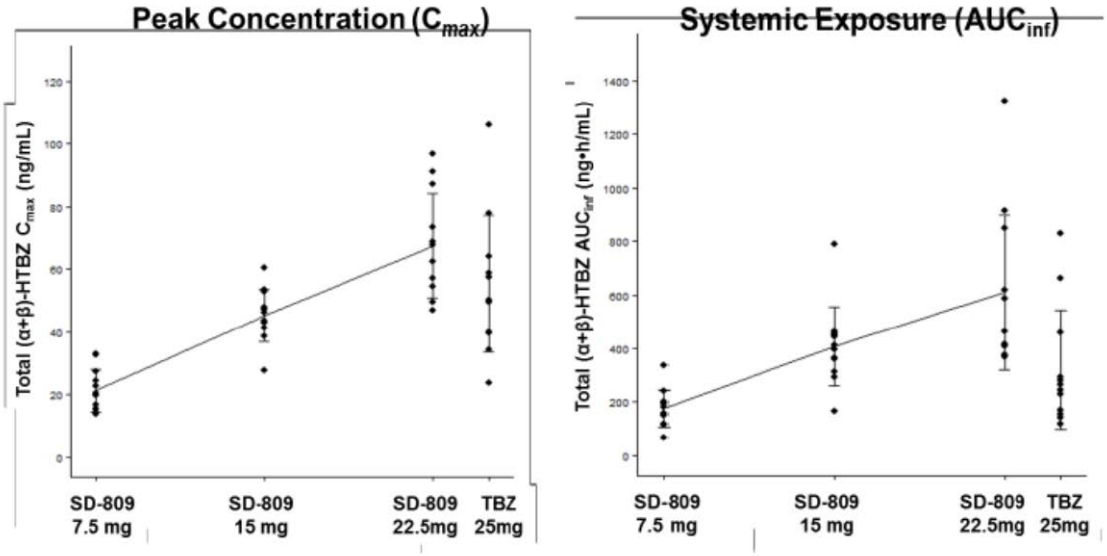
The PK profiles of single tablet doses of SD-809 7.5 mg, SD-809 15 mg, and SD-809 22.5 mg (one 7.5-mg tablet and one 15-mg tablet) administered following a standardized meal, and of a single dose of TBZ 25 mg administered following an overnight fast, were compared in a sequential group study in healthy adult male and female subjects (Study AUS-SD-809-CTP-07, Part 2). In general, the PK of the dihydro metabolites (HTBZ) was found to be linear and dose-proportional over a 3-fold dose range (7.5 mg to 22.5 mg). Following administration of single doses of SD-809, mean AUC_{inf} and mean C_{max} for the individual and total (α+β)-HTBZ increased in a dose-proportional manner.

Mean Plasma Concentration-Time Curves for Total (α+β)-HTBZ Following Administration of Single Doses of SD-809 or TBZ (Study AUS-SD-809-CTP-07, Part 2, N=12/ treatment)



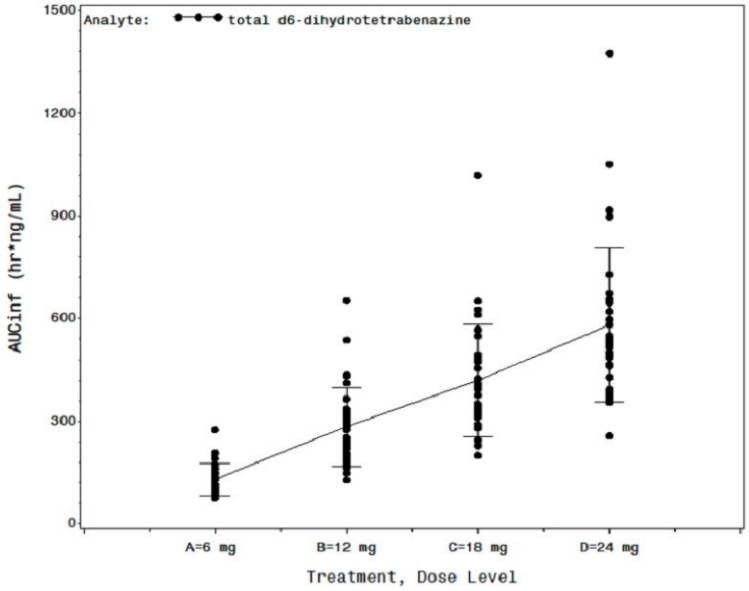
Reference: Study AUS-SD-809-CTP-07, Figure 5.
Abbreviation: HTBZ, dihydrotetrabenazine.
[a] SD-809 tablets administered following consumption of a standardized meal.
[b] Tetrabenazine tablets were Australia-sourced and were administered following an overnight fast.

Individual and Mean Total (α+β)-HTBZ Cmax and AUC After Administration of SD-809 or TBZ (Study AUS-SD-809-CTP-07 Part 2)



The dose proportional increase in exposure in Study AUS-SD-809-CTP-07 is consistent with the results obtained over the dose range of 6 mg to 24 mg in the bioavailability study with the final formulation (SD-809-C-11).

Dose Dependence of AUC_{inf} of Total d6-(α+β)-HTBZ in Study SD-809-C-11



2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is

known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The impact of intrinsic factors was studied in a population PK analysis. The population was 23 to 74 years old, 47.7% male, and 100% Caucasian.
Population PK analysis showed that age and gender did not influence SD-809 pharmacokinetics.
The pharmacokinetics of SD-809 and its primary metabolites have not been formally studied in specific populations, including pediatric, geriatric subjects and patients with renal or hepatic impairment. There was no apparent effect of gender on the PK of α-HTBZ or β-HTBZ.
Per the Xenazine label, the exposure to α-HTBZ and β-HTBZ was 30-39% greater in patients with hepatic impairment and the mean TBZ Cmax in hepatically impaired subjects was approximately 7- to 190-fold higher than that in healthy subjects. Similar to Xenazine, SD-809 is contraindicated for patients with hepatic impairment.

Impaired CYP2D6 Function
An in vivo drug-drug interaction (DDI) study conducted with SD-809, showed a 3-fold increase in total (α+β)-HTBZ exposures when a strong CYP2D6 inhibitor (paroxetine) was co-administered with SD-809. In addition, the SD-809 dose was capped at 18 mg BID (36 mg daily) in patients taking strong CYP2D6 inhibitors in the efficacy and safety trials. This data supports that the daily dose of SD-809 should not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.

2.4 EXTRINSIC FACTORS

2.4.1 Is SD-809 a substrate, inhibitor or inducer of CYP enzymes or major transporters?

In vitro metabolism studies (conducted with TBZ) indicated that there is no meaningful inhibition or induction of CYP-based enzymes by TBZ and its metabolites α-HTBZ and β-HTBZ at concentrations that are relevant for dosing.
In addition, the SD-809 metabolites with exposures >25% of (α+β)-HTBZ, e.g. 2-methylpropanoic acid metabolite of β-HTBZ (M1) and monohydroxy tetrabenazine (M4), have been evaluated in a panel of *in vitro* DDI studies.
The following *in vitro* studies were conducted with M1 and M4:

- Direct and time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 in human liver microsomes
- Induction of CYP1A2, CYP2B6 and CYP3A4 mRNA levels in primary cultures of cryopreserved human hepatocytes
- *In Vitro* Evaluation of M1/M4 as an inhibitor and substrate of human P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 transporters

The results of the *in vitro* studies indicate that M1/M4 is not expected to cause clinically relevant drug interactions. Details of the methods and results are provided in the individual study reviews.
Note: M1 is substrate of OAT3.

2.4.2 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.2.1 Influence of other drugs on SD-809:

SD-809, like TBZ, is rapidly converted in the liver by carbonyl reductase to its active metabolites α-HTBZ and β-HTBZ, which are subsequently metabolized principally by CYP2D6. Strong CYP2D6 inhibitors markedly increase exposure to the active metabolites of TBZ (Xenazine label). In the case of SD-809, the deuteration effect is expected to reduce the impact of CYP2D6 status due to genotype or concomitant medication usage. The sponsor conducted an *in vivo* DDI study with a strong CYP2D6 inhibitor (paroxetine) to evaluate the effect of a strong CYP2D6 inhibitor on SD-809 and its active metabolites' exposure.
This was an open-label, sequential, drug-drug interaction study in 24 healthy subjects (CYP2D6 extensive or intermediate metabolizers only). Paroxetine was administered for 9 days to ensure that steady-state levels of paroxetine were achieved to maximize its CYP2D6 inhibitory effects. The results of this study showed that the exposure of d6-α-HTBZ was increased 1.85-fold, and d6-β-HTBZ was increased 6.5-fold when SD-809 was co-administered with paroxetine. There was a 3-fold increase in mean $AUC_{0-\infty}$ for total d6-(α+β)-HTBZ from 624 ng hr/mL on Day 1 (SD-809 alone) to 1901 ng·hr/mL on Day 11 (SD-809 + paroxetine) and slower elimination (mean $t_{1/2}$, 9.75 hours on Day 1, compared with 16.0 hours on Day 11). Prolongation of the half-lives of d6-α-HTBZ and d6-β-HTBZ was associated with reduced formation of O-desmethyl metabolites of HTBZ on Day 11 (SD-809 + paroxetine) compared with Day 1 (SD-809 alone).

Mean Plasma Concentration of SD-809 and Primary Metabolites by Dose Day

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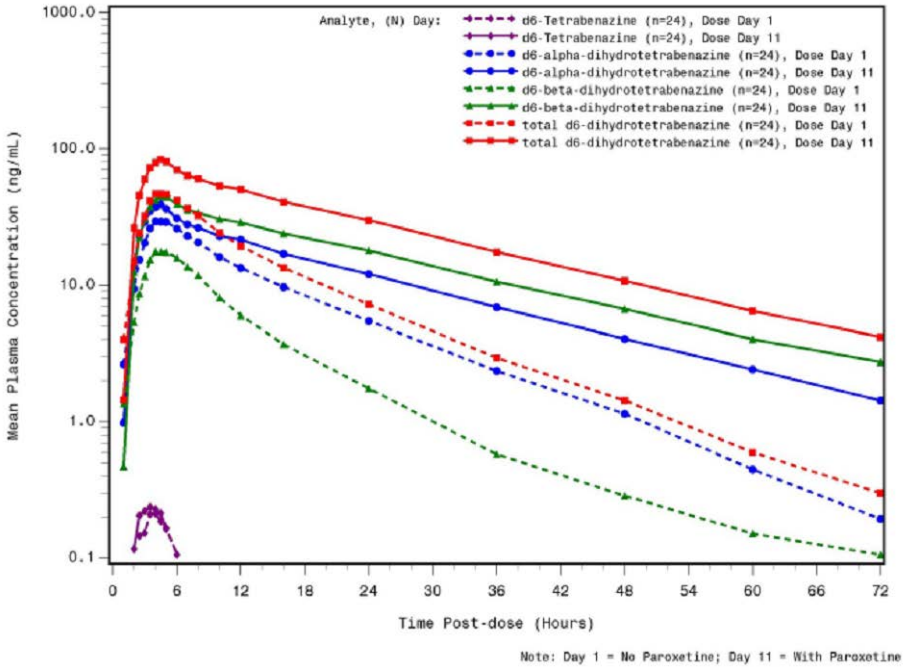


Mean plasma concentrations of d6-α HTBZ and d6-β HTBZ were higher in IM phenotype subjects on both Day 1 (SD-809 alone) and Day 11 (SD-809 + paroxetine) compared with subjects with a CYP2D6 EM phenotype.

Comparison of PK Parameters by Analyte, With and Without Paroxetine

Dose Day 1 = SD-809 alone Dose Day 11 = SD-809 + Paroxetine		% Ratio of LS Mean (90% Confidence Interval) ([Day 11] / [Day 1])		
		All Subjects (N=23)	Subjects with Phenotype EM (N=15)	Subjects with Phenotype IM (N=8)
Total d_6-(α+β)-HTBZ	C_{max} (ng/mL)	154.8 (137.4-174.4)	173.1 (149.8-200.1)	125.6 (105.4-149.6)
	AUC_{0-t} (ng·hr/mL)	303.6 (268.0-343.8)	324.9 (273.9-385.4)	267.3 (224.0-318.9)
	$AUC_{0-\infty}$ (ng·hr/mL)	314.7 (278.4-355.6)	329.8 (277.7-391.8)	288.1 (242.3-342.5)
	$t_{1/2}$ (hr)	165.5 (155.1-176.7)	164.6 (149.1-181.6)	167.3 (156.3-179.2)
d_6-α-HTBZ	C_{max} (ng/mL)	119.9 (108.1-132.9)	127.8 (111.8-146.1)	106.3 (90.0-125.4)
	AUC_{0-t} (ng·hr/mL)	181.6 (162.4-203.0)	192.2 (162.9-226.8)	163.3 (148.3-179.8)
	$AUC_{0-\infty}$ (ng·hr/mL)	185.0 (165.8-206.4)	193.6 (164.4-228.0)	169.8 (153.8-187.5)
	$t_{1/2}$ (hr)	150.6 (143.4-158.1)	155.5 (146.7-164.8)	141.8 (129.3-155.5)
d_6-β-HTBZ	C_{max} (ng/mL)	216.4 (185.0-253.2)	259.2 (216.7-310.1)	154.3 (126.0-189.0)
	AUC_{0-t} (ng·hr/mL)	641.3 (537.3-765.4)	744.6 (605.3-915.8)	484.7 (355.2-661.5)
	$AUC_{0-\infty}$ (ng·hr/mL)	649.9 (549.6-768.5)	731.5 (595.0-899.3)	520.6 (388.9-697.0)
	$t_{1/2}$ (hr)	286.4 (261.3-314.0)	287.4 (255.5-323.3)	284.6 (237.6-340.8)

AUC = area under concentration-time curve; C_{max} = maximum plasma concentration; EM = extensive metabolizer; HTBZ = dihydrotetrabenazine; IM = intermediate metabolizer; $t_{1/2}$ = half life.

PD Results: The SD-809 + paroxetine treatment exhibited greater QTcF interval mean increases from pre-dose compared to the monotherapies through Hour 8, with the

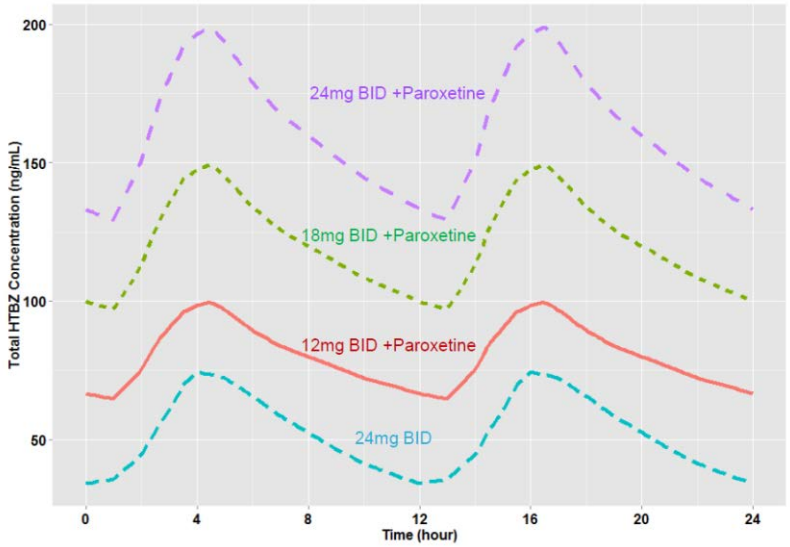
maximum mean QTcF increase of +9.2 msec at Hour 6 (to a mean value of 404.8 msec), compared to a maximum mean increase in QTcF of +1.5 msec at Hour 6 for SD-809 alone and +0.7 msec at Hour 5 for paroxetine alone.

Reviewer's Comments:
According to the sponsor, no adjustment in SD-809 dosing is needed in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809 based on the overlapping ranges in predicted total (α+β)-HTBZ exposures. The dose of SD-809 can be titrated based on efficacy of chorea control and tolerability for each patient.
However, results from the DDI study SD-809-C-08 show a 3-fold increase in total (α+β)-HTBZ exposures when paroxetine was co-administered with SD-809. In addition, in the DDI study, the SD-809 + paroxetine treatment exhibited greater QTcF interval mean increases from pre-dose compared to the monotherapies through Hour 8.
The sponsor used data from the phase 3 study to conduct additional simulations, which show that, in subjects with impaired CYP2D6 function, SD-809 at 48 mg/day (100% of the maximum recommended daily dose) is predicted to yield median AUC_{0-24} values that fall within the exposure range of tetrabenazine 50 mg/day in subjects with impaired CYP2D6 function. However, the effect of impaired CYP2D6 function on SD-809 pharmacokinetics might be underestimated by the analysis of data from the Phase 3 trial because of the limited number of subjects with impaired CYP2D6 function in this trial and the sparseness of the PK sampling. Moreover, the sponsor's simulation results show that, in subjects with impaired CYP2D6 function, SD-809 at 48 mg/day is predicted to yield higher C_{max} of total (α+β)-HTBZ than TBZ at 50 mg/day in subjects with impaired CYP2D6 function, although AUC_{0-24} seems to be in similar range (source: Summary of Clinical Pharmacology, Figure 10). The sponsor's PK modeling also predicts that SD-809 doses of 36 mg per day (75% of the maximum clinical dose) in subjects receiving strong CYP2D6 inhibitors (or CYP2D6 poor metabolizers) will result in α- and β-HTBZ exposures comparable to those observed with 50 mg per day of TBZ in CYP2D6 poor metabolizers (pre-NDA meeting background materials, page 38). In addition, the safety database (9 subjects who are PMs or on 2D6 inhibitors) is not large enough to support removing the adjustment in SD-809 dosing for PMs and patients on 2D6 inhibitors based on safety information only, especially considering that these patients had their dose capped at 18 mg BID (36 mg daily) in patients taking strong CYP2D6 inhibitors in the phase 3 trial (only one of the PMs was on 42 mg/day). Moreover, several of these subjects back-titrated to a lower maintenance dose (subjects 1, 20, 30).

To further evaluate the maximum daily dose in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809, predicted mean steady state PK profiles of total (α+β)-HTBZ at different doses of SD-809 with or without strong CYP2D6 inhibitor paroxetine were derived through nonparametric superposition using data from the dedicated DDI study (SD-809-C-08). Although the results (see figure below) show that total (α+β)-HTBZ exposure at 18 mg BID SD-809 dose in subjects with impaired CYP2D6 function is higher than that at 24 mg BID dose (the proposed maximum SD-809 dose for patients without impaired CYP2D6 function or CYP2D6 inhibition) in subjects with normal CYP2D6 function, such total (α+β)-HTBZ exposure is similar or lower than the total (α+β)-HTBZ exposure at approved maximum Xenazine dose (25 mg BID) in

CYP2D6 PM subjects and subjects on concomitant strong CYP2D6 inhibitors. Therefore, SD-809 dose adjustment is bridged to the Xenazine dosing recommendations in subjects with impaired CYP2D6 function. The 18 mg BID SD-809 dose (36mg/day) is considered to be acceptable.

Predicted Mean Steady-state PK Profiles of Total (α+β) HTBZ at Different Scenarios with or without Strong 2D6 Inhibitor Paroxetine



OCP Recommendation: The daily dose of SD-809 should not exceed 36 mg with a maximum single dose of 18 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The sponsor has not provided such information in the NDA. The sponsor proposes to include the following in the label: *Deutetrabenazine is a white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol.*
For formulation, see below Sect 2.5.2.

2.5.2 Is the proposed to-be-marketed formulation bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

SD-809 Formulation A (Study AUS-SD-809-CTP-07) is the SD-809 Drug Product that is planned for commercialization. This formulation has been used in the efficacy and safety tials.

Notes: The study drug name "SD-809-ER" has been used throughout the development program of SD-809. However, the sponsor proposes the Drug Product to be described as "SD-809 tablets".
The initial "Formulation A" were (b) (4) (7.5mg and 15mg tablets, used in the phase1 Studies SD-809-C-07 and SD-809-C-08). Later, e.g., in Study SD-809-C-11, the sponsor developed (b) (4): 6 mg, 12 mg and 18 mg. The commercial strengths are also (b) (4) strengths 6 mg, 9 mg and 12 mg. The sponsor calls all of the above "Formulation A".
Reviewer's Comment: According to the biopharmaceutics reviewer, Dr. Jing Li, the tablets 6 mg, 9 mg, 12 mg, and 18 mg are (b) (4) similar. In addition, the dissolution data are adequate to bridge the (b) (4) (7.5 and 15 mg tablets) to the (b) (4) formulation.

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					

Notes: The biopharmaceutics team has identified the presence of (b) (4) excipients in the proposed product; in addition, the in vivo PK and clinical data also indicate extended-release (ER) characteristics. However, an ER claim was not requested for SD-809 as, according to the sponsor, during preparation of the NDA, (b) (4) (b) (4) (b) (4) There is no other formulation of deutetrabenazine (b) (4) (b) (4)

(b) (4)

Comment: However, the Tmax was increased for the tablet compared to powder-in-capsule formulation. This issue will be addressed by the biopharmaceutics team.

Powder-in-capsule formulation (AUS-SD-809-CTP-06):

	Extensive Metabolizers		All Evaluable Subjects	
	SD-809 (n=13)	Tetrabenazine (n=13)	SD-809 (n=19)	Tetrabenazine (n=19)
C_{max} (ng/mL)[a]	67.9 (36.3)	60.1 (41.9)	74.6 (37.1)	61.6 (38.2)
T_{max} (hr)[b]	1.50 (0.67-2.00)	1.00 (0.67-2.00)	1.50 (0.67-2.00)	1.00 (0.67-2.50)
AUC_{inf} (ng·hr/mL)[a]	414 (45.1)	177 (50.3)	542 (53.8)	261 (69.6)
$t_{1/2}$ (hr)[a]	7.61 (37.8)	4.05 (57.4)	8.62 (38.2)	4.82 (50.8)

Tablet formulation (Study AUS-SD-809-CTP-07):

	d_6-Total (α+β)-HTBZ or Total (α+β)-HTBZ / Mean (CV%) (N=24) (Per-Protocol Pharmacokinetic Analysis Set)				
	SD-809 ER-A 15 mg Fed	SD-809 ER-B 15 mg Fed	SD-809 ER-A 15 mg Fasted	SD-809 ER-B 15 mg Fasted	Tetrabenazine 25 mg
C_{max} (ng/mL)	33.3 (33)	28.7 (39)	22.5 (36)	14.5 (42)	65.1 (33)
t_{max} (hr)	4.80 (35)	6.28 (31)	2.65 (70)	4.22 (67)	1.13 (33)
t_{lag} (hr)	0.81 (99)	1.02 (97)	0.23 (128)	0.29 (123)	0.06 (270)
AUC_{inf} (ng·hr/mL)	305 (46)	315 (46)	273 (45)	259 (47)	257 (69)
$t_{1/2}$ (hr)	6.99 (23)	7.02 (20)	9.35 (25)	9.95 (16)	4.46 (57)

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of SD-809 in relation to meals or meal types?

The effect of co-administration of high fat and high caloric meal on the bioavailability (BA) of SD-809 has been assessed for two tablet formulations (A and B) in study AUS-SD-809-CTP-07, see table above. The C_{max} of the HTBZ metabolites was increased 50% for formulation A and 100% for formulation B after administration with food than when fasting and AUC_{0-t} was increased slightly (11% for formulation A) when administered in the fed state. Formulation A was selected for further development based on its more consistent PK profile across subjects compared with Formulation B.
The relative BA values for total (α+β)-HTBZ met the 80% to 125% criterion for bioequivalence when SD-809 18 mg was administered following consumption of a high-fat, high-calorie meal and when it was administered following consumption of a standardized meal (Study SD-809-C-11).

SD-809-C-11: Comparison of PK Parameters for SD-809 18 mg by Meal Type

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		Treatment E vs Treatment C High-Fat Meal vs Standard Meal (SD-809 18 mg) N=30 (Per-Protocol PK Analysis Set)	
		% Ratio of LS Means Test/Reference	90% Confidence Interval
Total d_6-HTBZ	C_{max} (ng/mL)	104.2	(97.3-111.6)
	AUC_{0-t} (hr•ng/mL)	107.0	(101.4-112.9)
	AUC_{inf} (ng•hr/mL)	106.4	(100.9-112.2)
d_6-α-HTBZ	C_{max} (ng/mL)	101.6	(95.5-108.0)
	AUC_{0-t} (hr•ng/mL)	105.1	(100.2-110.2)
	AUC_{inf} (ng•hr/mL)	104.3	(99.6-109.3)
d_6-β-HTBZ	C_{max} (ng/mL)	109.2	(99.7-119.7)
	AUC_{0-t} (hr•ng/mL)	113.3	(104.6-122.8)
	AUC_{inf} (ng•hr/mL)	113.1	(104.7-122.1)

SD-809 was administered with food in all clinical studies.
The sponsor recommends SD-809 to be administered with food, this is acceptable.

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

Plasma concentrations of SD-809 and metabolites were measured in clinical studies using **validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods** (b) (4) **).**
Two validated assays were used: ALM.TBZ.1 for measuring the concentrations of TBZ and its α- and β-HTBZ metabolites in human plasma and ALM.SD809.1 for SD-809 and its deuterated α- and β-HTBZ metabolites with ranges 0.100 ng/mL to 10.0 ng/mL for SD-809 or TBZ and 0.500 ng/mL to 100 ng/mL for their HTBZ- metabolites.
Separate validated assays were used to measure the 9-O- and 10-O-desmethyl metabolites of deuterated and non-deuterated α-HTBZ and β-HTBZ (SD-809-CLN-050 and SD-809-CLN-051) with ranges 0.500 to 50.0 ng/mL for O-desmethyl-metabolites.
Details pertaining to assay methodology, assay validation, acceptance criteria, and performance of the assays during the analysis of study samples are provided in the individual study reviews.

The validation results of the LC-MS/MS bioanalytical assays for SD-809, TBZ, and their respective HTBZ- and O-desmethyl- metabolites are acceptable. The results are summarized in the table below.

Summary of Method Validation for Analysis of SD-809, TBZ, and their α-HTBZ, β-HTBZ, and O-Desmethyl Metabolites by LC-MS/MS in Human Plasma Containing Lithium Heparin as Anticoagulant

Document Control Number: Report Type	Analyte	Standard Curve Range (ng/mL)	Precision[a] (%CV)		Accuracy[b] over Assay Range (%)		Stability
			Intra	Inter	Intra	Inter	
SD-809-CLN-011: method validation report; SD-809-CLN-052: stability report	Tetrabenazine	0.1 to 10	2 to 8	4 to 14	-6 to 2	-11 to -3	Room temperature: 24 h Freeze/thaw: 3 cycles Long-term stability: at least 382 days @ -80°C
	Nondeuterated α-HTBZ	0.5 to 100	2 to 7	4 to 6	-1 to 9	-2 to 3	
	Nondeuterated β-HTBZ		2 to 4	3 to 7	-3 to 10	-4 to 0	
SD-809-CLN-012: method validation report; SD-809-CLN-052: stability report	SD-809	0.1 to 10	1 to 6	5 to 12	-1 to 13	-3 to 2	
	Deuterated α-HTBZ	0.5 to 100	2 to 4	3 to 8	-6 to -1	-4 to -2	
	Deuterated β-HTBZ		2 to 5	3 to 9	-6 to -1	-7 to -4	
SD-809-CLN-050: method validation report; SD-809-CLN-074: stability report	Nondeuterated 9-O-desmethyl α-HTBZ	0.5 to 50	2.3 to 3.3	2.5 to 6.2	-3.7 to 0.8	-8.3 to -3.3	Room temperature: 24 h Freeze/thaw: 4 cycles Long-term stability: up to 440 days @ -80°C
	Nondeuterated 10-O-desmethyl α-HTBZ		2.1 to 3.1	3.4 to 4.8	-5.4 to 0.8	-6.5 to -3.6	
	Nondeuterated 9-O-desmethyl β-HTBZ		0.9 to 2.4	2.6 to 5.4	-5.5 to 1.4	-7.6 to -4.2	
	Nondeuterated 10-O-desmethyl β-HTBZ		2.0 to 5.2	3.1 to 10.3	-6.6 to 4.2	-5.0 to -3.5	

Document Control Number: Report Type	Analyte	Standard Curve Range (ng/mL)	Precision[a] (%CV)		Accuracy[b] over Assay Range (%)		Stability
SD-809-CLN-051: method validation report; SD-809-CLN-074: stability report	Deuterated 9-O-desmethyl α-HTBZ	0.5 to 50	1.0 to 2.5	2.7 to 3.9	-8.6 to -0.8	-4.6 to -2.2	Room temperature: 24 h Freeze/thaw: 3 cycles Long-term stability: up to 441 days @ -80°C
	Deuterated 10-O-desmethyl α-HTBZ		1.7 to 3.4	2.9 to 3.5	-9.2 to -1.7	-5.1 to -0.8	
	Deuterated 9-O-desmethyl β-HTBZ		1.7 to 2.6	3.0 to 3.7	-6.8 to 0.2	-5.4 to -2.3	
	Deuterated 10-O-desmethyl β-HTBZ		1.8 to 7.1	3.9 to 6.9	-12.9 to 2.4	-5.8 to -2.9	

Abbreviations: CV, coefficient of variation; HTBZ, dihydrotetrabenazine; SD, standard deviation.
[a] Precision: (SD/Mean Measured Concentration) x 100
[b] Accuracy: [(Mean Measured Concentration – Nominal Concentration) x 100]/ Nominal Concentration

In addition, the following analytical methods were used in the mass balance study SD-809-C-12:

Whole Blood, Plasma, Urine and Feces Samples for Measurement of Total Radioactivity (b) (4) study no. ASX/03)

Total radioactivity was determined at (b) (4) by quantitative radiochemical analysis. Radioactivity in fecal homogenate and whole blood was determined after combustion in oxygen using an Automatic Sample Oxidiser (Tri-Carb®, Perkin Elmer). The combustion products are absorbed into CarboSorb E and mixed with the scintillator cocktail PermaFluor E^+ for measurement of radioactivity. Radioactivity in liquid samples (plasma and urine) was quantified directly by Liquid Scintillation Counting (LSC) using a liquid scintillation counter with automatic external standard quench correction. Samples were mixed with scintillant (Ultima Gold XR) and counted (2300TR Scintillation Counter, Perkin Elmer). Detected counts per minute (cpm) were converted to disintegrations per minute (dpm) using quench correction.

Metabolite Profiling and Identification (semi-quantitative methods) (b) (4) Study no ASX/04

Metabolite profiling and chemical structure identification were performed from plasma and urine samples using high performance LC with on-line radiodetection and LC-MS/MS. Metabolite profiling from feces samples was not performed.
The Metabolite Profiling and Identification results of the mass balance study are not acceptable. The clinical pharmacology reviewer's main concerns are listed below:

1. Bioanalytical Methods:

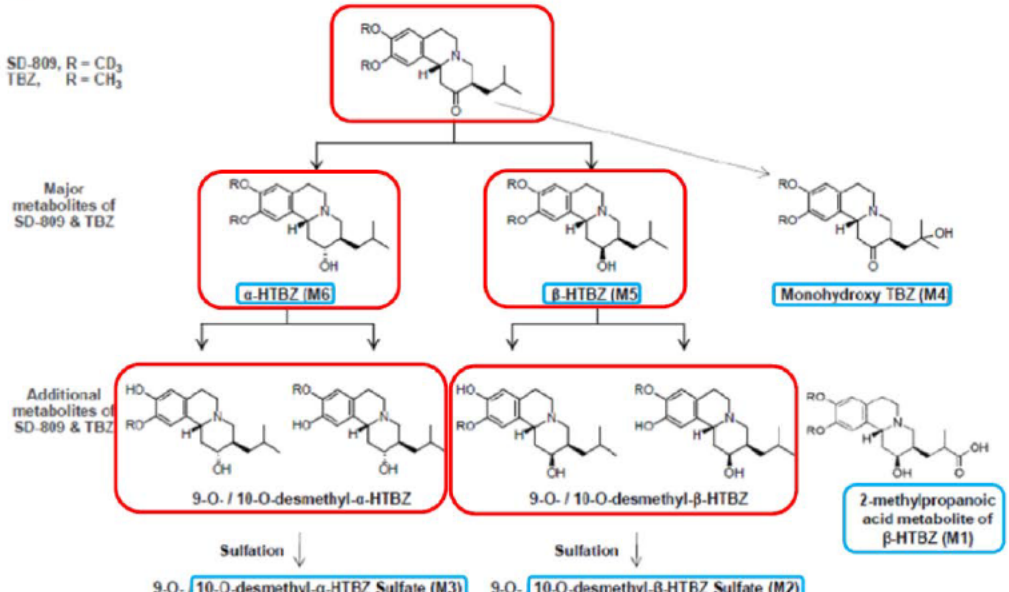
- Based on the semi-quantitative methods of analysis (Study no ASX/04), the Sponsor has changed positions on the status of M1 as a major human metabolite (MHM; >10% total drug-related exposure);

- Has not been able to demonstrate, with the semi-quantitative methods, that a known MHM of TBZ (per the Xenazine label), 9-O-desmethyl-β-DHTBZ, is a MHM in the patients dosed with TBZ in the mass balance study;

- Using the semi-quantitative methods, the exposure to the active metabolites (α+ β)-HTBZ (metabolites M5 + M6) after administration of 25 mg SD-809 was estimated to be 4x higher (instead of the expected 2x higher) than that following administration of 25 mg TBZ (see Table 10 below). The remaining studies in the clinical pharmacology program for SD-809 (using validated quantitative methods of analysis) show that an SD-809 dose that is half that of TBZ results in similar exposure to the respective (α+ β)-HTBZ.

Note: The validated LC-MS/MS assay [redacted] (b) (4) was used to quantify TBZ/SD-809 and 6 of their respective metabolites: these are shown in the red circled areas below.

Figure 2. Metabolic Pathway of SD-809 and Tetrabenazine



Red circles: Parent drug and 6 metabolites quantified by LC-MS/MS assay performed by [redacted] (b) (4)
Blue circles: Analytes identified by the semiquantitative radioactivity assay shown in Table 11.

***EOP2 Briefing package:* Comparison of metabolites exceeding 10% of total plasma sample (pooled up to 12h post-dose) radioactivity following oral administration of SD 809 or tetrabenazine**

Metabolite Number	Identification	Percentage of sample radioactivity	
		SD-809	TBZ (SD-808)
M1	Acid Metabolite of HTBZ	12.7	4.0
M2	Sulphate of O-desmethyl HTBZ	4.	18.7
M3	Sulphate of O-desmethyl HTBZ	4.5	15.4
M4	+ 16 amu Metabolite	19.9	11.7
M5	β-HTBZ	13.3	2.2
M6	α-HTBZ	15.9	5.0

Changes in the metabolic profile of SD-809 as compared to tetrabenazine are summarized as follows:

- *M4 is a major metabolite for both SD-809 and TBZ, likely a metabolite of HTBZ,*
- *M1 is a major metabolite of SD-809 (accounting for 12.7% of radioactivity), but a minor metabolite for TBZ (accounting for 4.0% of radioactivity).*

Sponsor Preliminary Response for EOP2 Meeting Discussion:

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

NDA Submission: M1 is a minor metabolite of SD-809 (9.2% of radioactivity), Table 10.

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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.

In the Response to Requests for Clarification Regarding Nonclinical and Biopharmaceutics Issues from the Mid-Cycle Communication Teleconference (Dec 22, 2015), the sponsor acknowledged the differences between the original data for Xenazine (NDA 21894) and the mass balance study SD-809-C-12 conducted for development of SD-809 related to the status of 9-O-desmethyl-β-DHTBZ (also referred to as 9-O-desmethyl-β-HTBZ) as a major metabolite of Xenazine. However, the sponsor made the following point:

In Prestwick study CAM/06, P16 was identified as "O-dealkylated HTBZ," without resolution of α- or β- diastereomers and without identification of the site of demethylation (i.e., the 9 or 10 positions). Thus, while the amalgam of these four metabolites is responsible for 31% of the radioactivity, it is not clear whether 9-O-desmethyl-β-DHTBZ is responsible for greater than 10%.

Reviewer's Comment: However, the levels of 9-O-desmethyl α-HTBZ, 10-O-desmethyl α-HTBZ and 10-O-desmethyl β-HTBZ are very low or BLQ after TBZ administration (see data from Study AUS-SD-809-CTP-07, Part 2: Summary of Steady State Pharmacokinetic Parameters by Treatment of 9-O-desmethyl-HTBZ Metabolites, Table below). Therefore, 9-O-desmethyl-β-DHTBZ is responsible for the majority of this 31% of the radioactivity.

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	N=24 (Per-Protocol Pharmacokinetic Analysis Set)	
	SD-809 ER 15 mg Fed N=11	Tetrabenazine 25 mg N=12
d_3-9-O-desmethyl α-HTBZ or 9-O-desmethyl α-HTBZ		
C_{max} (ng/mL)	1.34 (18)	6.41 (38)
t_{max} (hr)	2.95 (16)	1.67 (48)
AUC_{0-12} (ng·hr/mL)	11.5 (22)	50.8 (38)
$t_{1/2}$ (hr)	NC	12.3 (24)
d_3-10-O-desmethyl α-HTBZ or 10-O-desmethyl α-HTBZ		
C_{max} (ng/mL)	0.00 (0.0)	0.595 (34)
t_{max} (hr)	NC	1.00 [a] (22)
AUC_{0-12} (ng·hr/mL)	0.00 (0.0)	2.10 (87)
$t_{1/2}$ (hr)	NC	NC
d_3-9-O-desmethyl β-HTBZ or 9-O-desmethyl β-HTBZ		
C_{max} (ng/mL)	6.41 (15)	27.9 (23)
t_{max} (hr)	3.05 (14)	1.63 (44)
AUC_{0-12} (ng·hr/mL)	59.3 (15)	224 (23)
$t_{1/2}$ (hr)	16.2 (11)	17.1 (21)
d_3-10-O-desmethyl β-HTBZ or 10-O-desmethyl β-HTBZ		
C_{max} (ng/mL)	0.046 (332)	1.61 (34)
t_{max} (hr)	NC	1.50 (40)
AUC_{0-12} (ng·hr/mL)	0.023 (332)	4.92 (41)
$t_{1/2}$ (hr)	NC	NC

[a] n=11; NC=Not Calculable (n≤ 1)

2. Plasma pooling strategy

The plasma pooling for metabolite identification and profiling is questionable. Plasma samples from only 4 time points (2, 2.5, 6, and 12 h) were selected for pooling for metabolite profiling. Although the max concentration of radioactivity in plasma was observed at 3-4 h post- dose, these time points were not included in the pooling. This pooling strategy has the potential to change the percent of total plasma radioactivity for each metabolite and could be responsible for the discrepancy between the original data for Xenazine (NDA 21894) and the SD-809-C-12 study results related to the status of 9-O-desmethyl-β-DHTBZ as a MHM.

Additional evidence of how the change in the pooling technique can change the percent of total plasma radioactivity results for the metabolites can be seen by comparing the results in the two tables above: for example M2 after TBZ administration is 18.7% of total in the EOP2 Briefing package and 6.4% of total in Table 10.

Concentration of radioactivity in plasma after [^{14}C]-SD-809 (nominal 25 mg; 2.92 MBq) to male human subjects (Cohort 1)

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Time point (hour)	Subject number						Mean	CV (%)
	001	002	003	004	005	006		
Pre-dose	ND	ND	ND	ND	ND	ND	NC	NC
0.33	ND	ND	ND	ND	ND	ND	NC	NC
0.67	12.6	65.0	15.0	119.8	51.5	89.4	58.9	71.3
1	72.1	119.2	80.9	117.1	60.0	136.5	97.6	31.4
1.5	101.4	144.7	104.4	117.8	82.4	140.7	115.2	20.9
2	106.5	128.7	117.9	113.4	79.8	148.5	115.8	19.8
2.5	111.0	132.3	121.4	101.8	80.2	142.9	114.9	19.5
3	119.7	130.6	124.3	104.5	87.5	138.9	117.6	15.9
4	137.1	125.4	119.1	98.9	90.7	138.7	118.3	16.7
6	128.3	123.0	127.1	93.6	85.8	122.5	113.4	16.4
8	110.2	102.7	121.7	74.3	87.7	110.2	101.1	17.1
12	95.5	72.0	110.3	62.4	77.1	86.5	84.0	20.5
18	63.6	43.9	82.6	36.4	65.9	58.9	58.6	28.2
24	52.5	30.4	61.9	21.6	59.4	57.1	47.2	35.9
36	29.0	16.1	46.5	21.7	49.9	39.8	33.8	40.5
48	22.7	20.4	32.5	17.1	33.4	22.9	24.8	26.7
72	11.5	10.3	12.7	ND	14.6	11.6	10.1	51.0
96	ND	ND	ND	ND	7.9	ND	NC	NC
120	ND	ND	ND	ND	10.1	8.6	3.1	NC
144	ND	ND	ND	ND	ND	ND	NC	NC
168	ND	ND	ND	ND	ND	ND	NC	NC
192	NA	NA	ND	ND	ND	ND	NC	NC

CV Coefficient of variation
NA Not applicable (subject no longer in clinic)
NC Not calculable
ND Not detected (<2 x background radioactivity; included as zero in mean/CV calculation)
Results expressed as ng equivalents/mL

A request for information was sent to the sponsor regarding the plasma pooling strategy. According to the sponsor, the semi-quantitative analyses of metabolites by radioactivity were conducted on the metabolite profile samples from 2 to 12 hours via a per-subject "AUC pool" approach (Hamilton, 1981).
Reviewer's Comment: However, in Hamilton, all (nine) time points covering the whole concentration-time profile were used for pooling.

In addition, the sponsor claims that, in the mass-balance and metabolite identification study conducted with TBZ in NDA 21894, metabolite identification and semi-quantification was performed on samples that were collected out to 8 hours post dose.
Reviewer's Comment: However, in the mass-balance and metabolite identification study conducted with TBZ (NDA 21894), three plasma pools (0.25 – 1.5, 2 – 3 and 4 – 8 hours) were prepared using a total of 13 plasma samples, covering most of the concentration-time profile of TBZ, including Tmax.

In summary, the Metabolite Profiling and Identification results of the mass balance study SD-809-C-12 are not acceptable.
It is recommended that the sponsor assess the concentration of circulating SD-809-related metabolites for the purpose of determining if there are major metabolites in humans dosed with SD-809. The sponsor should use adequate plasma pooling methods.

APPEARS THIS WAY ON ORIGINAL

3.0 DETAILED LABELING RECOMMENDATION

Labeling recommendations will not be provided in this review cycle.

APPEARS THIS WAY ON ORIGINAL

Clinical Pharmacology Individual Study Review

PRODUCT (Generic Name):	Deutetrabenazine (SD-809)
PRODUCT (Brand Name):	Austedo
NDA:	208082
DOSAGE FORM:	tablets
DOSAGE STRENGTH:	6, 9, 12 mg
INDICATION:	Treatment of chorea associated with Huntington's disease
NDA TYPE:	Standard
SUBMISSION DATE:	May 29, 2015
SPONSOR:	Teva Pharmaceuticals, Inc
REVIEWER:	Hristina Dimova, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCPB DIVISION:	DCP-I
OND DIVISION:	HFD-120

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APPEARS THIS WAY ON ORIGINAL

PK and Initial Tolerability Studies

I. AUS-SD-809-CTP-06: A phase 1, randomized, double-blind, single-dose crossover study to compare the pharmacokinetics, safety and tolerability of SD-809 (d6-tetrabenazine) with tetrabenazine in healthy volunteers.

Objectives:

• To compare the pharmacokinetics of SD-809 (d6-tetrabenazine) and tetrabenazine and their respective α- and β-dihydrotetrabenazine (HTBZ) metabolites.
• To evaluate the safety and tolerability of a single dose of SD-809 and tetrabenazine.

Study Design	Randomized, double-blind, two-period, crossover study
Study Population*	21 healthy subjects, male and female, 18-50 years old * 19 subjects included in the PK analysis
Treatment Group	Each subject received a single oral dose of each treatment (see dosage and admin), separated by a minimum seven day wash-out period.
Dosage and Administration	Tetrabenazine (TBZ), 25 mg (powder in size 4 gelatin capsules) ** SD-809, 25 mg (powder in size 4 gelatin capsules) Subjects fasted for at least 4 hours pre and 4 hours post dosing
PK Sampling: plasma	pre-dose, 20 and 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post-dose for each treatment period
Analysis	LC-MS/MS method for TBZ/SD-809 and HTBZ metabolites Range: 0.100 ng/mL to 10.0 ng/mL for SD-809 or TBZ 0.500 ng/mL to 100 ng/mL for HTBZ metabolites
PK Assessment	C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, V_d/F, CL/F of TBZ and metabolites***
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	None

* Four subjects had diminished CYP2D6 function, defined as poor metabolizers (PM) in the study, although all of these PMs had at least one functional allele.
**TBZ used was synthesized by Auspex
*** Tetrabenazine (SD-808)
SD-809 (SD-809)
α-HTBZ (SD-946)
β-HTBZ (SD-947)
d6-α-HTBZ (SD-948)
d6-β-HTBZ (SD-949)

Bioanalytical Assays:

Two validated assays were used: ALM.TBZ.1 for measuring the concentrations of TBZ and its α- and β-HTBZ metabolites in human plasma and ALM.SD809.1 for SD-809 and its deuterated α- and β-HTBZ metabolites.
Assays were validated for clinical use at (b) (4).
In both assays, analytes and the Internal Standards (IS) were extracted from human plasma using a liquid-liquid extraction.

The IS for samples assayed with ALM.TBZ.1 were the deuterated forms of the analytes while the IS for samples assayed with ALM.SD809.1 were the non-deuterated forms of the analytes.
The analytes were separated by HPLC on a C18 column and detected using API4000 MS/MS detector in positive MRM mode.
Plasma concentrations of individual subjects at each time point and performance of the validated assays generating these results are reported in AUS-SD-809-CTP-06 Analytical Phase Report.

Reviewer's Comments:

The performance of the assays (ALM.TBZ.1 and ALM.SD809.1) for TBZ/SD-809 and α- and β-HTBZ metabolites during the analysis of the study samples is acceptable.
Details of the validation results are presented in Bioanalytical Study Reports.
The sponsor claims that the statistical analysis for the O-desmethyl metabolites followed the analysis plan for the parent drug and the alpha- and beta-dihydrotetrabenazine metabolites as described in the Pharmacokinetic Statistical Analysis Plan (PK-SAP), dated 25 Aug 2011. However, only α- and β-HTBZ metabolites are mentioned in the CSR and in 16.1.9.1 Statistical Analysis Plan (Sept 2011):
9.5.4 Drug Concentration Measurement: Tetrabenazine and its α- and β-HTBZ metabolites from individual patients were measured in one assay while SD-809 and its deuterated α- and β-HTBZ metabolites were measured in another.
This analysis is reported in SD-809-CLN-016 - Analytical Phase Report Addendum.
Some of the validation summary in this Addendum include validation results from Study 07, which was conducted later.
Also, it is not indicated in the report how the samples were split (from the ones analyzed for TBZ, α- and β-HTBZ) and how they were stored (study conducted 2 years earlier than the additional analysis of the samples). Therefore, the results for the O-desmethyl metabolites should be considered exploratory and interpreted with caution.

Pharmacokinetic Results:

Pharmacokinetics of Tetrabenazine and SD-809

Plasma concentrations of both TBZ and SD-809 were low relative to the concentrations observed for their metabolites. TBZ and SD-809 concentrations reached a max at approximately one hour, declined rapidly thereafter and were below the limit of detection in most subjects by three hours. Mean C_{max} was about 0.3 ng/ml for both TBZ and SD-809. Elimination half-lives for the majority of subjects were not calculable.
The pharmacokinetics of TBZ and SD-809 did not show appreciable differences in either EMs or the wider population (all evaluable subjects, including IMs).

Pharmacokinetics of α-HTBZ and d6-α-HTBZ

Plasma concentrations of α-HTBZ and d6-α-HTBZ were higher than those measured for β-HTBZ and parent drug.
In EMs, the mean half-lives were almost double for d6-α-HTBZ (7.95 hours) than for α-HTBZ (4.51 hours). This resulted in a greater than two fold increase in overall exposure (AUC_{inf} 316 versus 137 ng·hr/mL). C_{max} values were slightly higher (mean 44.4 versus

42.0 ng/mL) and T_{max} slightly later (median 1.5 versus 1.0 hours) for d6-α-HTBZ compared to α-HTBZ.

Summary of PK Parameters for α-HTBZ and d6-α-HTBZ after 25 mg d0- and d6-TBZ

	Extensive Metabolizers		All Evaluable Subjects	
	SD-809 (n=13)	Tetrabenazine (n=13)	SD-809 (n=19)	Tetrabenazine (n=19)
C_{max} (ng/mL)[a]	44.4 (29.9)	42.0 (39.6)	46.1 (30.4)	41.2 (36.0)
T_{max} (hr)[b]	1.50 (0.67-2.00)	1.00 (0.67-2.00)	1.5 (0.67-2.52)	1.00 (0.67-2.00)
AUC_{inf} (ng·hr/mL)[a]	316 (40.1)	137 (46.7)	373 (39.3)	189 (59.2)
$t_{1/2}$ (hr)[a]	7.95 (34.6)	4.51 (57.4)	8.97 (34.7)	5.47 (51.4)

Summary of PK Parameters for β-HTBZ and d6-β-HTBZ after 25 mg d0- and d6-TBZ

	Extensive Metabolizers		All Evaluable Subjects	
	SD-809 (n=13)	Tetrabenazine (n=13)	SD-809 (n=19)	Tetrabenazine (n=19)
C_{max} (ng/mL)[a]	24.8 (49.3)	18.2 (55.1)	29.6 (49.4)	20.5 (51.5)
T_{max} (hr)[b]	1.50 (1.00-2.07)	1.00 (0.67-2.00)	1.50 (0.67-2.50)	1.00 (0.67-2.50)
AUC_{inf} (ng·hr/mL)[a]	100 (61.3)	42.0 (61.7)	171 (94.0)	74.0 (99.5)
$t_{1/2}$ (hr)[a]	3.51 (61.5)	2.36 (35.9)	5.00 (79.7)	2.95 (57.2)

Summary Pharmacokinetic Parameters for SD-809 and Tetrabenazine after 25 mg Single Doses of SD-809 or Tetrabenazine

	Extensive Metabolizers		All Evaluable Subjects	
	SD-809 (n=13)	Tetrabenazine (n=13)	SD-809 (n=19)	Tetrabenazine (n=19)
C_{max} (ng/mL)[a]	0.303 (59.8)	0.292 (89.7)	0.327 (85.3)	0.314 (111.0)
T_{max} (hr)[b]	0.67 (0.33-1.50)	0.67 (0.33-1.52)*	0.67 (0.33-1.50)†	0.67 (0.33-2.00)‡
AUC_{last} (ng·hr/mL)[a]	0.26 (79.0)	0.18 (105.2)	0.30 (101.9)	0.26 (168.2)
$t_{1/2}$ (hr)[a]	n.c.	n.c.	n.c.	n.c.

a: Mean (%CV) calculated for C_{max}, AUC and $t_{1/2}$ (AUC_{last} presented for parent drug as AUC_{inf} not calculable)
b: Median (range) calculated for T_{max}.
* n=11
†=n=18
‡n=15
n.c. not calculable

Summary of Pharmacokinetic Parameters for total (α+β)-HTBZ and total d6-(α+β)-HTBZ after 25 mg Single Doses of SD-809 or Tetrabenazine

	Extensive Metabolizers		All Evaluable Subjects	
	SD-809 (n=13)	Tetrabenazine (n=13)	SD-809 (n=19)	Tetrabenazine (n=19)
C_{max} (ng/mL)[a]	67.9 (36.3)	60.1 (41.9)	74.6 (37.1)	61.6 (38.2)
T_{max} (hr)[b]	1.50 (0.67-2.00)	1.00 (0.67-2.00)	1.50 (0.67-2.00)	1.00 (0.67-2.50)
AUC_{inf} (ng·hr/mL)[a]	414 (45.1)	177 (50.3)	542 (53.8)	261 (69.6)
$t_{1/2}$ (hr)[a]	7.61 (37.8)	4.05 (57.4)	8.62 (38.2)	4.82 (50.8)

Note: TBZ used in study 06 was synthesized by Auspex. The PK results for TBZ and (α+β)-HTBZ are similar to the PK results when TBZ from (b) (4) source was used (in Study 07).

PK results from Study 07 (Table 4 in Sect 2.7.2):

Table 4. Pharmacokinetic Parameters Following Administration of Single Doses of SD-809 or Tetrabenazine (Study AUS-SD-809-CTP-07, Part 2; Per-Protocol PK Analysis Set, N=12/Treatment)

Parameter	SD-809 7.5 mg[a]	SD-809 15 mg[a]	SD-809 22.5 mg[a]	Tetrabenazine 25 mg[b]
		Parent		
C_{max} (ng/mL)	0.064 (107)	0.196 (24)	0.303 (49)	0.328 (91)
t_{max} (h)	2.75 (2.50-3.50) (n=6)	3.00 (2.00-3.50)	3.00 (2.50-4.00)	0.75 (0.50-1.52)
t_{lag} (h)	2.25 (1.00-3.00) (n=6)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	0.00 (0.00-1.00)
AUC_{last} (ng•h/mL)	0.039 (121)	0.219 (53)	0.428 (51)	0.302 (110)
$t_{½}$ (h)	NC	NC	NC	NC
		Total (α+β)-HTBZ		
C_{max} (ng/mL)	21.4 (32)	45.3 (18)	67.5 (25)	55.5 (39)
t_{max} (h)	3.00 (2.50-5.00)	3.26 (2.50-4.00)	3.75 (3.00-5.02)	1.25 (0.50-2.50)
t_{lag} (h)	1.00 (0.00-2.50)	1.00 (0.00-1.05)	0.00 (0.00-1.00)	0.00 (0.00-0.00)
AUC_{inf} (ng•h/mL)	176 (39)	408 (36)	610 (48)	320 (69)
$t_{½}$ (h)	7.18 (19)	7.66 (18)	8.38 (26)	5.57 (34)

In addition, the PK results for (α+β)-HTBZ are similar to the dose-adjusted PK results when TBZ from (b) (4) source was used (in study SD-809-C-21).

Study SD-809-C-21 Results:
Summary of PK Parameters for total (α+β)-HTBZ and total d6-(α+β)-HTBZ after Single Doses of SD-809 or Tetrabenazine

Metabolite	Parameter	Statistic	SD-809 12 mg N=41	SD-809 24 mg N=41	Tetrabenazine 50 mg N=41
(α+β)-HTBZ	C_{max} (ng/mL)	mean (CV%)	25.8 (31)	53.3 (30)	94.2 (44)
	t_{max} (h)	median (min, max)	4 (2, 5)	4 (1.5, 8)	1.5 (1, 5)
	$AUC_{(0-24)}$ (ng·h/mL)	mean (CV%)	234 (37)	503 (36)	608 (57)
	AUC_{inf} (ng·h/mL)[a]	mean (CV%)	252 (35) [n=36]	547 (34) [n=35]	577 (45) [n=38]
α-HTBZ	C_{max} (ng/mL)	mean (CV%)	16.1 (24)	32.6 (24)	59.4 (37)
	t_{max} (h)	median (min, max)	4 (2, 5)	4 (1.5, 8)	1.5 (1, 5)
	$AUC_{(0-24)}$ (ng·h/mL)	mean (CV%)	157 (24)	328 (25)	407 (44)
	AUC_{inf} (ng·h/mL)	mean (CV%)	ND	ND	ND
β-HTBZ	C_{max} (ng/mL)	mean (CV%)	9.73 (47)	20.8 (44)	34.9 (57)
	t_{max} (h)	median (min, max)	4 (2, 5)	4 (1.5, 8)	1.5 (1, 4)
	$AUC_{(0-24)}$ (ng·h/mL)	mean (CV%)	77.7 (66)	175 (61)	201 (87)
	AUC_{inf} (ng·h/mL)	mean (CV%)	ND	ND	ND

Source: Pharmokinetic Report Appendix 16.1.13, Table 8-A and Table 14.2.2.2.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma drug concentration; CV, coefficient of variation; HTBZ, dihydrotetrabenazine; min, minimum; max, maximum; ND, not determined; t_{max}, time to maximum plasma concentration.
[a] The (α+β)-HTBZ AUC_{inf} was calculated using the subset of subjects whose extrapolated AUC accounted for no more than 20% of AUC_{inf}.

Effect of CYP2D6 Phenotype of the PK of the Primary Metabolites of Tetrabenazine and SD-809

Four subjects were identified as PM (Subjects 001104, 001105, 001107 and 001204). The genotypes for these subjects were *4/*41,* 4/*41,* 4/*41 and *4/*10 for Subjects 001104, 001105, 001107 and 001204 respectively. The *4 designation represents a null allele and *41 and *10 represent an allelic variant that results in partial metabolic capacity.

Deuteration increased exposure to the active metabolites of SD-809 (d6-α-HTBZ and d6-β-HTBZ) relative to those from tetrabenazine in these subjects.

Comment: however PM had still 2x increased AUC_{inf} levels of total (α+β)-d6-TBZ compared to EM/IM after SD-809 administration. PM had 3x increased AUC_{inf} levels of total (α+β)-TBZ compared to EM/IM after TBZ administration, see tables below.

According to the sponsor, the ability of deuteration to affect the pharmacokinetics of the active metabolites of SD-809 in these subjects is consistent with their genetic potential for partial CYP2D6 metabolism. Note: This was confirmed by the pharmacogenomics reviewer.

14.2.4b Table of Summary of Pharmacokinetic Parameters by Treatment and Analyte (Phenotype = EM, IM
Treatment=Tetrabenazine (d0-tetrabenazine) 25 mg Analyte Name = total dihydrotetrabenazine

Phenotype		Cmax (ng/mL)	Tmax (hr)	AUCt (hr*ng/mL)	Lambda z (1/hr)	Thalf (hr)	AUCinf (hr*ng/mL)	CL/F (L/hr)
EM	101	52.9	2.00	132.9	0.248	2.80	136.2	184.7
EM	102	46.7	0.67	100.2	0.226	3.06	102.8	244.8
EM	103	26.1	1.00	71.1	0.381	1.82	76.1	330.7
EM	106	71.9	0.67	185.1	0.116	5.96	189.6	132.7
EM	108	44.0	1.00	100.2	0.215	3.23	102.7	245.0
IM	109	72.9	1.00	297.6	0.132	5.26	309.1	81.4
EM	110	59.5	1.00	179.8	0.232	2.98	184.9	136.1
EM	201	29.7	1.50	170.7	0.224	3.10	177.9	141.5
EM	202	55.6	1.50	300.2	0.119	5.80	314.4	80.0
EM	203	98.8	1.00	203.9	0.109	6.37	212.4	118.4
IM	205	34.6	2.00	179.4	0.187	3.71	182.4	137.9
EM	206	76.1	1.00	132.0	0.296	2.34	135.8	185.3
EM	207	31.8	1.00	91.1	0.321	2.16	93.4	269.3
IM	208	68.8	1.50	399.1	0.111	6.22	405.1	62.1
EM	209	91.1	0.67	374.2	0.070	9.96	384.1	65.5
EM	211	97.1	0.67	186.4	0.228	3.04	190.3	132.2
EM,IM	N	16	16	16	16	16	16	16
EM,IM	Mean	59.85	1.14	194.0	0.201	4.24	199.8	159.2
EM,IM	Std Dev	23.82	0.44	99.5	0.087	2.17	102.0	78.5
EM,IM	CV (%)	39.8	38.7	51.3	43.3	51.2	51.1	49.3
EM,IM	Median	57.55	1.00	179.6	0.219	3.16	183.6	137.0
EM,IM	Minimum	26.07	0.67	71.1	0.070	1.82	76.1	62.1
EM,IM	Maximum	98.80	2.00	399.1	0.381	9.96	405.1	330.7
EM,IM	GeoMean	55.16	1.06	172.1	0.182	3.80	177.4	141.8

14.2.4c Table of Summary of Pharmacokinetic Parameters by Treatment and Analyte (Phenotpye = PM
Treatment=Tetrabenazine (d0-tetrabenazine) 25 mg Analyte Name = total dihydrotetrabenazine

Phenotype		Cmax (ng/mL)	Tmax (hr)	AUCt (hr*ng/mL)	Lambda z (1/hr)	Thalf (hr)	AUCinf (hr*ng/mL)	CL/F (L/hr)
PM	104	54.2	1.50	641.9	0.078	8.90	648.7	38.8
PM	105	98.8	1.00	712.9	0.082	8.41	719.1	35.0
PM	107	60.6	2.50	380.0	0.108	6.41	385.6	65.3
PM	204	143.6	0.67	704.4	0.087	7.96	712.1	35.3
PM only	N	4	4	4	4	4	4	4
PM only	Mean	89.30	1.42	609.8	0.089	7.92	616.4	43.6
PM only	Std Dev	41.21	0.80	156.5	0.013	1.08	157.1	14.5
PM only	CV (%)	46.1	56.4	25.7	15.0	13.6	25.5	33.4
PM only	Median	79.70	1.25	673.2	0.085	8.18	680.4	37.1
PM only	Minimum	54.20	0.67	380.0	0.078	6.41	385.6	35.0
PM only	Maximum	143.60	2.50	712.9	0.108	8.90	719.1	65.3
PM only	GeoMean	82.62	1.26	591.6	0.088	7.86	598.2	42.1

Note: 3x increased AUC_{inf} levels of total (α+β)-HTBZ in PM compared to EM/IM after TBZ

14.2.4b Table of Summary of Pharmacokinetic Parameters by Treatment and Analyte (Phenotype = EM, IM
Treatment=SD-809 (d6-tetrabenazine) 25 mg Analyte Name = total d6- dihydrotetrabenazine

Phenotype		Cmax (ng/mL)	Tmax (hr)	AUCt (hr*ng/mL)	Lambda z (1/hr)	Thalf (hr)	AUCinf (hr*ng/mL)	CL/F (L/hr)
EM	101	83.0	1.50	418.7	0.094	7.40	428.0	58.8
EM	102	39.7	0.67	235.0	0.065	10.61	249.3	100.9
EM	103	43.7	1.00	182.4	0.230	3.01	188.6	133.4
EM	106	79.5	1.50	490.6	0.089	7.80	496.6	50.7
EM	108	37.5	2.00	215.1	0.161	4.30	221.9	113.3
IM	109	131.2	0.67	561.6	0.083	8.36	570.8	44.1
EM	110	74.4	1.50	474.7	0.103	6.75	483.6	52.0
EM	201	35.5	1.50	290.3	0.084	8.26	301.3	83.5
EM	202	116.3	1.00	776.7	0.067	10.34	787.9	31.9
EM	203	85.9	1.50	450.4	0.080	8.71	457.0	55.0
IM	205	44.8	1.50	430.0	0.096	7.25	442.7	56.8
EM	206	71.2	2.00	312.9	0.120	5.75	324.7	77.5
EM	207	49.1	2.00	258.1	0.142	4.88	269.4	93.4
IM	208	97.7	1.50	849.7	0.061	11.28	862.6	29.2
EM	209	82.7	0.67	730.7	0.051	13.70	742.8	33.9
EM	211	84.4	2.00	423.2	0.094	7.37	432.9	58.1
EM, IM	N	16	16	16	16	16	16	16
EM, IM	Mean	72.28	1.41	443.8	0.101	7.86	453.8	67.0
EM, IM	Std Dev	28.76	0.48	202.6	0.045	2.74	203.3	30.5
EM, IM	CV (%)	39.8	34.1	45.7	44.3	34.8	44.8	45.5
EM, IM	Median	76.95	1.50	426.6	0.091	7.60	437.8	57.5
EM, IM	Minimum	35.45	0.67	182.4	0.051	3.01	188.6	29.2
EM, IM	Maximum	131.20	2.00	849.7	0.230	13.70	862.6	133.4
EM, IM	GeoMean	66.83	1.32	402.1	0.094	7.38	412.9	60.9

14.2.4c Table of Summary of Pharmacokinetic Parameters by Treatment and Analyte (Phenotpye = PM
Treatment=SD-809 (d6-tetrabenazine) 25 mg Analyte Name = total d6- dihydrotetrabenazine

Phenotype		Cmax (ng/mL)	Tmax (hr)	AUCt (hr*ng/mL)	Lambda z (1/hr)	Thalf (hr)	AUCinf (hr*ng/mL)	CL/F (L/hr)
PM	104	108.8	1.00	1204.7	0.046	14.93	1244.9	20.2
PM	105	68.6	2.00	1013.4	0.048	14.42	1037.7	24.2
PM	107	83.6	2.00	742.6	0.080	8.64	755.6	33.3
PM	204	27.2	0.67	646.5	0.065	10.59	656.2	38.3
PM only	N	4	4	4	4	4	4	4
PM only	Mean	72.05	1.42	901.8	0.060	12.15	923.6	29.0
PM only	Std Dev	34.19	0.69	254.8	0.016	3.03	268.3	8.3
PM only	CV (%)	47.5	48.5	28.3	26.6	25.0	29.1	28.5
PM only	Median	76.10	1.50	878.0	0.057	12.50	896.7	28.8
PM only	Minimum	27.20	0.67	646.5	0.046	8.64	656.2	20.2
PM only	Maximum	108.80	2.00	1204.7	0.080	14.93	1244.9	38.3
PM only	GeoMean	64.18	1.28	875.0	0.059	11.85	894.6	28.1

Note: 2x increased AUC_{inf} levels of total (α+β)-d6-HTBZ in PM compared to EM/IM after SD-809 administration

In addition, the following metabolites were also analyzed in this study:

O-desmethyl Metabolites Analyzed

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Delivered compound: Tetrabenazine		Delivered compound: SD-809	
Compound number	Analyte	Compound number	Analyte
SD-971	9-O-desmethyl α-HTBZ	SD-975	d_3-9-O-desmethyl α-HTBZ
SD-972	10-O-desmethyl α-HTBZ	SD-976	d_3-10-O-desmethyl α-HTBZ
SD-973	9-O-desmethyl β-HTBZ	SD-977	d_3-9-O-desmethyl β-HTBZ
SD-974	10-O-desmethyl β-HTBZ	SD-978	d_3-10-O-desmethyl β-HTBZ

The highest plasma concentrations were observed for 9-O-desmethyl-β-HTBZ, followed by the 9-O-desmethyl-α-HTBZ with plasma concentrations of 10-O-desmethyl-β-HTBZ being very low. Plasma concentrations of both deuterated and non-deuterated 10-O-desmethyl-α-HTBZ could not be quantified in any subject.
For all the quantifiable O-desmethyl metabolites, plasma concentrations measured in subjects following administration of SD-809 were lower relative to those measured following administration of tetrabenazine.
A summary of the mean PK parameters of the O-desmethyl metabolites of SD-809 (d6-tetrabenazine) and tetrabenazine by analyte is provided below (however these results should be considered exploratory and interpreted with caution, see bioanalytical assay).

Summary of Key Pharmacokinetic Parameters by Analyte

(n=14)	Mean (Standard Deviation), n=14				
Analyte	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	$T_{½}$ (hr)
d_6-alpha-HTBZ	45.3 (15.8)	1.37 (0.61)	329 (145)	339 (145)	8.38 (2.78)
alpha-HTBZ	38.9 (13.5)	1.18 (0.45)	147 (76.0)	154 (79.0)	4.99 (2.52)
d_3-9-O-desmethyl α-HTBZ	2.15 (1.13)	4.15 (3.83)	21.0 (7.8)	35.4** (12.1)	11.0** (3.8)
9-O-desmethyl α-HTBZ	5.05 (1.95)	1.79 (1.01)	42.5 (20.0)	49.8** (29.8)	6.95** (3.28)
d_6-beta-HTBZ	26.9 (15.3)	1.48 (0.44)	111 (71)	116 (75)	3.92 (2.21)
beta-HTBZ	18.4 (10.4)	1.20 (0.43)	46.4 (30.2)	49.0 (31.0)	2.46 (0.82)
d_3-9-O-desmethyl β-HTBZ	6.29 (1.99)	2.66 (2.12)	92.4 (27.4)	107 (29)	15.5 (4.6)
9-O-desmethyl β-HTBZ	15.7 (4.3)	1.83 (0.89)	205 (67)	220 (69)	16.2 (3.7)
d_3-10-O-desmethyl β-HTBZ	0.59 (0.44)	1.45* (0.37)	0.68 (0.76)	***	***
10-O-desmethyl β-HTBZ	1.62 (0.60)	1.42 (0.59)	2.97 (1.37)		

Source: Table 14.2.4(ODM)

* n=10 for T_{max} not estimable for 4 subjects due to all concentrations below quantitation.
** n=4 for d_3-9-O-desmethyl α-dihydrotetrabenazine, n=8 for 9-O-desmethyl α-HTBZ
*** $T_{½}$ and $AUC_{0-\infty}$ not estimable in any subject

Note: The 2x increase in (α+β)-d6-HTBZ relative to (α+β)-d0-HTBZ is accompanied by a 2x decrease in d3-9-O-desmethyl β-DHTBZ relative to 9-O-desmethyl β-DHTBZ.

Safety Results:

No serious adverse events were reported in the study. No significant changes in laboratory parameters, vital signs, or ECGs were observed following either treatment.
A total of 37 TEAEs was reported in 15 of the 21 enrolled subjects during the study, most of these AEs were mild. The most common adverse events following both treatments were somnolence, nausea and headache.
One subject (an EM) withdrew consent for study participation approximately four hours following dosing with SD-809 in Period 1 due to AEs of headache, nausea, agitation and photophobia.

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II. AUS-SD-809-CTP-07: A Phase 1 Study to Evaluate the Pharmacokinetics of Two Extended Release (ER) Formulations of SD-809 with and without Food, compared to Tetrabenazine Tablets and the Pharmacokinetics and Dose Proportionality of the Selected Formulation Following Single and Multiple Doses

Objectives:

• Evaluate the safety and pharmacokinetics of two candidate formulations of SD-809 ER relative to tetrabenazine (TBZ)
• Evaluate the effect of food on the bioavailability of SD-809 ER
• Select a formulation of SD-809 ER for use in future clinical studies
• Evaluate the dose-proportionality of single and multiple doses of SD-809 ER
• Compare steady state pharmacokinetics of SD-809 ER and tetrabenazine

Study Design	Part 1: randomized, open-label, single-dose, five-way crossover study of TBZ and two SD-809 ER formulations in healthy subjects Part 2: open-label, single and multiple ascending dose study of SD-809 ER and TBZ in healthy subjects
Study Population	Two separate cohorts of 24 healthy subjects for Part 1 and Part 2. Healthy male or female subjects aged ≥18 and ≤50 years inclusive; CYP2D6 extensive or intermediate metabolizer phenotype.
Treatment Groups	5 treatment groups in Part 1, two treatment groups in Part 2 (see dosage and admin)
Dosage and Administration	Part 1: a single oral dose of each of the following: • Tetrabenazine 25 mg (fasted state) * • SD-809 ER 15 mg formulation A (fasted state) • SD-809 ER 15 mg formulation B (fasted state) • SD-809 ER 15 mg formulation A (fed state) • SD-809 ER 15 mg formulation B (fed state) Part 2: SD-809 Formulation A in the fed state and TBZ in the fasted state**
PK Sampling: plasma	See ***
Analysis	LC-MS/MS method for TBZ and metabolites, including deuterated and non-deuterated forms of α- and β-dihydrotetrabenazine (HTBZ) and the O-desmethyl-metabolites of α- and β-HTBZ Range: 0.100 ng/mL to 10.0 ng/mL for SD-809 or tetrabenazine 0.500 ng/mL to 100 ng/mL for HTBZ metabolites 0.500 to 50.0 ng/mL for O-desmethyl-metabolites
PK Assessment	C_{max}, t_{max}, AUC_{0-t}, AUC_{0-12}, AUC_{0-inf}, $t_{1/2}$, R_{ac}, V_d/F, CL/F of TBZ/SD-809 and metabolites
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	None

* TBZ from (b) (4) source was used
** Dosing in Part 2:

Day	Group 1 (N=12)	Group 2 (N=12)
D1*	SD-809 ER 7.5 mg x 1	Tetrabenazine 25 mg x 1
D4*	SD-809 ER 15 mg x 1	SD-809 ER 22.5 mg x 1
D7	SD-809 ER 7.5 mg BID	Tetrabenazine 25 mg BID
D8	SD-809 ER 7.5 mg BID	Tetrabenazine 25 mg BID
D9	SD-809 ER 7.5 mg BID	Tetrabenazine 25 mg BID
D10*	SD-809 ER 7.5 mg x 1	Tetrabenazine 25 mg x 1
D13	SD-809 ER 7.5 mg BID	SD-809 ER 7.5 mg BID
D14	SD-809 ER 15 mg BID	SD-809 ER 15 mg BID
D15	SD-809 ER 15 mg BID	SD-809 ER 22.5 mg BID
D16	SD-809 ER 15 mg BID	SD-809 ER 22.5 mg BID
D17*	SD-809 ER 15 mg x1	SD-809 ER 22.5 mg x 1

*** **Blood sampling in Part 1 and Part 2**:

Study Period	Screen		Single-Dose Regimen						Multiple-Dose Regimen 1						Multiple Dose Regimen 2							
Day	D-21-D-2	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19	D20 / Term [5]
Drug administration [4]			X			X			X	X	X	X			X	X	X	X	X			
PK blood sampling [10]			12X	2X	2X	13X	2X	1X	1X	1X	1X	12X [10]	2X [10]	2X [10]	1X [10]	1X	1X	1X	13X	2X	1X	1X
			Pre-dose	24 hrs	48 hrs	Pre-dose	24 hrs	48 hrs	Pre-dose	Pre-dose	Pre-dose	Pre-dose	24 hrs	48 hrs	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	24 hrs	48 hrs	72 hrs
			30 min	36 hrs	60 hrs	1 hr	36 hrs					30 min	36 hrs	60 hrs					1 hr	36 hrs		
			1 hr			2 hrs						1 hr							2 hrs			
			1.5 hrs			2.5 hrs						1.5 hrs							2.5 hrs			
			2 hrs			3 hrs						2 hrs							3 hrs			
			2.5 hrs			3.5 hrs						2.5 hrs							3.5 hrs			
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			4 hrs			5 hrs						4 hrs							5 hrs			
			6 hrs			6 hrs						6 hrs							6 hrs			
			8 hrs			7 hrs						8 hrs							7 hrs			
			12 hrs			8 hrs						12 hrs							8 hrs			
			16 hrs			12 hrs						16 hrs							12 hrs			
						16 hrs													16 hrs			

Bioanalytical Assays:

Two validated assays were used: ALM.TBZ.1 for measuring the concentrations of TBZ and its α- and β-HTBZ metabolites in human plasma and ALM.SD809.1 for SD-809 and its deuterated α- and β-HTBZ metabolites.

Separate validated assays were used to measure the 9-O- and 10-O-desmethyl metabolites of deuterated and non-deuterated α-HTBZ and β-HTBZ (SD-809-CLN-050 and SD-809-CLN-051).

Assays were validated at [redacted] (b) (4) in the following ranges:

0.100 ng/mL to 10.0 ng/mL for SD-809 or tetrabenazine

0.500 ng/mL to 100 ng/mL for HTBZ metabolites

0.500 to 50.0 ng/mL for O-desmethyl-metabolites

Reviewer's Comment: The validation of the assays and the performance of the assays for TBZ/SD-809 and the metabolites during the analysis of the study samples are acceptable. Details of the validation results are presented in Bioanalytical Study Reports.

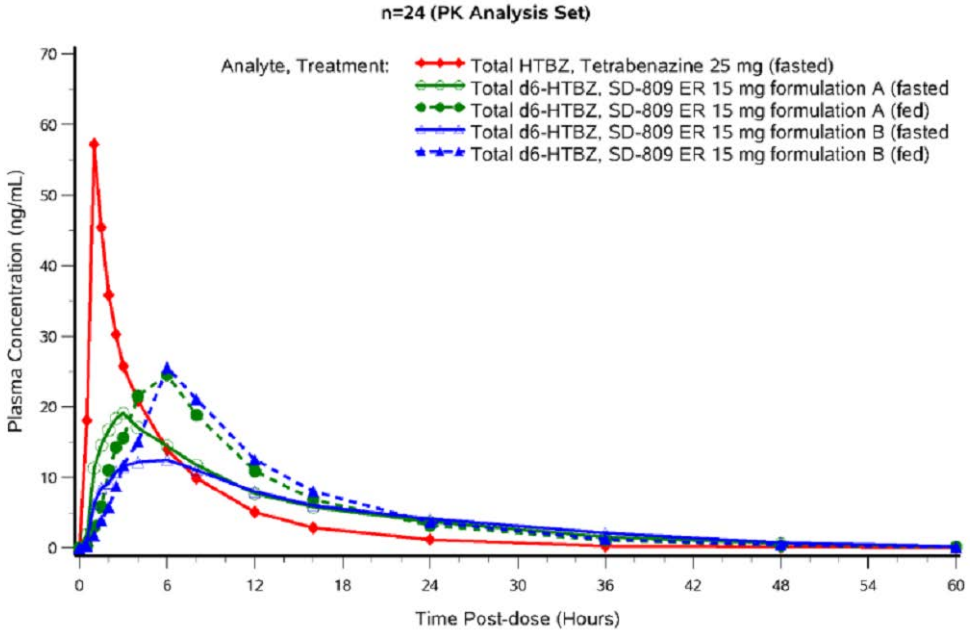
Pharmacokinetic Results:

Part 1:

The C_{max} values for total (α+β)-HTBZ were lower for both SD-809 ER formulations in the fed and fasted states at a dose level of 15 mg than for tetrabenazine at a dose level of 25 mg. The Tmax values were significantly later for total (α+β)-HTBZ for both SD-809 ER formulations in the fed and fasted states compared with tetrabenazine (2.5 to 6 hours compared with 1 hour). The apparent half-life was significantly longer for total (α+β)-HTBZ following SD-809 ER in the fed and fasted states compared with tetrabenazine.
Note: The $t_{1/2}$ appears to be longer in the fasted state for both formulations.

d_6-Total (α+β)-HTBZ or Total (α+β)-HTBZ / Mean (CV%) (N=24) (Per-Protocol Pharmacokinetic Analysis Set)					
	SD-809 ER-A 15 mg Fed	SD-809 ER-B 15 mg Fed	SD-809 ER-A 15 mg Fasted	SD-809 ER-B 15 mg Fasted	Tetrabenazine 25 mg
C_{max} (ng/mL)	33.3 (33)	28.7 (39)	22.5 (36)	14.5 (42)	65.1 (33)
t_{max} (hr)	4.80 (35)	6.28 (31)	2.65 (70)	4.22 (67)	1.13 (33)
t_{lag} (hr)	0.81 (99)	1.02 (97)	0.23 (128)	0.29 (123)	0.06 (270)
AUC_{inf} (ng·hr/mL)	305 (46)	315 (46)	273 (45)	259 (47)	257 (69)
$t_{1/2}$ (hr)	6.99 (23)	7.02 (20)	9.35 (25)	9.95 (16)	4.46 (57)

Mean Plasma Concentration of Total HTBZ by Treatment (Part 1)



There was a food effect for both SD-809 ER formulations, with significantly higher C_{max} of the HTBZ metabolites administration after food than when fasting and an increase of 50% for formulation A and 100% for formulation B.
The AUC_{0-t} was increased slightly (11% for formulation A) when administered in the fed state, but to a lesser extent as compared to C_{max}.
Based on the pharmacokinetic data observed in Part 1, SD-809 ER formulation A, was selected for use in Part 2.
Note: SD-809 was administered with food in all subsequent studies.

Comparison of Pharmacokinetic Parameters for SD-809 Formulations, Fed vs Fasted – Part 1

		% Ratio of LS Mean Fed/Fasted (90% Confidence Interval), N=24 (Per-Protocol Pharmacokinetic Analysis Set)	
		SD-809 ER A 15 mg fed/fasted	SD-809 ER B 15 mg fed/fasted
Total d_6-HTBZ	C_{max} (ng/mL)	149.7 (126.0-177.8)	199.5 (170.7-233.3)
	AUC_{0-t} (hr*ng/mL)	111.5 (104.6-118.9)	126.8 (118.9-135.1)
	AUC_{0-inf}* (hr*ng/mL)	110.6 (104.0-117.7)	123.8 (116.1-132.0)[a]
	$t_{1/2}$* (hr)	75.3 (70.7-80.3)	70.1 (65.8-74.7)[a]

* determined from subjects with estimable terminal half-life for both treatments
[a] n=23; [b] n=20, [c] n=17

Part 2:
With single doses and at steady state, the terminal elimination half-lives for d6-α-HTBZ, d6-β-HTBZ, and d6-(α+β)-HTBZ following all SD-809 ER doses administered were longer than their non-deuterated counterparts in the tetrabenazine control.
The median T_{max} of HTBZ analytes was 3 to 4 hours post-dose for both single dose and steady state across the dose range of SD-809 ER, compared with approximately 1 hour for tetrabenazine.
At steady state, the peak to trough fluctuation for total (α+β)-HTBZ of SD-809 was much lower (3 to 4 fold) than those observed for the corresponding analytes of tetrabenazine (approximately 11-fold).

	Mean (CV%) N=24 (Per-Protocol Pharmacokinetic Analysis Set)			
	SD-809 ER 7.5 mg Fed (n=12)	SD-809 ER 15 mg Fed (n=12)	SD-809 ER 22.5 mg Fed (n=12)	Tetrabenazine 25 mg (n=12)
Single Dose Total d_6-(α+β)-HTBZ or Total (α+β)-HTBZ				
C_{max} (ng/mL)	21.4 (32)	45.3 (18)	67.5 (25)	55.5(39)
t_{max} (hr)	3.17 (22)	3.21 (14)	3.79 (22)	1.42 (45)
t_{lag} (hr)	0.71 (106)	0.59 (88)	0.33 (148)	0.13 (181)
AUC_{inf} (ng·hr/mL)	176 (39)	408 (36)	610 (48)	320 (69)
$t_{1/2}$ (hr)	7.18 (19)	7.66 (18)	8.38 (26)	5.57 (34)
Steady State Total d_6-(α+β)-HTBZ or Total (α+β)-HTBZ				
C_{max} (ng/mL)	31.5 (26)	72.0 (20)	111 (43)	94.9 (31)
t_{max} (hr)	3.17 (16)	2.78 (15)	3.75 (21)	1.34 (46)
AUC_{0-12} (ng·hr/mL)	203 (34)	443 (28)	769 (46)	416 (57)
$t_{1/2}$ (hr)	8.76 (22)	9.06 (28)	9.50 (24)	6.30 (31)
C_{min} (ng/mL)	10.1 (48)	21.1 (41)	39.5 (59)	13.4 (89)
C_{max} / C_{min}	3.50 (31)	3.75 (30)	3.03 (19)	10.8(58)

A descriptive summary of key steady-state pharmacokinetic parameters of the O-desmethyl HTBZ metabolites for the dose administered on Day 17 to Group 1 (SD-809 ER formulation A 15 mg Fed) and on Day 10 to Group 2 (tetrabenazine 25 mg Fasted) is provided below.

Summary of Steady State Pharmacokinetic Parameters by Treatment of 9-O-desmethyl-HTBZ Metabolites– Part 2

	N=24 (Per-Protocol Pharmacokinetic Analysis Set)	
	SD-809 ER 15 mg Fed N=11	Tetrabenazine 25 mg N=12
d_3-9-O-desmethyl α-HTBZ or 9-O-desmethyl α-HTBZ		
C_{max} (ng/mL)	1.34 (18)	6.41 (38)
t_{max} (hr)	2.95 (16)	1.67 (48)
AUC_{0-12} (ng·hr/mL)	11.5 (22)	50.8 (38)
$t_{1/2}$ (hr)	NC	12.3 (24)
d_3-10-O-desmethyl α-HTBZ or 10-O-desmethyl α-HTBZ		
C_{max} (ng/mL)	0.00 (0.0)	0.595 (34)
t_{max} (hr)	NC	1.00 [a] (22)
AUC_{0-12} (ng·hr/mL)	0.00 (0.0)	2.10 (87)
$t_{1/2}$ (hr)	NC	NC
d_3-9-O-desmethyl β-HTBZ or 9-O-desmethyl β-HTBZ		
C_{max} (ng/mL)	6.41 (15)	27.9 (23)
t_{max} (hr)	3.05 (14)	1.63 (44)
AUC_{0-12} (ng·hr/mL)	59.3 (15)	224 (23)
$t_{1/2}$ (hr)	16.2 (11)	17.1 (21)
d_3-10-O-desmethyl β-HTBZ or 10-O-desmethyl β-HTBZ		
C_{max} (ng/mL)	0.046 (332)	1.61 (34)
t_{max} (hr)	NC	1.50 (40)
AUC_{0-12} (ng·hr/mL)	0.023 (332)	4.92 (41)
$t_{1/2}$ (hr)	NC	NC

[a] n=11; NC=Not Calculable (n≤ 1)

At steady state, the plasma levels of O-desmethyl metabolites of HTBZ were about 75% lower following administration of 15 mg SD-809 ER compared with 25 mg tetrabenazine (even though exposure to the active moieties α-HTBZ and β-HTBZ for these dose levels were similar).

Assessment of Accumulation and Time Dependence

The ratios of steady-state pharmacokinetics of α-HTBZ and β-HTBZ compared with their corresponding single-dose values are presented by treatment below.

	Ratios (Steady State / Single Dose) Geometric Mean (CV%) N=24 (Per-Protocol Pharmacokinetic Analysis Set)			
	SD-809 ER 7.5 mg BID Fed (n=12)	SD-809 ER 15 mg BID Fed (n=11)	SD-809 ER 22.5 mg BID Fed (n=12)	Tetrabenazine 25 mg BID (n=12)
	Total d_6-(α+β)-HTBZ or Total (α+β)-HTBZ			
[C_{max},SS]/[C_{max},SD]	1.49 (23)	1.57 (9)	1.56 (35)	1.76 (53)
Rac	1.82 (16)	1.77 (11)	2.00 (30)	1.70 (31)
[AUC_{0-12},SS]/[AUC_{0-inf},SD]	1.17 (14)	1.13 (13)	1.26 (17)	1.39 (33)
[$t_{1/2}$,SS]/[$t_{1/2}$,SD]	1.21 (11)	1.16 (17)	1.14 (9)	1.15 (34)

CV: coefficient of variation; SD: single dose; SS: steady state; HTBZ: dihydrotetrabenazine; AUC: area under the concentration time curve; C_{max}: maximum observed plasma concentration; Rac: Accumulation ratio, defined as $AUC_{0-\tau}$ at steady state divided by $AUC_{0-\tau}$ following a single dose where τ is the dose interval used for multiple dosing; $t_{1/2}$: half-life

Linearity with dose was assessed using a power regression model. The estimates of the exponents of dose for each of C_{max} and AUC were slightly greater than unity although these differences were not statistically significant. The r^2 value was at least 85% for each of these parameters, indicating that linear dose dependence was able to explain most of the variation across dose levels for these parameters.

Table of Linear Regression Analysis of α- and β-HTBZ Pharmacokinetic Parameters across Treatments and Dose Levels

Estimation of beta for model: Parameter = beta * Dose, zero intercept
Determined from linear regression model: Parameter) = Dose / noint

			Estimation of Beta				
	Analyte	PK Parameter	Estimate	Standard Error	Lower CL	Upper CL	R-square
Single Dose	d6-alpha-HTBZ	Cmax	1.79	0.06	1.67	1.90	0.97
	d6-beta-HTBZ	Cmax	1.22	0.07	1.08	1.35	0.91
	total d6-HTBZ	Cmax	3.00	0.11	2.76	3.23	0.95
	d6-alpha-HTBZ	AUCinf	18.32	0.94	16.41	20.24	0.92
	d6-beta-HTBZ	AUCinf	8.74	1.06	6.58	10.89	0.66
	total d6-HTBZ	AUCinf	26.89	1.93	22.98	30.81	0.85
Steady State	d6-alpha-HTBZ	Cmax	3.00	0.15	2.70	3.31	0.92
	d6-beta-HTBZ	Cmax	1.84	0.15	1.53	2.15	0.81
	total d6-HTBZ	Cmax	4.83	0.30	4.23	5.43	0.89
	d6-alpha-HTBZ	AUC(0-12)	20.89	1.02	18.81	22.96	0.92
	d6-beta-HTBZ	AUC(0-12)	11.53	1.34	8.81	14.26	0.69
	total d6-HTBZ	AUC(0-12)	32.42	2.31	27.72	37.11	0.85

In conclusion, the pharmacokinetics of d6-α-HTBZ, d6-β-HTBZ, and d6-(α+β)-HTBZ are approximately linear with dose with the data suggesting increases in AUC and C_{max} which are slightly greater than dose proportional.
The dose of SD-809 ER, estimated to provide total (α+β)-HTBZ exposure comparable to that from tetrabenazine 25 mg (determined from regression models of single-dose exposure AUC_{inf} and steady state AUC_{0-12}), was 11.4 – 13.2 mg.

Figure of Single Dose Pharmacokinetic Parameters across Dose Levels by Analyte (Part 2)

Cmax (ng/mL)

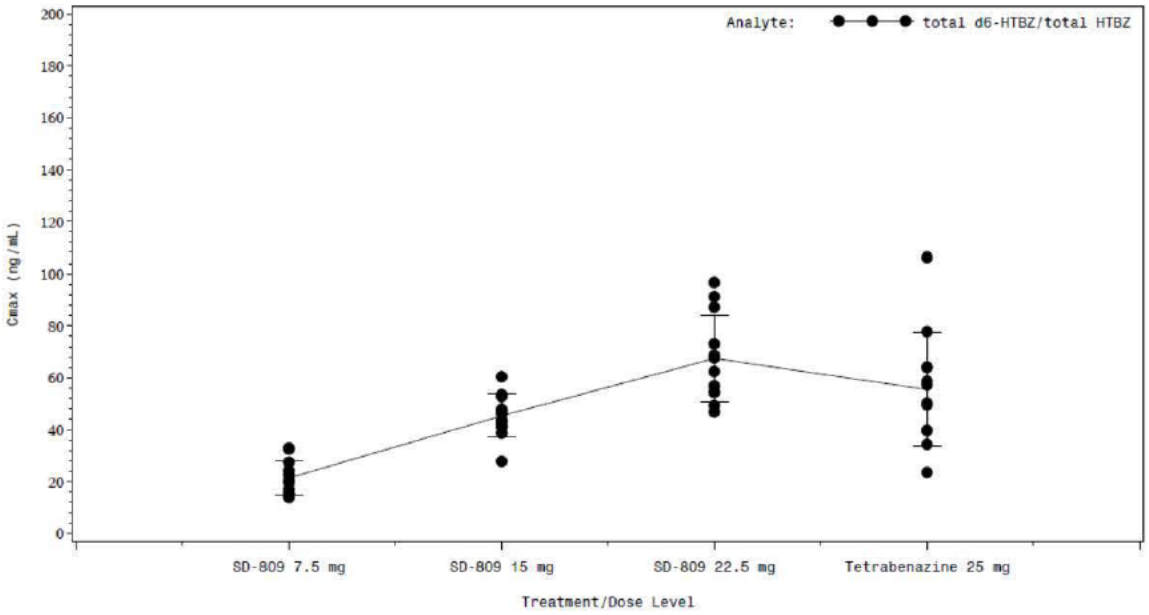


Figure of Single Dose Pharmacokinetic Parameters across Dose Levels by Analyte (Part 2)

AUC(0-12) (hr*ng/mL)

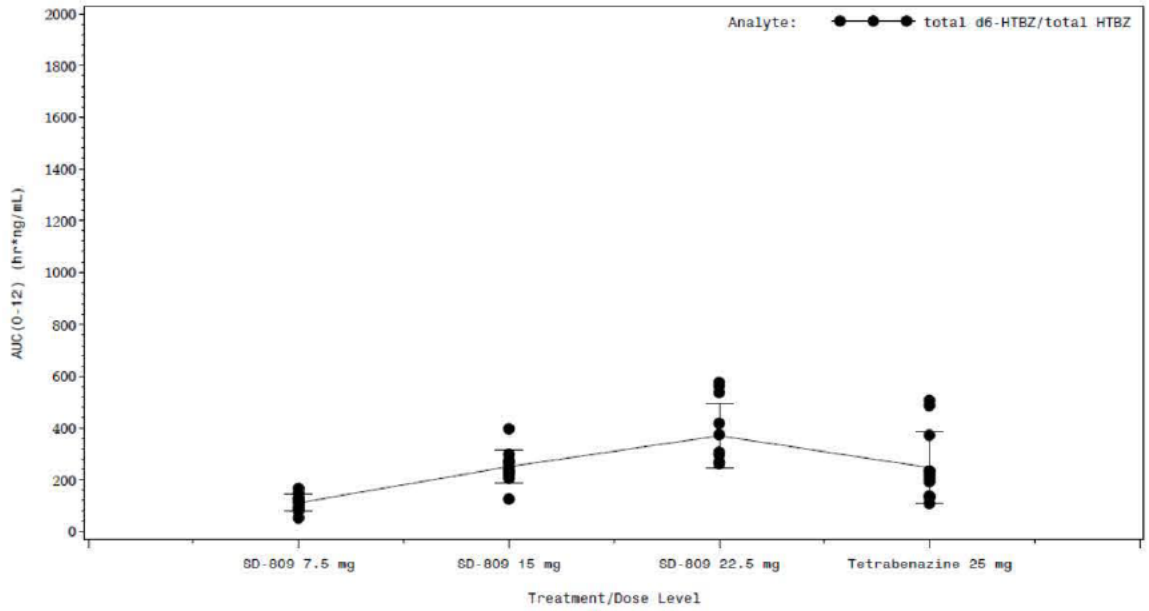
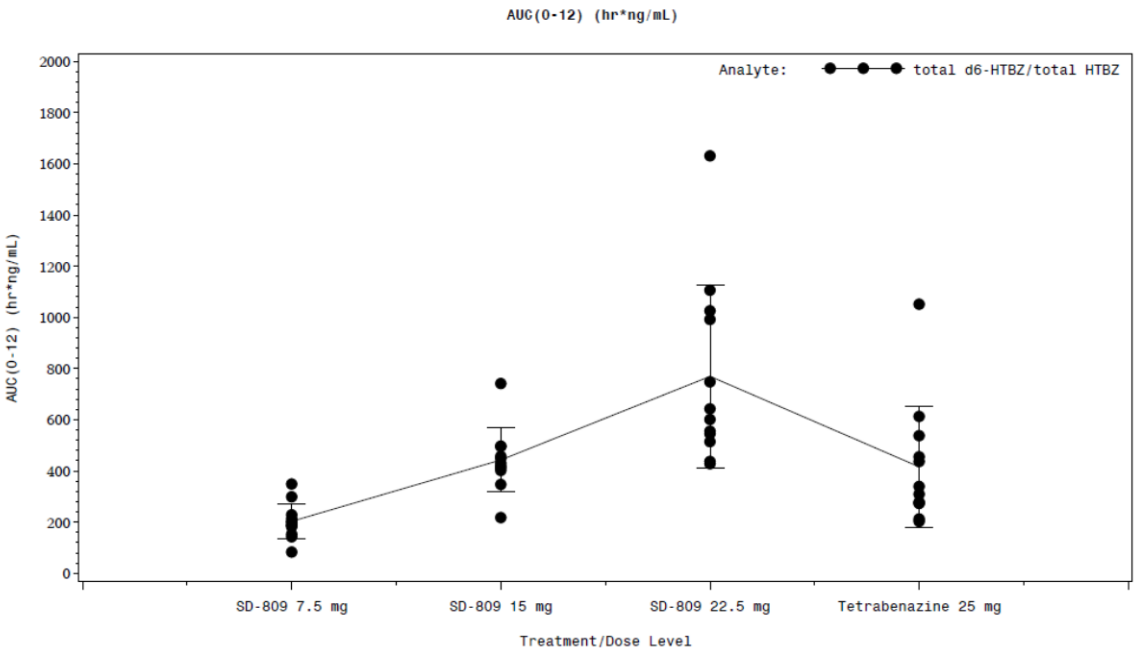


Figure of Steady State Pharmacokinetic Parameters across Dose Levels by Analyte (Part 2)



Safety:

Part 1: single 15 mg doses of SD-809 ER Formulation A and Formulation B were both well tolerated and had a comparable safety profile under fed or fasting conditions. No significant differences were observed between the two formulations compared to each other or to tetrabenazine in terms of incidence, type, severity, relationship, or frequency of TEAEs.

Part 2: both single and multiple doses of SD-809 ER were well tolerated. Somnolence and headache were the most frequently reported AEs assessed as possibly drug-related.

Somnolence exhibited a dose-response relationship, occurring in 0%, 25%, and 67% of the subjects treated with 7.5 mg BID, 15 mg BID, and 22.5 mg BID SD-809 ER regimens, respectively (and in 50% of subjects receiving 25 mg BID tetrabenazine). Headache was not dose related, being reported in 25%, 25%, and 0% of subjects following treatment with 7.5 mg BID, 15 mg BID, and 22.5 mg BID SD-809 ER, respectively (and in 0% of subjects receiving 25 mg BID tetrabenazine).

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III. SD-809-C-12: An Open-Label, Two-Period Study Designed to Evaluate and Compare the Mass Balance Recovery, Metabolite Profile and Metabolite Identification of Oral Doses of Both [^{14}C]-SD-809 and [^{14}C]-Tetrabenazine in Healthy Male Subjects

Objectives:

• To determine the mass balance recoveries after single oral doses of ^{14}C-SD-809 and [^{14}C]-tetrabenazine (TBZ)
• To determine the routes and rates of excretion of SD-809 and TBZ
• To provide plasma, urine and feces samples for metabolite profiling and structural identification following oral doses of [^{14}C]-SD-809 and [^{14}C]-tetrabenazine
• To determine the pharmacokinetics of total radioactivity in plasma after a single oral dose of [^{14}C]-SD-809 and [^{14}C]-tetrabenazine
• To determine the pharmacokinetics of SD-809, d6-alpha-dihydrotetrabenazine (d6-α-HTBZ) and d6-beta-dihydrotetrabenazine (d6-β-HTBZ) in plasma after a single oral dose of [^{14}C]-SD-809

Study Design	2-period, 2-cohort, open-label study in healthy male subjects
Study Population	6 healthy male subjects/cohort (total of 12) between 35 and 65 years; CYP2D6 extensive or intermediate metabolizer phenotype.
Treatment Groups	Cohort 1: Single oral dose of 25 mg [^{14}C]-SD-809 Cohort 2: Single oral dose of 25 mg [^{14}C]-tetrabenazine
Dosage and Administration*	Cohort 1: Single oral dose of 25 mg [^{14}C]-SD-809 containing NMT 2.92 MBq (79 μCi) [^{14}C] in the fasted state Cohort 2: Single oral dose of 25 mg [^{14}C]-TBZ containing NMT 2.92 MBq (79 μCi) [^{14}C] in the fasted state
PK Sampling:	Blood/Plasma: pre-dose, 20 and 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192 and 216 hour for total radioactivity and PK analysis (plasma only) for the metabolites with validated assays. One pooled plasma sample/cohort for metabolite identification (semi-quatitative analysis)** Urine and feces: pre-dose, 0–6, 6–12, 12–24 h, then daily until Day 7 (144 h post-dose) with final collection on 168 h post-dose**
Analysis***	Total radioactivity: quantitative radiochemical analysis Validated LC-MS/MS method for TBZ/SD-809 and deuterated and non-deuterated forms of α- and β-dihydrotetrabenazine (HTBZ) and the O-desmethyl-metabolites of α- and β-HTBZ in plasma Semi-quantitative methods for all other metabolites of TBZ/SD-809*
PK Assessment	Plasma: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-12}, AUC_{0-inf}, $t_{1/2}$, MRT of TBZ/SD-809 and metabolites Urine and feces: Ae and %Fe and Total Ae and %Total Fe, where total represents urine and feces combined
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry

*Unlabelled SD-809 and TBZ drug substances were provided by [redacted] (b) (4) Chemistry for radiolabelling. The radiolabeled products were formulated as 25 mg hard gelatin capsules.
** Urinary metabolites were identified and quantified from a single urine cohort sample pooled over the 0 to 72 h. Plasma metabolites were identified and quantified from individual plasma samples pooled over the 2 to 12 h post-dose, e.g. 2-, 2.5-, 6-, and 12-h time points.
** Four different analyses/reports were generated; these are described under Analytical Methods

Analytical Methods

Whole Blood, Plasma, Urine and Feces Samples for Measurement of Total Radioactivity [redacted] study no. ASX/03)

Blood samples were collected into lithium heparin tubes. Urine and feces samples were collected into polypropylene containers; samples were shipped daily following completion of the collection period.

Total radioactivity was determined at [redacted] by quantitative radiochemical analysis.

Radioactivity in fecal homogenate and whole blood was determined after combustion in oxygen using an Automatic Sample Oxidiser (Tri-Carb®, Perkin Elmer). The combustion products are absorbed into CarboSorb E and mixed with the scintillator cocktail PermaFluor E^+ for measurement of radioactivity.

Radioactivity in liquid samples (plasma and urine) was quantified directly by Liquid Scintillation Counting (LSC) using a liquid scintillation counter with automatic external standard quench correction. Samples were mixed with scintillant (Ultima Gold XR) and counted (2300TR Scintillation Counter, Perkin Elmer). Detected counts per minute (cpm) were converted to disintegrations per minute (dpm) using quench correction.

Plasma Samples for Bioanalytical Analysis [redacted] (16.1.13.1 Bioanalytical Report)

Blood samples (4 mL) were collected into lithium heparin tubes, centrifuged at 1500 g for 10 min at 4°C within 30 min of sample collection and the resultant plasma was placed on dry ice within 20 min of completion of centrifugation. An 1 mL aliquot of plasma was transferred to a polypropylene tube and the remaining plasma was transferred to a duplicate tube. The samples were stored at approximately -80°C until shipped to [redacted] for analysis. **Comment**: If these duplicate samples are still available, they can be used to analyze M1 and M4 using a validated assay.

Plasma concentrations of SD-809, TBZ and their respective α- and β- HTBZ metabolites and O-desmethyl-metabolites of α- and β-HTBZ metabolites were determined using validated turbo ion spray liquid chromatography with tandem mass spectrometry (LC-MS/MS). The lower limit of quantification (LLOQ) for SD-809 and TBZ was 0.100 ng/mL, and for the associated metabolites was 0.500 ng/mL.

Reviewer's Comments: The same assays have been used for the analysis of PK samples of most of the clinical studies in the SD-809 development. Details of the validation results are presented in Bioanalytical Study Reports. The validation and the performance of the assays for TBZ/SD-809 and their metabolites during the analysis of the study samples are acceptable.

Metabolite Profiling and Identification [redacted] Study no ASX/04

Metabolite profiling and chemical structure identification were performed from plasma and urine samples using high performance LC with on-line radiodetection and LC-MS/MS. Metabolite profiling from feces samples was not performed.

Urine and Feces Samples

For metabolite characterization, 0.5% of total urine sample weight for each subject was collected over the following collection periods to create a 0 to 72 h pool: 0 to 6 h, 6 to 12 h, 12 to 24 h, 24 to 48 h, and 48 to 72 h. Subsequently, each of the 6 individual pools was combined into a cohort pool using a fixed volume from each subject. The 0 to 72 h cohort pool accounted for 90% of total urinary radioactivity in the SD-809 cohort and 91% in the tetrabenazine cohort. Samples were analyzed by (b) (4).

Plasma Samples for Metabolite Characterization

Blood samples (5 × 4 mL) were collected into lithium heparin tubes, centrifuged and the resultant plasma was placed on dry ice and stored at approximately -80°C until shipped to (b) (4) for analysis.

A time proportional AUC plasma pool for the purposes of metabolite identification and profiling was constructed for each subject across the 2-, 2.5-, 6-, and 12-h time points in the following proportion: 2 h, 0.57 mL; 2.5 h, 0.91 mL; 6 h, 2.16 mL; 12 h; 1.36 mL (total of 5.00 mL). **Note:** An Information Request was sent to the sponsor to clarify why only 4 time points were used for pooling and how the selection of these time points was made; the sponsor's response is provided in the Appendix.

Mass Balance Results:

Excretion balance of [^{14}C]-SD-809

After administration of single oral doses (nominal 25 mg; 79 Ci, 2.92 MBq) of [^{14}C]-SD-809 to six healthy subjects, 74.78 – 86.48 % dose was excreted in the urine up to 240 hours after administration; the majority of the urinary radioactivity was recovered within 48 hours of dosing.

In the ten days after dose administration 7.70 – 11.32 % dose was recovered in the feces; the majority of the fecal radioactivity was recovered within 144 hours.

The total recovery (urine + feces) from the subjects was in the range 83.79 – 96.89 % (see tables below).

Concentration of radioactivity in individual urine samples – Cohort 1

Time point (hour)	Subject number					
	001	002	003	004	005	006
Pre-dose	ND	ND	ND	ND	ND	ND
0 - 6	10173	28500	15551	14009	7519	9699
6 - 12	61845	111112	51972	71665	67901	58884
12 - 24	77733	19664	30817	31836	69683	83635
24 - 48	41902	17938	19266	8960	28833	29914
48 - 72	14104	4358	5804	2359	8783	14470
72 - 96	2662	1918	2131	1041	4310	7509
96 - 120	1130	1037	1562	484	1771	2935
120 – 144	743	461	614	355	1094	1081
144 – 168	537	394	563	265	545	668
168 – 192	NA	NA	408	196	474	578
192 – 216	NA	NA	385	NA	NA	NA
216 - 240	NA	NA	288	NA	NA	NA

NA Not applicable (subject no longer in clinic)
ND Not detected (<2 x background radioactivity
Results expressed as dpm/g

Recovery of drug related material in urine and feces after administration of a single oral dose of [^{14}C]-SD-809 (nominal 25 mg; 2.92 MBq) to male healthy subjects (Cohort 1)

Sample	Time point (hour)	Subject number						Mean	CV (%)
		001	002	003	004	005	006		
Urine	Pre-dose	ND	ND	ND	ND	ND	ND	NC	NC
	0 - 6	6.40	14.41	3.45	9.85	3.63	6.73	7.41	56.09
	6 - 12	20.81	24.45	16.76	20.33	12.50	16.71	18.59	22.34
	12 - 24	18.40	18.59	15.95	20.10	19.54	22.00	19.10	10.55
	24 - 48	26.28	16.22	22.08	18.57	24.79	21.55	21.58	17.39
	48 - 72	8.20	5.67	8.38	6.45	9.57	9.11	7.90	19.33
	72 - 96	3.35	2.69	3.43	2.89	8.94	4.25	4.26	55.33
	96 - 120	1.62	1.16	2.02	1.41	2.90	2.23	1.89	33.37
	120 – 144	0.83	0.75	1.11	0.93	1.65	1.18	1.08	30.27
	144 – 168	0.59	0.49	0.66	0.55	1.00	0.78	0.68	27.49
	168 – 192	NA	NA	0.46	0.42	0.65	0.50	0.51	19.79
	192 – 216	NA	NA	0.31	NA	NA	NA	NC	NC
	216 - 240	NA	NA	0.17	NA	NA	NA	NC	NC
	Subtotal	86.48	84.43	74.78	81.50	85.17	85.04	82.90	5.20
Faeces	Pre-dose	NS	NS	NS	NS	NS	ND	NC	NC
	0 – 24	0.03	0.08	0.09	NS	NS	NS	0.03	125.38
	24 – 48	0.03	NS	4.69	3.54	NS	0.43	1.45	145.25
	48 – 72	3.05	2.37	NS	2.99	0.96	2.60	2.00	62.05
	72 – 96	2.75	5.70	2.16	2.70	0.89	NS	2.37	82.79
	96 – 120	3.14	NS	0.58	1.06	1.16	2.87	1.47	85.96
	120 – 144	0.66	1.61	NS	0.28	2.69	0.81	1.01	98.16
	144 – 168	0.75	NS	0.98	0.60	1.38	NS	0.62	88.38
	168 – 192	NA	NA	0.28	0.15	0.62	1.01	0.52	74.74
	192 – 216	NA	NA	0.11	NA	NA	NA	NC	NC
	216 - 240	NA	NA	0.12	NA	NA	NA	NC	NC
	Subtotal	10.41	9.76	9.01	11.32	7.70	7.72	9.32	15.67
	Total	96.89	94.19	83.79	92.82	92.87	92.76	92.22	4.80

CV Coefficient of variation
NA Not applicable (subject no longer in clinic)
NC Not calculable
ND Not detected (<2 x background radioactivity; included as zero in mean/CV calculation)
NS No sample (included as zero in mean/CV calculation)
Results expressed as % dose administered

Maximal concentrations of radioactivity were seen between 0.67 and 6 hours in plasma and between 1 and 8 hours in whole blood. Maximal concentrations for each subject ranged from 90.7 to 148.5 ng equivalents/mL in plasma and 64.9 – 116.7 ng equivalents/g in whole blood. Radioactivity in plasma was less than 2 x background for the majority of subjects by 96 hours.

Reviewer's Comment: For most of the subjects, the max concentration of radioactivity in plasma was observed at 3-4 h post- (SD-809) dose, see table below. However, these time points were not selected for plasma pooling for the metabolite identification and profiling, instead, the sponsor selected the 2-, 2.5-, 6-, and 12-h time points. An Information Request was sent to the sponsor to clarify how the selection of the plasma samples for pooling was made; the sponsor's response is provided in the Appendix.

Concentration of radioactivity in plasma after [^{14}C]-SD-809 (nominal 25 mg; 2.92 MBq) to male human subjects (Cohort 1)

Time point (hour)	Subject number						Mean	CV (%)
	001	002	003	004	005	006		
Pre-dose	ND	ND	ND	ND	ND	ND	NC	NC
0.33	ND	ND	ND	ND	ND	ND	NC	NC
0.67	12.6	65.0	15.0	119.8	51.5	89.4	58.9	71.3
1	72.1	119.2	80.9	117.1	60.0	136.5	97.6	31.4
1.5	101.4	144.7	104.4	117.8	82.4	140.7	115.2	20.9
2	106.5	128.7	117.9	113.4	79.8	148.5	115.8	19.8
2.5	111.0	132.3	121.4	101.8	80.2	142.9	114.9	19.5
3	119.7	130.6	124.3	104.5	87.5	138.9	117.6	15.9
4	137.1	125.4	119.1	98.9	90.7	138.7	118.3	16.7
6	128.3	123.0	127.1	93.6	85.8	122.5	113.4	16.4
8	110.2	102.7	121.7	74.3	87.7	110.2	101.1	17.1
12	95.5	72.0	110.3	62.4	77.1	86.5	84.0	20.5
18	63.6	43.9	82.6	36.4	65.9	58.9	58.6	28.2
24	52.5	30.4	61.9	21.6	59.4	57.1	47.2	35.9
36	29.0	16.1	46.5	21.7	49.9	39.8	33.8	40.5
48	22.7	20.4	32.5	17.1	33.4	22.9	24.8	26.7
72	11.5	10.3	12.7	ND	14.6	11.6	10.1	51.0
96	ND	ND	ND	ND	7.9	ND	NC	NC
120	ND	ND	ND	ND	10.1	8.6	3.1	NC
144	ND	ND	ND	ND	ND	ND	NC	NC
168	ND	ND	ND	ND	ND	ND	NC	NC
192	NA	NA	ND	ND	ND	ND	NC	NC

CV Coefficient of variation
NA Not applicable (subject no longer in clinic)
NC Not calculable
ND Not detected (<2 x background radioactivity; included as zero in mean/CV calculation)
Results expressed as ng equivalents/mL

Excretion balance of [^{14}C]-Tetrabenazine

After administration of single oral doses (nominal 25 mg; 79 Ci, 2.92 MBq) of [^{14}C]-TBZ to six healthy subjects, 76.42 – 82.93 % dose was excreted in the urine up to 216 hours after administration; the majority of the urinary radioactivity was recovered within 48 hours of dosing.

In the nine days after dose administration 7.80 – 13.54 % dose was recovered in the feces; the majority of the fecal radioactivity was recovered within 96 hours.

The total recovery (urine + feces) from the subjects was in the range 84.22 - 93.63 % (see tables below).

Concentration of radioactivity in individual urine samples – cohort 2

Time point (hour)	Subject number					
	007	008	009	010	011	012
Pre-dose	ND	ND	ND	ND	ND	ND
0 - 6	12797	37399	41199	65226	NS	34082
6 - 12	34590	55348	65407	29095	110118	35405
12 - 24	19588	29903	28383	23065	NS	28532
24 - 48	18678	10978	12499	12430	20785	9989
48 - 72	16553	4259	3665	3975	3304	2914
72 - 96	4851	1706	1253	1537	1507	1305
96 - 120	2597	1068	697	901	677	802
120 – 144	2255	552	423	488	344	466
144 – 168	928	377	338	435	461	381
168 – 192	474	264	143	NA	NA	265
192 – 216	NA	277	NA	NA	NA	176
216 - 240	NA	NA	NA	NA	NA	NA

NA Not applicable (subject no longer in clinic)
ND Not detected (<2 x background radioactivity
NS No sample
Results expressed as dpm/g

Recovery of drug related material in urine and feces after administration of a single oral dose of [^{14}C]-Tetrabenazine (nominal 25 mg; 2.92 MBq) to healthy subjects (Cohort 2)

Sample	Time point (hour)	Subject number						Mean	CV (%)
		007	008	009	010	011	012		
Urine	Pre-dose	ND	ND	ND	ND	ND	ND	NC	NC
	0 - 6	4.96	13.77	15.26	22.65	NS	20.71	12.89	68.67
	6 - 12	14.99	15.88	18.88	16.76	39.89	14.82	20.20	48.30
	12 - 24	12.64	15.05	17.32	16.98	NS	12.53	12.42	51.69
	24 - 48	22.46	19.92	17.56	15.67	30.49	16.51	20.44	26.97
	48 - 72	12.26	8.28	6.34	5.74	4.76	5.16	7.09	39.74
	72 - 96	6.88	3.72	2.54	2.49	1.98	2.70	3.39	53.32
	96 - 120	3.36	1.96	1.39	1.29	1.20	1.72	1.82	44.31
	120 – 144	1.83	1.06	0.83	0.79	0.63	0.80	0.99	43.84
	144 – 168	1.18	0.77	0.53	0.56	0.58	0.65	0.71	34.41
	168 – 192	0.64	0.38	0.42	NA	NA	0.46	0.48	24.16
	192 – 216	NA	0.35	NA	NA	NA	0.36	0.36	NC
	Subtotal	81.20	81.14	81.07	82.93	79.53	76.42	80.38	2.76
Faeces	Pre-dose	NS	ND	NS	ND	ND	ND	NC	NC
	0 – 24	ND	0.03	NS	NS	0.12	0.60	0.13	189.84
	24 – 48	ND	0.52	2.05	0.23	7.91	0.46	1.86	163.83
	48 – 72	0.88	2.53	3.42	4.43	3.28	3.36	2.98	40.06
	72 – 96	5.14	4.12	3.62	3.55	1.26	1.65	3.22	46.17
	96 – 120	2.22	1.04	0.74	0.83	0.61	0.79	1.04	57.36
	120 – 144	2.98	1.29	0.81	0.61	0.22	0.58	1.08	91.87
	144 – 168	0.36	0.41	0.31	0.40	0.14	0.18	0.30	38.24
	168 – 192	0.85	0.73	0.39	NA	NA	0.14	0.53	61.34
	192 – 216	NA	0.38	NA	NA	NA	0.04	0.21	NC
	Subtotal	12.43	11.05	11.34	10.05	13.54	7.80	11.04	18.01
	Total	93.63	92.19	92.41	92.98	93.07	84.22	91.42	3.90

CV Coefficient of variation
NA Not applicable (subject no longer in clinic)
NC Not calculable
ND Not detected (<2 x background radioactivity; included as zero in mean/CV calculation)
NS No sample (included as zero in mean/CV calculation)
Results expressed as % dose administered

Maximal concentrations of radioactivity were seen between 1 and 4 hours in plasma and whole blood and ranged from 68.0 to 230.3 ng equivalents/mL in plasma and 43.0 -171.0 ng equivalents/g in whole blood. Radioactivity in plasma was less than 2 x background for the majority of subjects by 72 hours.

Concentration of radioactivity in plasma after [^{14}C]-TBZ (nominal 25 mg; 2.92 MBq) to male subjects (Cohort 2)

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Time point (hour)	Subject number						Mean	CV (%)
	007	008	009	010	011	012		
Pre-dose	ND	ND	ND	ND	ND	ND	NC	NC
0.33	ND	37.0	ND	ND	15.9	ND	8.8	172.4
0.67	ND	132.9	112.5	19.1	165.1	ND	71.6	103.0
1	10.8	160.5	155.3	65.1	230.3	107.1	121.5	63.9
1.5	25.4	156.9	159.4	132.5	219.6	183.2	146.2	45.2
2	42.3	143.5	149.3	144.4	187.2	186.1	142.1	37.2
2.5	53.2	133.0	132.4	167.1	171.3	197.6	142.4	35.3
3	57.8	116.3	129.1	143.2	148.6	189.2	130.7	33.2
4	68.0	116.3	110.9	139.6	127.6	156.2	119.8	25.2
6	64.6	92.4	92.3	106.7	108.5	124.9	98.2	20.8
8	51.7	80.9	76.2	71.5	84.3	101.7	77.7	21.1
12	40.3	55.6	64.4	59.3	63.7	67.9	58.5	16.9
18	31.7	41.8	42.0	36.3	40.6	35.3	38.0	11.0
24	30.6	34.0	26.5	21.8	30.6	30.0	28.9	14.6
36	24.5	25.6	18.4	14.4	15.2	18.5	19.4	24.0
48	16.8	13.8	11.1	11.3	10.3	12.6	12.7	18.8
72	9.8	ND	ND	ND	ND	ND	NC	NC
96	10.0	10.3	ND	ND	ND	ND	3.4	154.9
120	ND	ND	ND	ND	ND	ND	NC	NC
144	ND	ND	ND	ND	ND	ND	NC	NC
168	ND	ND	ND	ND	ND	ND	NC	NC
192	ND	ND	ND	NA	NA	ND	NC	NC
216	NA	ND	NA	NA	NA	ND	NC	NC

CV Coefficient of variation
NA Not applicable (subject no longer in clinic)
NC Not calculable
ND Not detected (<2 x background radioactivity; included as zero in mean/CV calculation)
Results expressed as ng equivalents/mL

Conclusion: The mean recovery of radioactivity was 92.22 % dose for [^{14}C]-SD-809 and 91.42% for [^{14}C]-TBZ. For both products, the majority of the recovered dose was excreted into the urine, with averages of 82.90 % for [^{14}C]-SD-809 and 80.38 % for [^{14}C]-TBZ. The time course of radioactivity in plasma and whole blood was similar between TBZ and SD-809.

Metabolite Profiling and Identification Results:

Notes: Multiple Information Requests were sent to the sponsor and a Telecon was held with the sponsor on 25 Sept 2015 to clarify different aspects of the methods used and the results. The sponsor's responses and the Telecon Memo are provided in the Appendix.

The following were the Clinical Pharmacology reviewer's main concerns:

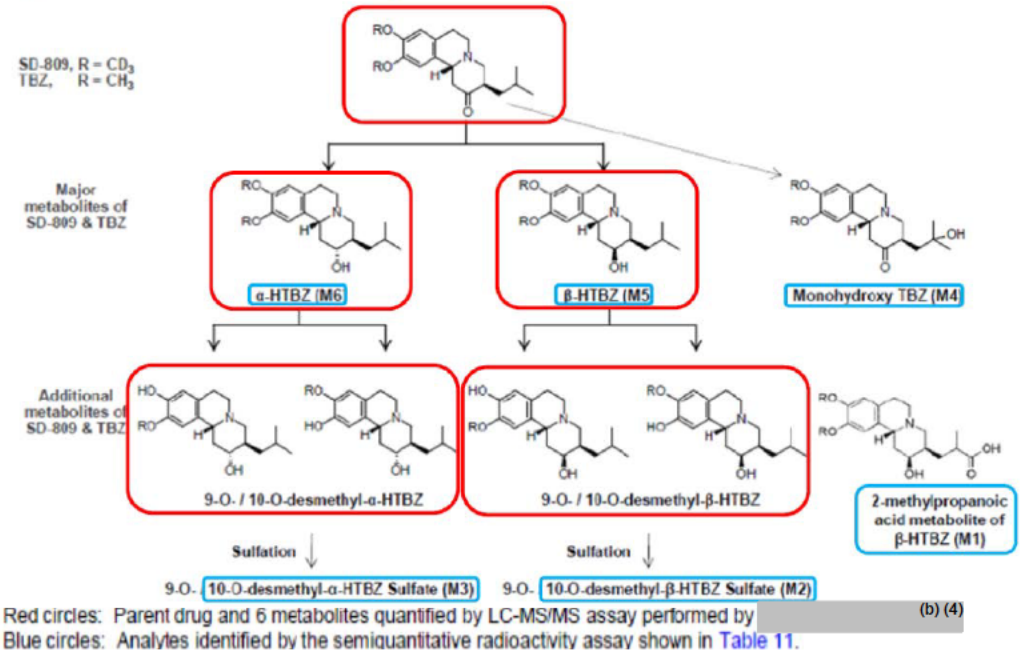
1. Bioanalytical Methods:

- Based on the semi-quantitative methods of analysis (b) (4) (b) (4) Study no ASX/04), the Sponsor has changed positions on the status of M1 as a major human metabolite (MHM; >10% total drug-related exposure);
- Has not been able to demonstrate, with the semi-quantitative methods, that a known MHM of TBZ (per the Xenazine label), 9-O-desmethyl-β-DHTBZ, is a MHM in the patients dosed with TBZ in the mass balance study;
- Using the semi-quantitative methods, the exposure to the active metabolites (α+ β)-HTBZ (metabolites M5 + M6) after administration of 25 mg SD-809 was estimated to be 4x higher (instead of the expected 2x higher) than that following administration of 25 mg TBZ (see Table 10 below). The remaining studies in the clinical pharmacology program for SD-809 (using validated quantitative methods

of analysis) show that an SD-809 dose that is half that of TBZ results in similar exposure to the respective (α+ β)-HTBZ.

Note: A validated LC-MS/MS assay [redacted](b) (4)) was used to quantify TBZ/SD-809 and 6 of their respective metabolites: these are shown in the red circled areas below

Figure 2. Metabolic Pathway of SD-809 and Tetrabenazine



Red circles: Parent drug and 6 metabolites quantified by LC-MS/MS assay performed by [redacted](b) (4)
Blue circles: Analytes identified by the semiquantitative radioactivity assay shown in Table 11.

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.

Notes:

- M1 is not present in rats and would represent an uncharacterized safety issue for SD-809 according to the nonclinical reviewer.
- The sponsor did not clarify why only the six metabolites shown in the red circled in Figure 2 were quantified using a validated LC-MS/MS assay but the metabolites circled in blue were not quantified using this validated assay.

Comparison of metabolites exceeding 10% of total plasma sample (pooled up to 12h post-dose) radioactivity following oral administration of SD 809 or tetrabenazine (EOP2 Briefing package):

Metabolite Number	Identification	Percentage of sample radioactivity	
		SD-809	TBZ (SD-808)
M1	Acid Metabolite of HTBZ	12.7	4.0
M2	Sulphate of O-desmethyl HTBZ	4.	18.7
M3	Sulphate of O-desmethyl HTBZ	4.5	15.4
M4	+ 16 amu Metabolite	19.9	11.7
M5	β-HTBZ	13.3	2.2
M6	α-HTBZ	15.9	5.0

Changes in the metabolic profile of SD-809 as compared to tetrabenazine are summarized as follows:

- *M4 is a major metabolite for both SD-809 and TBZ, likely a metabolite of HTBZ,*
- *M1 is a major metabolite of SD-809 (accounting for 12.7% of radioactivity), but a minor metabolite for TBZ (accounting for 4.0% of radioactivity).*

Sponsor Preliminary Response for EOP2 Meeting Discussion:

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

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Table 1. Summary of SD-809 and Tetrabenazine Metabolite Characterization

Metabolite in Figure 2 (Sequence 0009; Section 1.11.3)	Percentage of Total Circulating Drug-Related Material [Mean (SD)] [a]		Classification of Major vs Minor Metabolite Based on Requirement for Safety Testing [b] and Subsequent Studies		Percentage of α-HTBZ plus β-HTBZ ([α+β]-HTBZ or total active) Based on Plasma Radioactivity or Traditional Bioanalysis (Mean)		Classification of Major vs Minor Metabolites Based on Requirement for DDI Evaluation [c] and Subsequent Studies	
Test article	SD-809	TBZ	SD-809	TBZ	SD-809	TBZ	SD-809	TBZ
α-HTBZ (M6)* (active)	13.0 (4.6)	4.0 (1.4)	Major	Minor	n/a	n/a	n/a	n/a
β-HTBZ (M5) * (active)	8.3 (4.2)	1.8 (1.5)	Minor	Minor	n/a	n/a	n/a	n/a
2-methylpropanoic acid β-HTBZ (M1)	9.2 (3.6)	4.1 (2.0)	Minor; evaluated in in vitro genotoxicity studies	Minor	52 [d]	79 [d]	Major; evaluated in in vitro DDI studies (Section 2.6.4.8)	Major
Sulfate of O-desmethyl-β-HTBZ (M2)	2.5 (1.1)	6.4 (2.9)	Minor	Minor	15 [d]	126 [d]	Minor	Major
Sulfate of O-desmethyl-α-HTBZ (M3)	4.0 (1.5)	16.4 (5.6)	Minor	Major	24 [d]	310 [d]	Minor	Major
Monohydroxy tetrabenazine (M4)	12.9 (3.2)	15.6 (4.9)	Major [e]	Major	69 [d]	291 [d]	Major; to be evaluated in in vitro DDI studies	Major
9-desmethyl-β-DHTBZ **	< 10%	< 10%	Minor	Minor	14 [f]	65 [f]	Minor	Major
9-desmethyl-α-DHTBZ **	< 10%	< 10%	Minor	Minor	3 [f]	15 [f]	Minor	Minor

Abbreviations: AUC = area under concentration time curve; DDI = drug drug interaction; DPM = disintegrations per minute; h = hour; n/a = not applicable; * HTBZ = dihydrotetrabenazine; ** DHTBZ = dihydrotetrabenazine

a: Percentage plasma sample radioactivity in AUC 2-12 h plasma pools; References: SD-809-C-12, Section 16.1.13.4; Appendix 16.1.13.3, Table 9 and Table 10.

b: ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

c: Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012, draft guidance.

d: The mean DPM attributed to metabolites M1, M2, M3, and M4 expressed as a percentage of the DPM attributed to M5+M6 (total [α+β] HTBZ), calculated for each individual. Reference: calculated from SD-809-C-12, Section 16.1.13.4.

e: M4 is also a metabolite in rat.

f: The mean AUC_{tau} for the metabolites 9-desmethyl-α-DHTBZ and 9-desmethyl-β-DHTBZ at steady state expressed as the AUC_{tau} of total [α+β] HTBZ. Reference: calculated from AUS-SD-809-CTP-07, Table 14.2.5.4.

Note: In addition, the urine metabolite U1 (corresponding to M1) was 5 times greater in the SD-809 cohort pool relative to that of the TBZ pool.

Summary of Urine Metabolites

Metabolite Number	Identification	Percentage of Total Sample Radioactivity (In Cohort Pool)	
		SD-809 S001–S006 Cohort 1	Tetrabenazine S007–S012 Cohort 2
U1 (M1 in plasma)	2-methylpropanoic acid metabolite of β-HTBZ	13.9	2.7
U2	Mono-hydroxy β-HTBZ (2 isomers)	9.3	1.2
U3 (M2 in plasma)	Sulphate of O-desmethyl β-HTBZ	10.5	14.2
U4	Co-Elution: Glucuronide of α-HTBZ Sulphate of O-desmethyl HTBZ Mono-hydroxy α-HTBZ	15.3	3.8
U5 (M3 in plasma)	Sulphate of O-desmethyl α-HTBZ	16.7	27.7
Total of Metabolites U1 to U5		65.7	49.6
Total of Additional Minor Metabolites[a]		27.2	30.6
Grand Total		92.9	80.2

[a] Additional minor urinary metabolites included mono-hydroxy tetrabenazine, β-HTBZ, α-HTBZ, mono-hydroxy β-HTBZ, sulphate of O-desmethyl HTBZ, glucuronide of α-HTBZ and mono-hydroxy α-HTBZ

In the Response to Requests for Clarification Regarding Nonclinical and Biopharmaceutics Issues from the Mid-Cycle Communication Teleconference (Dec 22, 2015), the sponsor acknowledged "the differences between the original data for Xenazine (NDA 21894) and the mass balance study SD-809-C-12 conducted for development of SD-809 related to the status of 9-O-desmethyl-β-DHTBZ (also referred to as 9-O-

desmethyl-β-HTBZ) as a major metabolite of Xenazine". However, the sponsor made the following point:
In Prestwick study CAM/06, P16 was identified as "O-dealkylated HTBZ," without resolution of the α- or β- diastereomers and without identification of the site of demethylation (i.e., the 9 or 10 positions). Thus, while the amalgam of these four metabolites is responsible for 31% of the radioactivity, it is not clear whether 9-O-desmethyl-β-DHTBZ is responsible for greater than 10%.
Reviewer's Comment: However, the levels of 9-O-desmethyl α-HTBZ, 10-O-desmethyl α-HTBZ and 10-O-desmethyl β-HTBZ are very low or BLQ after TBZ administration, see data from Study AUS-SD-809-CTP-07, Part 2: Summary of Steady State PK Parameters by Treatment of 9-O-desmethyl-HTBZ Metabolites (page 16). Therefore, 9-O-desmethyl-β-HTBZ is responsible for the majority of this 31% of the radioactivity.

2. Plasma pooling strategy

The plasma pooling for metabolite identification and profiling is questionable (see Appendix and comments under Plasma Samples for Metabolite Characterization). Plasma samples from only 4 time points (2, 2.5, 6, and 12 h) were selected for pooling for metabolite profiling. Although the max concentration of radioactivity in plasma was observed at 3-4 h post- (SD-809) dose, these time points were not included in the pooling. This pooling strategy has the potential to change the percent of total plasma radioactivity for each metabolite and could be responsible for the discrepancy between the original data for Xenazine (NDA 21894) and the SD-809-C-12 study results related to the status of 9-O-desmethyl-β-DHTBZ as a MHM. Additional evidence of how the change in the pooling technique can change the percent of total plasma radioactivity results for the metabolites can be seen by comparing the results in the two tables above: for example M2 after TBZ administration is 18.7% of total in the EOP2 Briefing package and 6.4% of total in Table 1.

Notes: A request for information was sent to the sponsor regarding the plasma pooling strategy. According to the sponsor, the semi-quantitative analyses of metabolites by radioactivity were conducted on the metabolite profile samples from 2 to 12 hours via a per-subject "AUC pool" approach (Hamilton, 1981).
Reviewer's Comment: However, in Hamilton, all (nine) time points covering the whole concentration-time profile were used for pooling.

In addition, the sponsor claims that, in the mass-balance and metabolite identification study conducted with TBZ in NDA 21894, metabolite identification and semi-quantification was performed on samples that were collected out to 8 hours post dose.
Reviewer's Comment: However, in the mass-balance and metabolite identification study conducted with TBZ (NDA 21894), three plasma pools (0.25 – 1.5, 2 – 3 and 4 – 8 hours) were prepared using a total of 13 plasma samples, covering most of the concentration-time profile, including T_{max}.

In summary, the Metabolite Profiling and Identification results of study SD-809-C-12 are not acceptable.
It is recommended that the sponsor assess the concentration of circulating SD-809-related metabolites for the purpose of determining if there are major metabolites in humans dosed with SD-809. The sponsor should use adequate plasma pooling methods.
In addition, as the sponsor is unable to reference the activity of the metabolites M1 and M4 from past experience with Xenazine, M1 and M4 need to be evaluated in in vitro studies (VMAT2 and off-target binding). This could be done post approval as a PMR.

3. DDI Potential of SD-809 Metabolites:

The Clinical Pharmacology Drug-Drug Interaction (DDI) Guidance defines a major metabolite as having exposure >25% of parent. In the case of TBZ/SD-809, (α+β)-HTBZ can be considered as parent (since α and β-HTBZ are active and TBZ levels are so low that comparison to TBZ would show that almost all of the metabolites are greater than 25% of TBZ). According to Table 11 (see the sponsor response to IR Sept 24, 2015 in the Appendix), both M1 and M4 are greater than 25% of (α+β)-HTBZ (M1 is 40% of (α+β)-HTBZ and M4 is 56% of (α+β)-HTBZ). *In vitro* DDI study results were submitted for M1 but not for M4.
Note: As the sponsor is unable to reference the DDI potential of M4 from past experience with Xenazine, M4 will be evaluated in the following *in vitro* studies and the results from these studies will be submitted before Jan 15, 2016:
☐ Direct and time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 in human liver microsomes
☐ Induction of CYP1A2, CYP2B6 and CYP3A4 mRNA levels in primary cultures of cryopreserved human hepatocytes
☐ Inhibition of major transporters by M4
☐ Substrate determination for P-gp, BCRP, OATP1B, OAT1, OAT3, and OCT2

Comment: The drug interaction potential strategy for M4 proposed in Teva's Response to FDA Telecon Request for Information Regarding Metabolites (20 Oct 2015) is acceptable.

Safety Results:

Single oral doses of 25 mg [^{14}C]-SD-809 and [^{14}C]-tetrabenazine were well tolerated in this study. All adverse events were mild in severity. There were no clinically significant findings in clinical laboratory assessments, vital signs parameters, ECG measurements, or physical examinations.

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Bioavailability Studies

IV. SD-809-C-11: A Relative Bioavailability Study of Three Dose Strengths of SD-809 ER

Objectives:

• To evaluate the relative bioavailability of three dose strengths and four dose levels of SD-809 when administered as single doses following a standard meal.
• To evaluate the effect of a high-fat meal on the relative bioavailability of a single 18-mg dose of SD-809 compared to a standard meal.

Study Design	Randomized, open-label, 5-way crossover study of single doses of SD-809 tablets in healthy subjects
Study Population	N = 32 subjects, male and female, 18-45 years old, CYP2D6 extensive or intermediate metabolizers
Treatment Group	Treatment A: 6 mg SD-809 (1 x 6 mg tablet) following a standard meal Treatment B: 12 mg SD-809 (1 x 12 mg tablet) following a standard meal Treatment C: 18 mg SD-809 (1 x 18 mg tablet) following a standard meal Treatment D: 24 mg SD-809 (1 x 18 mg tablet and 1 x 6 mg tablet) following a standard meal Treatment E: 18 mg SD-809 (1 x 18 mg tablet) following a high-fat meal
Dosage and Administration	See trt group
PK Sampling: plasma	predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72 and 96 h post (each) dose
Analysis	LC-MS/MS method for SD-809 and HTBZ metabolites Range: 0.100 ng/mL to 10.0 ng/mL for SD-809 0.500 ng/mL to 100 ng/mL for HTBZ metabolites
PK Assessment	C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, CL/F of SD-809 and metabolites
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	none

Bioanalytical Assay:

Plasma samples were assayed for SD-809 and its α-HTBZ and β-HTBZ metabolites by validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods. The range was from 0.100 to 10.0 ng/mL for SD-809 and 0.500 to 100 ng/mL for both d6-α- and β-HTBZ. Details of the validation are presented in 4.1.4 Bioanalytical Study Reports. The validation of the assays and the performance of the assays for SD-809 and its metabolites during the analysis of the study samples are acceptable.

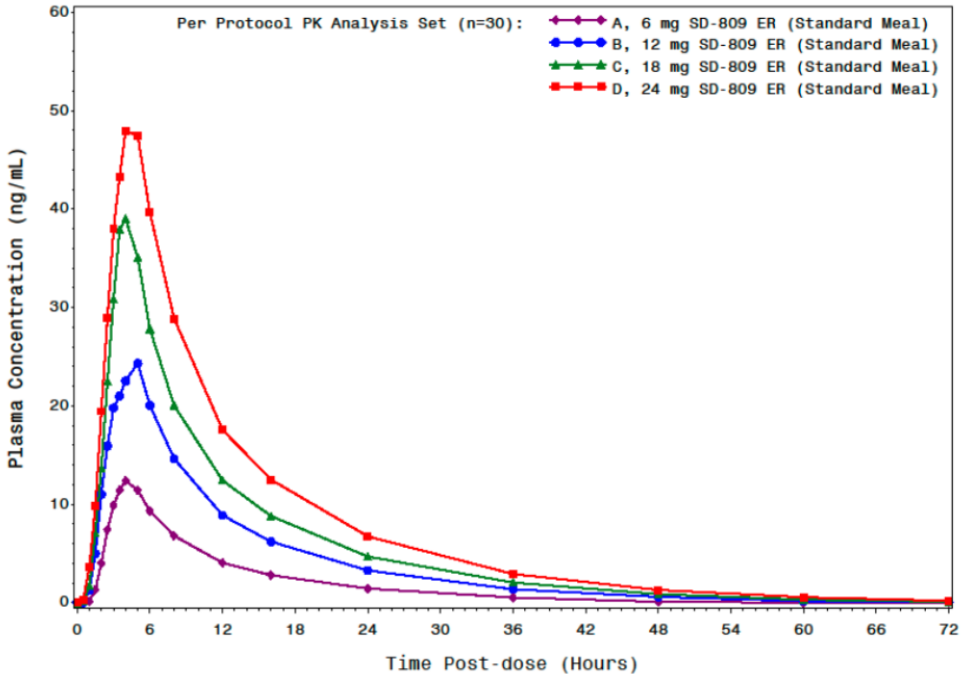
Pharmacokinetic Results:

The following study drugs were administered during the course of the study: SD-809 Tablets 6 mg, 12 mg and 18 mg. All strengths Manufactured by: (b) (4) (b) (4).

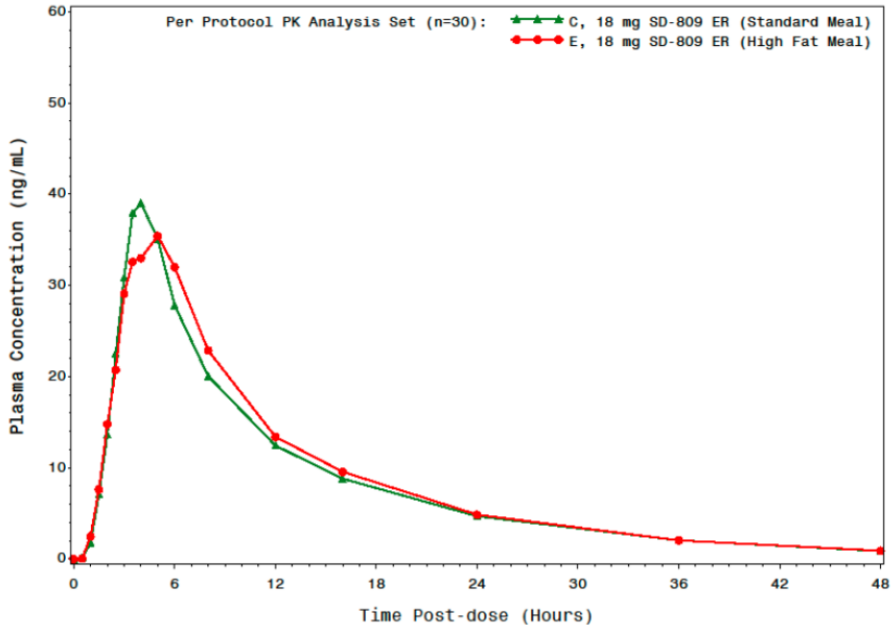
Reviewer's Comment: However, the SD-809 commercial formulation (and the one used in the efficacy trials SD-809-C-15 and SD-809-C-16) was supplied as tablet formulation

at strengths of 6 mg, 9 mg, and 12 mg. According to the CMC reviewer, the strengths of 6, 9, 12, and 18 mg are (b) (4) similar.

Mean Plasma Concentration of Total (α+β)-d6-HTBZ by Dose Level



Mean Plasma Concentration of Total (α+β)-d6-HTBZ by Meal Type



Summary of Key PK Parameters by Analyte and Treatment

	Mean (CV%) N=30 (Per-Protocol PK Analysis Set)				
	A: 6 mg SD-809 Standard Meal	B: 12 mg SD-809 Standard Meal	C: 18 mg SD-809 Standard Meal	D: 24 mg SD-809 Standard Meal	E: 18 mg SD-809 High-Fat Meal
Parent Drug (SD-809)					
C_{max} (ng/mL)	0.054 (186)	0.167 (81)	0.272 (73)	0.351 (67)	0.358 (44)
t_{max} (hr)	3.25[a] (22)	3.76[b] (35)	3.26[c] (31)	3.42 (37)	3.62 (34)
t_{lag} (hr)	2.56[a] (32)	2.46[b] (49)	2.16[c] (44)	1.88 (52)	2.07 (55)
AUC_{0-t} (ng·hr/mL)	0.030 (223)	0.215 (104)	0.391 (80)	0.706 (73)	0.653 (50)
$t_{1/2}$ (hr)	N.C.	N.C.	0.819[d] (7.2)	1.20[e] (36)	0.855[d] (6.1)
Total d_6-(α+β)-HTBZ					
C_{max} (ng/mL)	15.5 (22)	32.1 (25)	47.8 (25)	60.9 (23)	49.0 (17)
t_{max} (hr)	3.74 (26)	3.90 (33)	3.63 (23)	3.92 (30)	4.09 (30)
t_{lag} (hr)	1.20 (47)	1.07 (62)	0.87 (68)	0.88 (75)	0.92 (59)
AUC_{inf} (ng·hr/mL)	132 (35)	289 (40)	419 (39)	580 (39)	436 (30)
$t_{1/2}$ (hr)	8.64 (21)	9.79 (25)	10.2 (33)	10.4 (23)	10.2 (24)
d_6-α-HTBZ					
C_{max} (ng/mL)	10.0 (21)	20.2 (22)	30.1 (22)	37.6 (18)	30.4 (18)
t_{max} (hr)	3.65 (26)	3.90 (33)	3.60 (24)	3.82 (29)	4.09 (30)
t_{lag} (hr)	1.20 (47)	1.07 (62)	0.87 (68)	0.88 (75)	0.92 (59)
AUC_{inf} (ng·hr/mL)	102 (28)	213 (31)	307 (31)	419 (31)	316 (24)
$t_{1/2}$ (hr)	9.97 (26)	10.4 (25)	10.7 (24)	10.8 (23)	10.7 (20)
d_6-β-HTBZ					
C_{max} (ng/mL)	5.57 (31)	11.9 (35)	17.9 (35)	23.4 (32)	18.8 (20)
t_{max} (hr)	3.85 (26)	3.92 (34)	3.69 (23)	3.90 (31)	4.09 (33)
t_{lag} (hr)	1.63 (37)	1.35 (50)	1.10 (54)	1.10 (61)	1.13 (49)
AUC_{inf} (ng hr/mL)	33.9 (63)	79.1 (65)	114 (63)	164 (63)	122 (47)
$t_{1/2}$ (hr)	4.01 (53)	4.74 (40)	4.87 (36)	5.19 (38)	4.76 (34)

CV=coefficient of variation; C_{max}=maximum observed plasma concentration; T_{max}=time of the maximum observed plasma concentration; T_{lag}=time prior to first measurable (non-zero) plasma concentration; AUC=area under the concentration time curve; $t_{1/2}$=half-life; N.C.=not calculable.
Key: [a] n=8; [b] n=23; [c] n=29; [d] n=3; [e] n=5.

The dose dependence of the PK of SD-809 was investigated by assessing the relative bioavailability of the dose-normalized PK parameters of the metabolites of SD-809 at four dose levels (6, 12, 18, and 24 mg), when administered with a standard meal.

Dose-Normalized Comparison of SD-809 PK Parameters Administered With a Standard Meal

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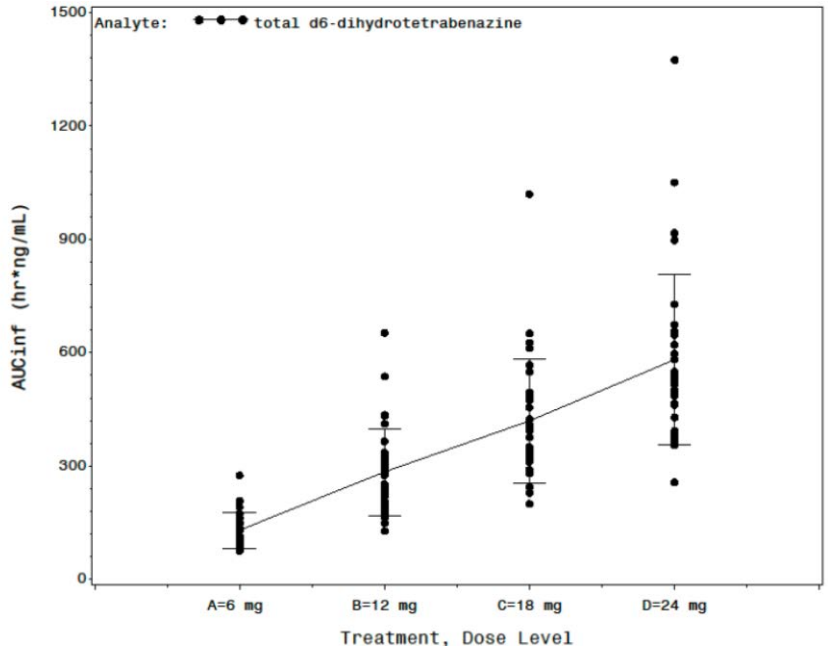
		% Ratio of Dose-Normalized LS Mean Test/Reference (90% Confidence Interval), N=30 (Per-Protocol PK Analysis Set)			
		B vs A: 12 mg vs 6 mg, Standard Meal	C vs A: 18 mg vs 6 mg, Standard Meal	C vs B: 18 mg vs 12 mg, Standard Meal	D vs C: 24 mg vs 18 mg, Standard Meal
Total d_6-HTBZ	C_{max} (ng/mL)	102.8 (96.0-110.1)	101.9 (96.5-107.6)	99.1 (92.6-106.1)	96.1 (90.2-102.4)
	AUC_{0-t} (hr•ng/mL)	113.2 (107.7-119.0)	110.7 (105.2-116.5)	97.8 (93.3-102.6)	105.0 (99.1-111.3)
	AUC_{inf} (ng•hr/mL)	108.6 (103.5-113.8)	105.3 (100.3-110.4)	97.0 (92.6-101.5)	103.9 (98.2-110.0)
d_6-α-HTBZ	C_{max} (ng/mL)	100.8 (95.0-107.1)	99.8 (95.3-104.6)	99.0 (93.0-105.3)	94.4 (89.2-99.9)
	AUC_{0-t} (hr•ng/mL)	110.8 (106.2-115.6)	108.2 (103.6-113.1)	97.7 (93.8-101.8)	103.6 (98.5-109.1)
	AUC_{inf} (ng•hr/mL)	104.1 (100.0-108.4)	100.5 (96.6-104.6)	96.5 (92.8-100.4)	102.2 (97.3-107.3)
d_6-β-HTBZ	C_{max} (ng/mL)	105.7 (96.6-115.6)	105.7 (97.6-114.5)	100.0 (91.3-109.6)	99.0 (90.9-107.9)
	AUC_{0-t} (hr•ng/mL)	126.6 (116.0-138.1)	126.0 (115.5-137.5)	99.6 (92.3-107.4)	110.3 (101.1-120.3)
	AUC_{inf} (ng•hr/mL)	116.5 (107.7-125.9)	113.3 (104.4-122.8)	97.3 (90.7-104.3)	108.8 (100.3-118.1)

A regression analysis test indicated a linear dose dependence (with 95% CI for the exponent 0.95 - 1.19) over the dose range studied (6 mg to 24 mg). A similar analysis was performed for C_{max} and AUC_{0-t} for total d6-(α+β)-HTBZ and for C_{max}, AUC_{0-t}, and AUC_{inf} for α-HTBZ and β-HTBZ separately. Only AUC_{0-t} for β-HTBZ showed an exponent that was concluded to be different from one.

The dose dependence of AUC_{inf} of total d6-(α+β)-HTBZ is presented in the figure below as the individual values along with the means and standard deviations at each dose level.



Note: The highest AUC_{inf} at each dose level was for Subject 011, who was an intermediate metabolizer.

Conclusions: There was a linear dose dependence of PK parameters C_{max}, AUC_{0-t}, and AUC_{inf} of the HTBZ metabolites of SD-809 across the dose range of 6 mg to 24 mg

administered with a standard meal, as shown by the power regression analysis of C_{max} and AUC as a function of dose.

Comparison of PK Parameters for SD-809 18 mg by Meal Type

		Treatment E vs Treatment C High-Fat Meal vs Standard Meal (SD-809 18 mg) N=30 (Per-Protocol PK Analysis Set)	
		% Ratio of LS Means Test/Reference	90% Confidence Interval
Total d_6-HTBZ	C_{max} (ng/mL)	104.2	(97.3-111.6)
	AUC_{0-t} (hr•ng/mL)	107.0	(101.4-112.9)
	AUC_{inf} (ng•hr/mL)	106.4	(100.9-112.2)
d_6-α-HTBZ	C_{max} (ng/mL)	101.6	(95.5-108.0)
	AUC_{0-t} (hr•ng/mL)	105.1	(100.2-110.2)
	AUC_{inf} (ng•hr/mL)	104.3	(99.6-109.3)
d_6-β-HTBZ	C_{max} (ng/mL)	109.2	(99.7-119.7)
	AUC_{0-t} (hr•ng/mL)	113.3	(104.6-122.8)
	AUC_{inf} (ng•hr/mL)	113.1	(104.7-122.1)

The relative bioavailability of d6-HTBZ metabolites for administration of SD-809 18 mg with a high-fat meal compared with administration with a standard meal met the criteria for bioequivalence for C_{max}, AUC_{0-t}, and AUC_{inf}. These results demonstrated that the SD-809 formulation was not sensitive to meal composition.

Safety results:

There were no serious AEs in this study. Constipation and abdominal distension were the AEs with highest incidence, each reported by four subjects.

Two subjects discontinued early: Subject 025 withdrew consent for study participation for personal reasons after Period 2. Subject 003 was discontinued by the PI due to an AE of syncope that occurred prior to dosing in Period 4, 5 days postdose following Treatment A (6 mg standard meal). According to the sponsor, the AE was not related to study medication (plasma concentrations of SD-809, α-HTBZ and β-HTBZ were all below LOQ by 24 hours postdose in Period 3).

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Healthy Subject PD and PK/PD Studies

V. SD-809-C-21: A Randomized Double-Blind, Placebo- and Positive-Controlled Crossover Study to Evaluate the Effects of Single Doses of SD-809 (Deutetrabenazine) and Tetrabenazine on the Corrected QT Interval

Objectives:

- To evaluate the effects of SD-809 (deutetrabenazine) and tetrabenazine (TBZ) on the corrected QT (QTc) interval
- To evaluate the safety and pharmacokinetics of SD-809

Study Design	Randomized, double-blind, placebo- and positive-controlled, six-period, crossover study
Study Population	48 heathy subjects, males and females, 18-50 years old, CYP2D6 extensive or intermediate metabolizers
Treatment Group	Trt A: 12 mg SD-809 plus moxifloxacin placebo and placebo for TBZ* Trt B: 24 mg SD-809 plus moxifloxacin placebo and placebo for TBZ Trt C: SD-809 placebo plus moxifloxacin placebo and placebo for TBZ Trt D: 400 mg moxifloxacin plus SD-809 placebo and placebo for TBZ Trt E: 50 mg TBZ plus moxifloxacin placebo and SD-809 placebo Trt F: Placebo for TBZ plus moxifloxacin placebo and SD-809 placebo
Dosage and Administration	Within each treatment period, subjects received a single dose of study drug. Treatments A, B, C, and D were administered in the fed state, following a standard breakfast; trt. E and F were administered under fasting conditions. Washout periods of a minimum 5-day between doses.
PK Sampling: plasma	Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 24 h post dose
Analysis	LC-MS/MS method for SD-809/TBZ and HTBZ metabolites Range: 0.100 ng/mL to 10.0 ng/mL for SD-809/TBZ 0.500 ng/mL to 100 ng/mL for HTBZ metabolites
PK Assessment	C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, CL/F of SD-809 and metabolites
Safety Assessment	Vital signs, adverse events, ECG, clinical chemistry
PD Assessment	Electrocardiograms were collected continuously via a Holter monitor from approximately 1.5 hours prior to each study drug administration through 24 hours after dosing. Primary outcome measures: ☐ The placebo-adjusted change from baseline in QTcF (ΔΔQTcF) at each time point (same as PK sample collection time points) after a single low dose (12 mg) and high dose (24 mg) of SD-809 ☐ ΔΔQTcF at each time point after a single dose (50 mg) of TBZ

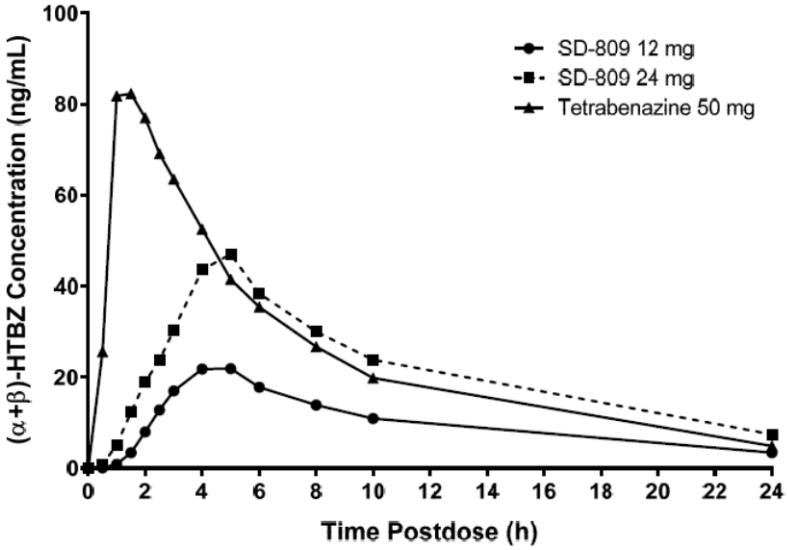
* Tetrabenazine from (b) (4) source was used in this study.

Bioanalytical Assays:

Two validated assays were used: ALM.TBZ.1 for measuring the concentrations of TBZ and its α- and β-HTBZ metabolites in human plasma and ALM.SD809.1 for SD-809 and its deuterated α- and β-HTBZ metabolites.
Note: The internal standards for ALM TBZ.1 were the analytes for ALM SD-809.1 and vice versa. The assays were validated in the following ranges:
0.100 ng/mL to 10.0 ng/mL for SD-809 or tetrabenazine
0.500 ng/mL to 100 ng/mL for HTBZ metabolites
Reviewer's Comment: The validation of the assays and the performance of the assays for TBZ/SD-809 and the metabolites during the analysis of the study samples are acceptable. Details of the validation results are presented in Bioanalytical Study Reports.

Pharmacokinetic Results:
Selection of Doses: The 24-mg SD-809 dose is the maximum single dose in the proposed SD-809 product labeling and was predicted to provide comparable exposure (AUC) to a 50-mg dose of TBZ. A 50-mg dose of TBZ has been shown to induce QTc prolongation of approximately 8 msec (Lundbeck, 2012 Label). Additional studies of TBZ 50 mg in the presence of CYP2D6 inhibitors did not further increase the effect on the QTc interval. Thus, evaluation of higher doses of SD-809 was not deemed necessary.
Reviewer's comment: According to the QT Interdisciplinary Review Team, the design of this study is not adequate to evaluate the effect of study drugs on the QT interval (single-dose, no supratherapeutic dose, please refer to the PK/PD results section).

Mean Total (α+β)-HTBZ Plasma Concentration Profiles for SD-809 (12 mg and 24 mg) and Tetrabenazine 50 mg (N=41)



The pharmacokinetics for total (α+β)-HTBZ after SD-809 administration in the 12-24 mg dose range appeared dose-proportional (C_{max} and AUC with the 24-mg dose were approximately twice the C_{max} and AUC with the 12-mg dose).

Summary of Plasma PK Parameters of Total (α+β)-HTBZ (N=41)

Parameter	SD-809 12 mg N=41	SD-809 24 mg N=41	Tetrabenazine 50 mg N=41
C_{max} (ng/mL) mean (CV%)	25.8 (31)	53.3 (30)	94.2 (44)
t_{max} (h) median (min, max)	4 (2, 5)	4 (1.5, 8)	1.5 (1, 5)
$AUC_{(0—24)}$ (ng·h/mL) mean (CV%)	234 (37)	503 (36)	608 (57)
AUC_{inf} (ng·h/mL) mean (CV%)[a]	252 (35) [n=36]	547 (34) [n=35]	577 (45) [n=38]

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma drug concentration; CV, coefficient of variation; HTBZ, dihydrotetrabenazine; min, minimum; max, maximum; t_{max}, time to maximum plasma concentration.
[a] The (α+β)-HTBZ AUC_{inf} was calculated using the subset of subjects whose extrapolated AUC accounted for no more than 20% of AUC_{inf}.

Reviewer's comment: Based on the above plot and the PK results, it appears that the Mean Total (α+β)-HTBZ exposure (AUC_{0-24h}) after 24 mg SD-809 is lower than after 50 mg TBZ. According to sponsor's simulations and proposed conversion ratio, they should be similar.

PK/PD results:

QT Interdisciplinary Review Team Comments:

The applicant has chosen to conduct a single dose study despite known accumulation of the active metabolites. The Pharmacokinetic analysis indicates that the metabolite exposure reached a single 24-mg dose is lower than metabolite exposure following the highest therapeutic dose at steady state. There is a clear limitation of this TQT study that the plasma alpha- and beta-HTBZ concentrations achieved with the single dose of 24 mg SD-809 do not cover the expected steady state exposure (C_{max}) following the highest therapeutic dose of 24 mg b.i.d. and the worst case clinical scenario (CYP2D6 poor metabolizer or administered a strong CYP2D6 inhibitor). Similar to Xenazine, a statistic significant exposure response relationship between the sum concentration of the active metabolites (α+β) and QT has been observed. Clinically relevant QT prolongation might be expected in some patients at the highest therapeutic dose of 24 mg b.i.d., especially in CYP2D6 poor metabolizer or patients co-administered a strong CYP2D6 inhibitor.

Safety results:

No SAEs were reported. All AEs were mild or moderate in severity, and most were assessed as not related to study drug.

The most common AEs were headache (9 subjects [19%]), dizziness (7 subjects [15%]), dermatitis contact (6 subjects [13%]), and restlessness (5 subjects [10%]). All five AEs of restlessness occurred with tetrabenazine treatment.

One subject withdrew from the study due to an AE, a moderate, unrelated event of foot fracture that occurred during the washout period after the moxifloxacin treatment period.

There were no notable changes in chemistry, hematology, urinalysis, vital signs, safety ECGs, or physical examinations during the study.

Extrinsic Factor PK Studies

VI. SD-809-C-08: A Drug Interaction Study of SD-809 ER and Repeated Doses of Paroxetine

Objective: to evaluate the effect of a potent CYP2D6 inhibitor on the pharmacokinetics and safety of a single dose of SD-809 ER.

Study Design	Open-label, sequential, drug-drug interaction study in 24 healthy subjects
Study Population	24 healthy male and female subjects who were CYP2D6 extensive or intermediate metabolizers, 18-50 years old
Treatment Group	Each subject received an oral dose of SD-809 22.5 mg, administered as one 15 mg tablet and one 7.5 mg tablet* on Days 1 and 11 and 20 mg paroxetine on Days 4 to 12.
Dosage and Administration	Subjects received a single 22.5 mg oral dose of SD-809 on Day 1 followed by a 72-hour washout. Subjects then received paroxetine on Days 4 to 12 to achieve steady-state. On Day 11, another single dose of SD-809 was administered followed by a 72-hour washout. SD-809 was administered approximately 30 minutes following the start of a standardized breakfast meal with moderate fat content (35%).
PK Sampling: plasma	SD-809: Pre-dose and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours post-dose Paroxetine: 1 h pre-dose on Days 9 and 10.
Analysis	LC-MS/MS assays for SD-809 and metabolites, including deuterated α- and β-dihydrotetrabenazine (HTBZ) and the O-desmethyl-metabolites of α- and β-HTBZ Range: 0.100 ng/mL to 10.0 ng/mL for SD-809 0.500 ng/mL to 100 ng/mL for HTBZ metabolites 0.500 to 50.0 ng/mL for O-desmethyl-metabolites LC-MS/MS assay for paroxetine, range 0.500 to 50.0 ng/mL
PK Assessment	C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, V_d/F, CL/F of SD-809 and metabolites
Safety Assessment	Adverse events, vital signs, electrocardiograms, clinical chemistry
PD Assessment	change from baseline in QTcF, with changes in QTcB as a secondary analysis

* These are the initial Formulation A strengths, manufactured by (b) (4)
Later, e.g., in Study SD-809-C-11, different strengths (6mg, 12mg, 18 mg) were used. The commercial strengths are 6mg, 9mg and 12 mg.

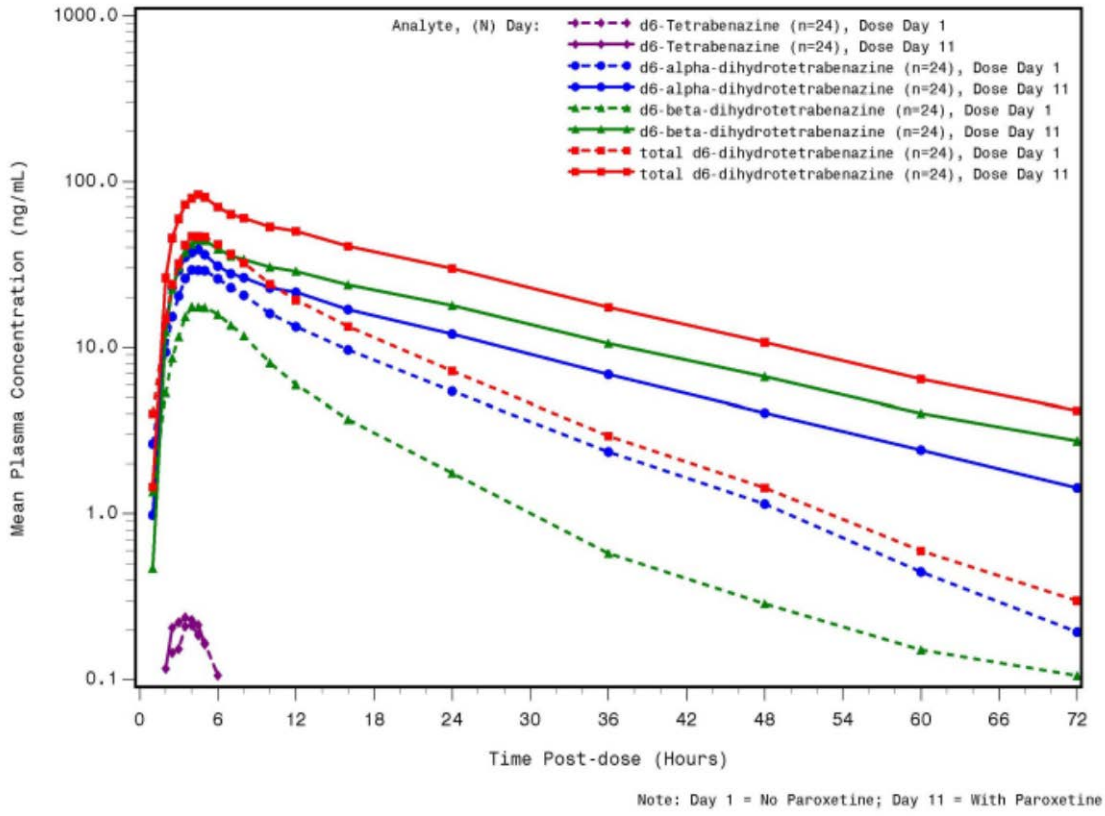
Bioanalytical Assays:
The following validated LC-MS/MS assays were used for the analysis of SD-809, its metabolites and paroxetine in plasma samples in this study: ALM SD-809.1, ALM004 and ALM014.
The ranges of the first assay (ALM SD-809.1) were from 0.100 to 10.0 ng/mL for SD-809 and 0.500 to 100 ng/mL for deuterated α- and β-HTBZ.

The validated range for the second assay (ALM004) was from 0.500 to 50.0 ng/mL for the 9-O- and 10-O-desmethyl metabolites of α-HTBZ and β-HTBZ.
Another validated LC-MS/MS assay (ALM014) with a range from 0.500 to 50.0 ng/mL was used to quantify paroxetine in plasma.
Samples were analyzed in a total of 23 analytical runs.
Reviewer's Comment: The accuracy, precision (including the standard curves), reproducibility, specificity, recovery, and frozen stability of the analytical methods are acceptable. The performance of the assays during the study samples analysis is also acceptable.

Discussion of Study Design:
This was an open-label, sequential, drug-drug interaction study in 24 healthy subjects (CYP2D6 extensive or intermediate metabolizers only). Paroxetine, a potent CYP2D6 inhibitor, is used in drug-drug interaction studies and is also a frequent concomitant medication in the intended patient population. The recommended initial dose of paroxetine for most clinical indications is 20 mg QD, without regard to meals. Paroxetine was administered for 9 days (Days 4 to 12) to ensure that steady-state of paroxetine were achieved to maximize its CYP2D6 inhibitory effects; trough plasma concentrations of paroxetine were also assessed on Days 9 through 13 to document achievement of steady-state concentrations of paroxetine.
Reviewer's Comment: The study design is adequate to assess the DDI between a potent CYP2D6 inhibitor and SD-809.

Pharmacokinetic Results:
Subject 011 was excluded from the PPPK analysis set as this subject's CYP2D6 phenotype could not be determined due to the presence of multiple copies of one allele. It was concluded that it is possible that this subject could exhibit the phenotype of an ultra-rapid metabolizer. This possibility was supported by the trough plasma concentrations of paroxetine, a CYP2D6 substrate, observed for this subject that were all BLQ. Subject 011 was therefore excluded from the PPPK analysis set.

Mean Plasma Concentration of SD-809 and Primary Metabolites by Dose Day



Plasma concentrations of the HTBZ metabolites d6-α-HTBZ and d6-β HTBZ were higher in subjects receiving SD-809 plus paroxetine (Day 11) compared with the same subjects receiving SD-809 alone (Day 1). There was a 3-fold increase in mean $AUC_{0-\infty}$ for d6-(α+β)-HTBZ from 624 ng hr/mL on Day 1 (SD-809 alone) to 1901 ng·hr/mL on Day 11 (SD-809 + paroxetine) and slower elimination (mean $t_{1/2}$, 9.75 hours on Day 1, compared with 16.0 hours on Day 11). Increased exposure of d6-α-HTBZ (1.85-fold), and d6-β-HTBZ (6.5-fold) was observed when SD-809 was co-administered with paroxetine. Prolongation of the half-lives of d6-α-HTBZ and d6-β-HTBZ was associated with reduced formation of O-desmethyl metabolites of HTBZ on Day 11 (SD-809 + paroxetine) compared with Day 1 (SD-809 alone). Therefore, dosing adjustment is needed in CYP2D6 poor metabolizers or patients on CYP2D6 potent inhibitors.
Key PK parameters of SD-809 and its metabolites are presented for all subjects and by phenotype in the following tables.

Summary of Key PK Parameters of Primary Analytes after SD-809 22.5 mg Administration with or without Paroxetine

APPEARS THIS WAY ON ORIGINAL

Dose Day 1 = SD-809 alone Dose Day 11 = SD-809 + Paroxetine	Mean (CV%)					
	All Subjects (N=23)		Subjects with Phenotype EM (N=15)		Subjects with Phenotype IM (N=8)	
	Dose Day 1	Dose Day 11	Dose Day 1	Dose Day 11	Dose Day 1	Dose Day 11
Parent Drug (SD-809 = d_6-tetrabenazine)						
C_{max} (ng/mL)	0.360 (60)	0.377 (53)	0.308 (44)	0.349 (57)	0.457 (66)	0.428 (49)
t_{max} (hr)	3.64 (38)	3.11 (28)	3.57 (36)	3.07 (26)	3.75 (44)	3.19 (32)
t_{lag} (hr)	1.87 (64)	1.67 (48)	1.74 (60)	1.70 (51)	2.13 (70)	1.63 (46)
AUC_{last} (ng·hr/mL)	0.768 (53)	0.815 (60)	0.644 (40)	0.741 (67)	1.00 (55)	0.952 (50)
Total d_6-(α+β)-HTBZ						
C_{max} (ng/mL)	61.8 (26)	95.9 (25)	56.0 (25)	97.8 (27)	72.8 (19)	92.2 (21)
t_{max} (hr)	4.19 (34)	3.81 (29)	4.09 (28)	3.58 (27)	4.38 (44)	4.25 (30)
t_{lag} (hr)	0.87 (122)	0.63 (113)	0.73 (121)	0.54 (120)	1.13 (121)	0.81 (104)
AUC_{inf} (ng·hr/mL)	624 (49)	1901 (34)	489 (35)	1622 (35)	874 (39)	2423 (19)
$t_{1/2}$ (hr)	9.75 (28)	16.0 (24)	8.57 (23)	14.0 (20)	12.0 (23)	19.8 (13)
d_6-α-HTBZ						
C_{max} (ng/mL)	37.4 (22)	45.4 (25)	35.8 (21)	46.6 (27)	40.5 (22)	43.2 (21)
t_{max} (hr)	4.12 (32)	3.48 (25)	4.09 (28)	3.37 (26)	4.19 (40)	3.69 (25)
t_{lag} (hr)	0.87 (122)	0.63 (113)	0.73 (121)	0.54 (120)	1.13 (121)	0.81 (104)
AUC_{inf} (ng·hr/mL)	427 (34)	780 (28)	363 (31)	706 (29)	546 (22)	921 (18)
$t_{1/2}$ (hr)	10.5 (28)	15.5 (18)	9.12 (20)	14.0 (14)	13.0 (23)	18.1 (11)
d_6-β-HTBZ						
C_{max} (ng/mL)	24.6 (36)	51.5 (25)	20.4 (33)	52.0 (28)	32.6 (22)	50.5 (21)
t_{max} (hr)	4.14 (34)	3.94 (26)	4.05 (28)	3.68 (26)	4.32 (45)	4.44 (24)
t_{lag} (hr)	1.20 (83)	0.85 (74)	1.17 (72)	0.74 (81)	1.26 (103)	1.06 (64)
AUC_{inf} (ng·hr/mL)	199 (90)	1121 (40)	128 (46)	916 (40)	333 (75)	1507 (20)
$t_{1/2}$ (hr)	5.91 (48)	16.2 (28)	4.84 (24)	13.7 (19)	7.93 (50)	21.1 (15)
d_3-9-O-desmethyl α-HTBZ						
C_{max} (ng/mL)	1.29 (28)	0.501(73)	1.36 (18)	0.549(57)	1.17 (45)	0.410 (112)
t_{max} (hr)	5.53 (36)	6.07 (83) [n=16]	5.37 (29)	5.05 (35) [n=12]	5.82 (46)	9.14 (109) [n=4]
AUC_{0-t} (ng·hr/mL)	13.9 (48)	4.57 (128)	13.9 (39)	4.31 (122)	13.8 (65)	5.06 (144)
$t_{1/2}$ (hr)	NC	NC	NC	NC	NC	NC
d_3-10-O-desmethyl α-HTBZ						
C_{max} (ng/mL)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
t_{max} (hr)	NC	NC	NC	NC	NC	NC
AUC_{0-t} (ng·hr/mL)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
$t_{1/2}$ (hr)	NC	NC	NC	NC	NC	NC
d_3-9-O-desmethyl β-HTBZ						
C_{max} (ng/mL)	4.37 (29)	1.60 (36)	4.47 (20)	1.59 (31)	4.16 (45)	1.61 (47)
t_{max} (hr)	6.68 (63)	16.41 (38)	5.50 (33)	15.37 (33)	8.89 (72)	18.35 (44)
AUC_{0-t} (ng·hr/mL)	92.0 (32)	68.4 (37)	85.1 (28)	65.7 (38)	105 (33)	73.5 (35)
$t_{1/2}$ (hr)	16.2(14) [n=21]	24.5 (12) [n=10]	15.9 (15) [n=14]	23.8 (12) [n=8]	16.8 (13) [n=7]	27.4 (9) [n=2]

Mean plasma concentrations of d6-α HTBZ and d6-β HTBZ were higher in IM phenotype subjects on both Day 1 (SD-809 alone) and Day 11 (SD-809 + paroxetine) compared with subjects with a CYP2D6 EM phenotype.

Comparison of PK Parameters by Analyte, With and Without Paroxetine

Dose Day 1 = SD-809 alone Dose Day 11 = SD-809 + Paroxetine		% Ratio of LS Mean (90% Confidence Interval) ([Day 11] / [Day 1])		
		All Subjects (N=23)	Subjects with Phenotype EM (N=15)	Subjects with Phenotype IM (N=8)
Total d_6-(α+β)-HTBZ	C_{max} (ng/mL)	154.8 (137.4-174.4)	173.1 (149.8-200.1)	125.6 (105.4-149.6)
	AUC_{0-t} (ng·hr/mL)	303.6 (268.0-343.8)	324.9 (273.9-385.4)	267.3 (224.0-318.9)
	$AUC_{0-\infty}$ (ng·hr/mL)	314.7 (278.4-355.6)	329.8 (277.7-391.8)	288.1 (242.3-342.5)
	$t_{1/2}$ (hr)	165.5 (155.1-176.7)	164.6 (149.1-181.6)	167.3 (156.3-179.2)
d_6-α-HTBZ	C_{max} (ng/mL)	119.9 (108.1-132.9)	127.8 (111.8-146.1)	106.3 (90.0-125.4)
	AUC_{0-t} (ng·hr/mL)	181.6 (162.4-203.0)	192.2 (162.9-226.8)	163.3 (148.3-179.8)
	$AUC_{0-\infty}$ (ng·hr/mL)	185.0 (165.8-206.4)	193.6 (164.4-228.0)	169.8 (153.8-187.5)
	$t_{1/2}$ (hr)	150.6 (143.4-158.1)	155.5 (146.7-164.8)	141.8 (129.3-155.5)
d_6-β-HTBZ	C_{max} (ng/mL)	216.4 (185.0-253.2)	259.2 (216.7-310.1)	154.3 (126.0-189.0)
	AUC_{0-t} (ng·hr/mL)	641.3 (537.3-765.4)	744.6 (605.3-915.8)	484.7 (355.2-661.5)
	$AUC_{0-\infty}$ (ng·hr/mL)	649.9 (549.6-768.5)	731.5 (595.0-899.3)	520.6 (388.9-697.0)
	$t_{1/2}$ (hr)	286.4 (261.3-314.0)	287.4 (255.5-323.3)	284.6 (237.6-340.8)

AUC = area under concentration-time curve; C_{max} = maximum plasma concentration; EM = extensive metabolizer; HTBZ = dihydrotetrabenazine; IM = intermediate metabolizer; $t_{1/2}$ = half life.

PD Results:

Mean QTc intervals remained <450 msec at all time points.

The SD-809 + paroxetine treatment exhibited greater QTcF interval mean increases from pre-dose compared to the monotherapies through Hour 8, with the maximum mean QTcF increase of +9.2 msec at Hour 6 (to a mean value of 404.8 msec), compared to a maximum mean increase in QTcF of +1.5 msec at Hour 6 for SD-809 alone and +0.7 msec at Hour 5 for paroxetine alone.

Reviewer's Comment: This (in addition to the PK results) argues against the sponsor's claim [redacted (b) (4)] [redacted (b) (4)] Also, please refer to the QT Interdisciplinary Review Team comments in the PK/PD results section of Study SD-809-C-21.

Safety Results:

There were no serious adverse events (SAEs), or discontinuations due to AEs in this study. Of the 45 reported TEAEs, 42 were mild in severity and 3 were moderate (all headache). No subjects had clinically significant orthostatic blood pressure changes after dosing with SD-809 alone. One subject (a 25-year-old Hispanic White male with EM phenotype) experienced orthostatic changes 4.5 hours after dosing with SD-809 + paroxetine, with no AEs reported; at that time point, his blood pressure and heart rate were 114/63 mmHg and 62 bpm supine and 65/42 mmHg and 117 bpm standing. These orthostatic changes resolved within an hour.

Efficacy and Safety Studies

VII. SD-809-C-15: A Randomized, Double Blind, Placebo Controlled Study of SD-809 Extended Release for the Treatment of Chorea associated with Huntington Disease

Objective: to evaluate the efficacy, safety, and tolerability of SD-809 in adults with chorea associated with Huntington Disease (HD).

Study Design	Randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of SD-809 in adults with chorea associated with HD
Study Population	Adult subjects with HD
Treatment Groups	90 subjects were randomized 1:1 to receive either SD-809* or placebo
Dosage and Administration**	The starting dose was SD-809 6 mg or placebo. The dose of study drug was to be adjusted weekly in increments of 6 mg per day (SD-809 or placebo) during the titration phase until there was adequate control of chorea**. Overall treatment period was 12 weeks, including 8-week titration phase and 4-week maintenance phase.
PK Sampling	Two PK samples/subject on Weeks 9 and 12
PK Assessment	popPK (separate report)
Efficacy Assessment	Primary: Change from baseline in Total Maximal Chorea Score (TMC)
Safety Assessment	Vital signs, body weight, adverse events, ECGs, clinical chemistry, anxiety and depression subscores

* SD-809 6 mg (batch number N451173), SD-809 9 mg (N451737), and 12 mg (N451174)
** The maximum total daily dose of SD-809 was 48 mg per day (24 mg twice daily), unless the subject was receiving a strong CYP2D6 inhibitor, in which case the maximum total daily dose was 36 mg (18 mg twice daily).

Bioanalytical Assays:
A validated LC-MS/MS assay was used for quantification of SD-809 and the HTBZ metabolites in study plasma samples.
The ranges of the assay were from 0.100 to 10.0 ng/mL for SD-809 and 0.500 to 100 ng/mL for deuterated α- and β-HTBZ.
Reviewer's Comment: The accuracy, precision (including the standard curves), reproducibility, specificity, recovery, and frozen stability of the analytical methods are acceptable. The performance of the assays during the study samples analysis is also acceptable.

Pharmackinetic Results:
Weeks 9 and 12 PK Sampling:
Subjects were to record the start time of their last meal and the time of their last dose in their diary and to bring the diary with them to the clinic visit. Subjects took their usual

morning dose of study drug at home and had PK blood sampling upon arrival in the clinic on these visits.
Subjects had a second PK sample drawn at least 2 hours (Week 9) or 3 hours (Week 12) after their initial sample.
Subjects who withdrew early from the study were to have a single blood sample collected for PK at the Early Termination Visit if the last dose was within the prior 48 hours, if possible.
A population PK dataset was constructed based on PK data collected in 44 subjects with chorea associated to HD in study SD-809-C-15 (popPK report).

Categorical Covariates		Number (% of Total)
Sex	Female	23 (52.3)
	Male	21 (47.7)
CYP2D6 Phenotype	Poor Metabolizer	3 (6.82)
	No-poor Metabolizer	38 (86.4)
	Unknown	3 (6.82)
Strong CYP2D6 Inhibitor[a]	Absence	37 (84.1)
	Presence	7 (15.9)
Dose Regimens of SD-809	6 mg BID	Week 9: 2 (4.7) Week 12: 2 (4.7)
	12 mg BID	Week 9: 1 (2.3) Week 12: 1 (2.3)
	15 mg BID	Week 9: 2 (4.7) Week 12: 3 (7.0)
	18 mg BID	Week 9: 11 (25.6) Week 12: 12 (27.9)
	21 mg BID	Week 9: 8 (18.6) Week 12: 7 (16.3)
	24 mg BID	Week 9: 19 (44.2) Week 12: 18 (41.9)

BID=Twice daily dose; CYP2D6=Cytochrome P450 2D6 enzyme
[a] Paroxetine, Bupropion, Fluoxetine[1]

Notes: Seven subjects received a concomitant strong CYP2D6 inhibitor, and 1 subject with a PM phenotype received a concomitant strong CYP2D6 inhibitor.
The majority of subjects (>75%) received 18, 21, or 24 mg BID doses of SD-809 at the Week 9 visit.

In subjects with functional CYP2D6, the median CL/F of α-HTBZ was approximately 1.25-fold higher than with impaired CYP2D6 at Week 9. The median CL/F of β-HTBZ in subjects with functional CYP2D6 was approximately 3.5 to 4-fold higher than those with impaired CYP2D6 on Week 9 or Week 12.

Descriptive Statistics of Exposure Parameters of Total (α+β)-HTBZ Derived with the Final Population PK Models at Week 9

SD-809 Dose	CYP2D6 Status	Geometric Mean (CV%) Arithmetic Mean (SD) Median [Min-Max]			
		C_{max} (ng/mL)	C_{min} (ng/mL)	C_{ave} (ng/mL)	AUC_{0-24} (ng×h/mL)
18 mg BID	Functional CYP2D6 N=34	78.1 (39.3) 84.1 (37.4) 76.5 [32.4-240]	27.7 (105.2) 38.4 (34.4) 34.0 [3.08-184]	49.3 (60.4) 57.5 (36.6) 53.1 [12.2-210]	1183 (60.4) 1379 (879) 1275 [292-5042]
	Impaired CYP2D6 N=9	134 (22.4) 137 (28.0) 143 [87.7-174]	89.5 (35.4) 93.8 (27.1) 100 [44.5-129]	110 (27.9) 114 (27.4) 121 [63.7-148]	2645 (27.9) 2727 (659) 2905 [1529-3562]
24 mg BID	Functional CYP2D6 N=34	104 (39.3) 112 (49.9) 102 [43.2-320]	37.0 (105.2) 51.2 (45.8) 45.3 [4.11-245]	65.7 (60.4) 76.6 (48.8) 70.8 [16.2-280]	1577 (60.4) 1839 (1172) 1700 [390-6722]
	Impaired CYP2D6 N=9	179 (22.4) 183 (37.3) 191 [117-232]	119 (35.4) 125 (36.1) 134 [59.4-172]	147 (27.9) 151 (36.6) 161 [85.0-198]	3526 (27.9) 3636 (878) 3873 [2039-4749]

AUC_{0-24}=Area under the 0-24 h concentration-time curve; C_{ave}=Average concentration; C_{max}=Maximum concentration; C_{min}=Minimum concentration; CV=Coefficient of variation; CYP2D6=Cytochrome P450 2D6 enzyme; HTBZ=Dihydrotetrabenazine; Max=Maximum; Min=Minimum; N=Number of subjects; SD=Standard deviation

Reviewer's Comment: The total (α+β)-HTBZ exposure (C_{max}, C_{min}, C_{ave} and AUC) in subjects with impaired CYP2D6 function was more than 2x higher than in subjects with functional CYP2D6.

Further details about PK and PK/PD analysis is provided in the pharmacometrics review.

Pharmacometrics Reviewer Summary: The SD-809 dose should be adjusted in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809. A maximum dose of 18 mg BID (36 mg daily) is recommended.

Safety Results:

Adverse Events in Subjects with Impaired CYP2D6 Function

A total of 21 subjects (10 SD-809 subjects; 11 placebo subjects) had impaired CYP2D6 function, including subjects with the CYP2D6 poor metabolizer phenotype and subjects receiving a strong CYP2D6 inhibitor at Baseline.

There were no notable differences in the most common AEs between the subgroup of subjects with impaired CYP2D6 function and the subgroup of subjects without impaired CYP2D6 function, however, the strength of these comparisons is limited by the small sample size of subjects with impaired CYP2D6 function.

The only AEs that occurred in more than one subject with impaired CYP2D6 function over the entire treatment period were irritability (2 SD-809; 2 placebo), somnolence (2 SD-809; 1 placebo), diarrhea (2 SD-809; 0 placebo), and fatigue (2 SD-809; 0 placebo). All of the AEs in subjects with impaired CYP2D6 function were mild to moderate in severity and none of these subjects experienced a serious AE.

Reviewer's Comment: Three subjects with impaired CYP2D6 function back-titrated to a lower maintenance dose (Subjects 1, 20, 30).

VIII. SD-809-C-16: An Open-Label, Long-Term Safety Study of SD-809 ER in Subjects with Chorea Associated with Huntington Disease.

Objectives:

☐ Evaluate the safety and tolerability of titration and maintenance therapy with SD-809
☐ Evaluate the safety and tolerability of switching subjects from Xenazine to SD-809
☐Evaluate the pharmacokinetics of Xenazine, SD-809, and their respective α- and β-HTBZ metabolites in subjects switching from Xenazine to SD-809

Study Design	Open-label, single-arm, two-cohort study: The Rollover Cohort had completed Study SD-809-C-15 (First-HD), including a 1-week washout; The Switch Cohort switched overnight from stable dosing (≥8 weeks) with Xenazine® (tetrabenazine) to SD-809.
Study Population	112 subjects with HD, including 37 Switch subjects and 75 Rollover subjects
Treatment Group	2 cohorts, see Study Design
Dosage and Administration*	Rollover subjects were titrated to an optimal dose of SD-809, beginning with 6 mg SD-809. Titration was permitted through Week 8. Switch subjects were converted from their existing Xenazine dosing regimen to an SD-809 regimen predicted to provide comparable daily exposure (AUC) of total (α+β)-HTBZ relative to the subject's prior Xenazine dose**. Study drug was administered with meals, with total daily doses of 12 mg and higher administered in two divided doses.
PK Sampling: plasma	Rollover Cohort: only if subject withdrew early from the study or experienced an SAE: a single blood PK sample Switch Cohort: PK data were collected in 12 subjects using a rich sampling scheme (5 samples/subject over 6 hours post-dose) and in 24 subjects using a sparse sampling scheme (2 samples/subject)***
Analysis	LC-MS/MS method for TBZ/SD-809 and HTBZ metabolites Range: 0.100 ng/mL to 10.0 ng/mL for SD-809 or TBZ 0.500 ng/mL to 100 ng/mL for HTBZ metabolites
PK Assessment	TBZ/SD-809 and metabolites plasma concentrations
Efficacy	Observed values and changes in the Unified Huntington Disease Rating Scale (UHDRS) Total Maximal Chorea (TMC) score and Total Motor Score (TMS)
Safety Assessment	Adverse events, vital signs, body weight, electrocardiograms, clinical chemistry, anxiety and depression subscores

* The maximum total daily dose of SD-809 was 72 mg per day (36 mg twice daily), unless the subject was receiving a strong CYP2D6 inhibitor, in which case the maximum total daily dose was 36 mg (18 mg bid).
**The mean dose of Xenazine at Baseline was 42 mg and, after the overnight switch, the mean dose of SD-809 was 20 mg. No dose change was allowed during the first week. After Week 1, SD-809 dose could be adjusted to optimize chorea control.

*** **ARC-Switch Pharmacokinetic Sampling Plan**

Cohort	Visit	Day 0 (Xenazine)	Week 8* (SD-809)
Rich Sampling (N=12)	Morning only	Predose, 0.5, 1, 2, and 6 h post-dose	Predose, 1.5, 2.5, 4, and 6 h postdose
Sparse Sampling (N=25)	Morning	Predose and 1-2 h postdose	Predose and 2-4 h postdose
	Afternoon	1st sample during the visit and 2nd at least 1 h† afterward	1st sample during the visit and 2nd at least 2 h† afterward

* If a subject requires a dose change at Week 8, the Week 8 visit assessments should be conducted except for PK sampling which should be postponed until Week 15.
† The second PK sample for sparse sampling (afternoon) should be taken as late as possible

Bioanalytical Assays:

Two validated assays were used: ALM.TBZ.1 for measuring the concentrations of TBZ and its α- and β-HTBZ metabolites in human plasma and ALM.SD809.1 for SD-809 and its deuterated α- and β-HTBZ metabolites.

Assays were validated for the following analytes:

Tetrabenazine (SD-808)
SD-809 (SD-809)
α-HTBZ (SD-946)
β-HTBZ (SD-947)
d6-α-HTBZ (SD-948)
d6-β-HTBZ (SD-949)

In both assays, analytes and the Internal Standards (IS) were extracted from human plasma using a liquid-liquid extraction. The analytes were separated by HPLC on a C18 column and detected using API4000 MS/MS detector in positive MRM mode. The IS for samples assayed with ALM.TBZ.1 were the deuterated forms of the analytes while the IS for samples assayed with ALM.SD809.1 were the non-deuterated forms of the analytes.

Reviewer's Comments:

The performance of the assays (ALM.TBZ.1 and ALM.SD809.1) for TBZ/SD-809 and α- and β-HTBZ metabolites during the analysis of the study samples is acceptable.
Details of the validation results are presented in Bioanalytical Study Reports.

Pharmackinetic Results:

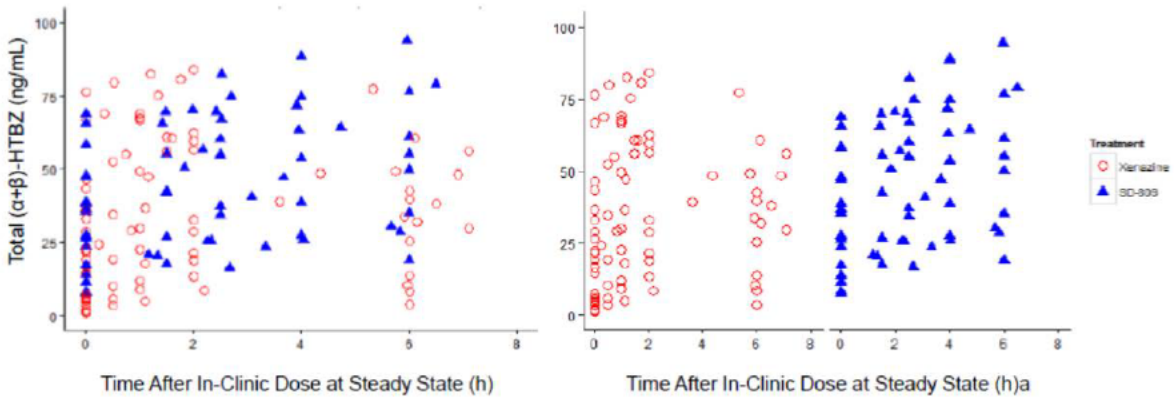
PK Bridging Strategy

Exposure to the active α-HTBZ and β-HTBZ metabolites of SD-809 and TBZ was evaluated in Phase 1 studies, in which TBZ was administered as unformulated powder-in-capsule and as commercially available tablets sourced from (b) (4) (b) (4). A US approved Xenazine tablets was not available for use in the Phase 1 studies. Xenazine was only available as a baseline medication in Study SD-809-C-16.

To establish a bridge between Xenazine and SD-809 exposure over the intended dose range, two approaches were used.

In the first, non-normalized plasma concentrations of total (α+β)-HTBZ were compared from samples collected pre and post in-clinic visit, allowing comparison of Xenazine (baseline visit) with SD-809 (Week 8 visit).

Non-normalized total (α+β)-HTBZ plasma concentrations at Baseline (Xenazine) and at Week 8 (SD-809)



Comment: However, at Week 8 the SD-809 dose for the same subject could be different (after 2:1 conversion) from that at Week 0 (Xenazine).

Therefore, in addition to presenting all available concentration data as in the figure above, PK parameters were analyzed (normalized) to enable comparison across a variety of dose levels. The parameters were normalized to the highest recommended single dose for each treatment (24 mg of SD-809 and 37.5 mg of Xenazine or tetrabenazine).

Cmax Comparison between Xenazine and SD-809 in ARC-SWITCH, Dose-normalized (from the pharmacometrics review)

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

Notes: Data came from ARC-SWITCH study (rich sampling subgroup; n=11 for both Xenazine and SD-809).
Due to the approximate 9-hour half-life of total (α+β)-HTBZ for SD-809 at steady state and the approximate 6-hour half-life of total (α+β)-HTBZ for Xenazine, the 6-hour sampling interval in ARC-Switch was not long enough for adequate estimation of AUC values for comparison of Xenazine and SD-809.

Reviewer's Comments: Since the sponsor has conducted an efficacy study using the SD-809 commercial formulation, the goal of this bridging was to ensure that total (α+β)-HTBZ plasma concentrations after SD-809 administration are in the range (not higher) than these after Xenazine administration. The sponsor does not need to demonstrate BE. The results of this analysis show that C_{max} of SD-809 at highest proposed dose is not higher than C_{max} of Xenazine at highest approved dose. Further details of the bridging strategy analysis will be provided in the pharmacometrics review.
This strategy is also considered acceptable by OND/ODEI and ORP.
Additional bridging is required to provide evidence that the exposures to TBZ/SD-809 metabolites are similar for both TBZ and SD-809 and that the metabolites are not

expected to represent an increased safety risk for patients after dose adjustment. This will be discussed in the Mass balance study SD-809-C-12 review.

Efficacy Results:

The following efficacy conclusions are reported by the sponsor, details and PK/PD analysis will be provided in the pharmacometrics review.

Efficacy in Rollover Cohort

- Improvements observed in the mean TMC score were consistent with those observed in First-HD.

Efficacy in Switch Cohort

- Subjects who switched overnight from a stable dosing regimen of Xenazine to an AUC-matched dosing regimen of SD-809 experienced no loss in control of chorea, as assessed by the mean UHDRS TMC score and TMS, through Week 1.
- Dose adjustment was permitted after Week 1; at Week 8, mean decreases from Baseline in TMC score and TMS were observed (p=0.03), indicating potential improvement in chorea control following SD-809 dose adjustment.

Safety Results:

In the Rollover Cohort, 39 (52.0%) subject experienced AEs**,** with the AEs assessed as mild or moderate in intensity in 36 (92.3%) of these 39 subjects. The most common AEs were fall (13%), somnolence (8%), depression (8%), and insomnia (8%).

Five subjects had an AE that led to a dose reduction or dose suspension. Three subjects experienced serious AEs (anxiety, major depression, suicidal ideation, dehydration, encephalopathy), with one of these serious AEs (major depression) leading to study withdrawal. Three additional subjects withdrew from the study due to an AE (worsening chorea, suicidal ideation, and depression).

In the Switch Cohort, 21 (56.8%) subjects experienced at least one AE, with AEs assessed as mild to moderate in 20 of the 21 subjects. The most common AEs were somnolence (24%), anxiety (8%), and fall (8%).

There were no adverse events of chorea or worsening chorea during the reporting period, including the first week after the conversion from Xenazine to SD-809.

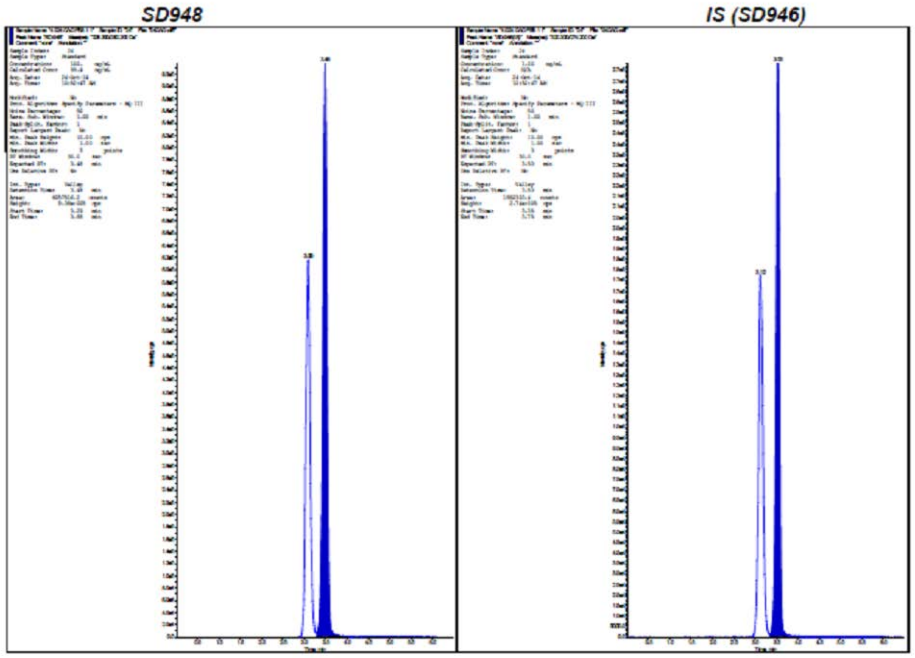
Two subjects experienced serious AEs (pneumonia and dehydration), no subjects withdrew from the study due to an AE, and four subjects had an AE that led to a dose reduction or dose suspension.

Bioanalytical Reports

IX. SD-809-CLN-011 Validation Report for Method TBZ.1: Determination of Tetrabenazine and its metabolites in Human Plasma by LC-MS/MS

The analytical method ALM TBZ.1 was developed at the (b) (4), (b) (4). The method involves the extraction of the analytes (SD808, SD946 and SD947) and the internal standards (IS) from human plasma using liquid-liquid extraction.
Analytes: Tetrabenazine (SD-808)
α-HTBZ (SD-946)
β-HTBZ (SD-947)
IS: SD809 = d6-tetrabenazine (d6-TBZ)
SD948 = d6-α-dihydrotetrabenazine (d6-α-HTBZ)
SD949 = d6-β-dihydrotetrabenazine. (d6-β-HTBZ)
Note: The internal standards for method ALM TBZ.1 were the analytes for method ALM SD-809.1 and vice versa.
The analytes and the IS were separated by HPLC on a C18 column and the eluates monitored by an API 4000 MS/MS detector in positive MRM mode.
Note: The analytes α-HTBZ and β-HTBZ were used within the assay only as mixed working solutions (see fig 11), likely in order to distinguish between the closely eluting α-HTBZ and β-HTBZ in case the retention time (RT) has slightly shifted.

FIGURE 11: REPRESENTATIVE CHROMATOGRAM OF EXTRACTED STANDARD 8 (100 ng/mL)



The method range is from 0.100 to 10.0 ng/mL for SD808 and 0.500 to 100 ng/mL for both SD946 and SD947 using a 200 µL aliquot of human plasma.
The validation results are presented in the table below.

Document Control Number: Report Type	Analyte	Standard Curve Range (ng/mL)	Precision[a] (%CV)		Accuracy[b] over Assay Range (%)		Stability
			Intra	Inter	Intra	Inter	
SD-809-CLN-011: method validation report; SD-809-CLN-052: stability report	Tetrabenazine	0.1 to 10	2 to 8	4 to 14	-6 to 2	-11 to -3	Room temperature: 24 h Freeze/thaw: 3 cycles Long-term stability: at least 382 days @ -80°C
	Nondeuterated α-HTBZ	0.5 to 100	2 to 7	4 to 6	-1 to 9	-2 to 3	
	Nondeuterated β-HTBZ		2 to 4	3 to 7	-3 to 10	-4 to 0	
SD-809-CLN-012: method validation report; SD-809-CLN-052: stability report	SD-809	0.1 to 10	1 to 6	5 to 12	-1 to 13	-3 to 2	
	Deuterated α-HTBZ	0.5 to 100	2 to 4	3 to 8	-6 to -1	-4 to -2	
	Deuterated β-HTBZ		2 to 5	3 to 9	-6 to -1	-7 to -4	

Specificity: No evidence of interference was observed in six individual sources of plasma. No significant effect on the quantification of SD808, SD946 or SD947 was observed using six individual sources of plasma.
Recovery: The recovery at each concentration (QCL, QCM and QCH) was required to be consistent and reproducible. The mean recovery for each QC level were to be greater than 50%. Recovery of the internal standard was required to be similar to that of the analyte.
To determine recovery of SD808, SD946 and SD947 from the plasma extraction process, six replicates of extracted quality control samples at three concentration levels (0.300, 3.00 and 7.50 ng/mL) were injected along with six replicates of unextracted SD808, SD946 and SD947 prepared at the same concentration levels in solution. Overall recovery of SD808 was 67.0%. Overall recoveries of SD946 and SD947 were 89.0% and 88.8%, respectively.
To determine the total recovery of the ISs (SD809, SD948 and SD949) from the same plasma extraction process, the mean of the IS peak areas from 18 different extracted quality control samples were compared with peak areas from 18 unextracted IS injections prepared at the same nominal concentration in solutions. Overall recovery of the ISs were 68.0%, 83.7% and 83.6% for SD809, SD948 and SD949, respectively.

The validation of the bioanalytical assay TBZ.1 is acceptable.

APPEARS THIS WAY ON ORIGINAL

X. SD-809-CLN-012 Validation Report for Method SD809.1: Determination of SD-809 and its metabolites in Human Plasma by LC-MS/MS

The analytical method SD809.1 was developed at the (b) (4) (b) (4). The method involves the extraction of the analytes (SD809, SD948 and SD949) and the internal standards (IS) from human plasma using liquid-liquid extraction.
Analytes: SD809 = d6-tetrabenazine (d6-TBZ)
SD948 = d6-α-dihydrotetrabenazine (d6-α-HTBZ)
SD949 = d6-β-dihydrotetrabenazine. (d6-β-HTBZ)
IS: Tetrabenazine (SD-808)
α-HTBZ (SD-946)
β-HTBZ (SD-947)
The analytes and the IS were separated by HPLC on a C18 column and the eluates monitored by an API 4000 MS/MS detector in positive MRM mode.
Notes: The internal standards for method TBZ.1 were the analytes for method SD-809.1 and vice versa.
Same as in method TBZ.1, the analytes α-HTBZ and β-HTBZ were used within the assay only as mixed working solutions (see fig 11 under method TBZ.1).

The validation results for method SD-809.1 are presented in the same table as for method TBZ.1 (under IX. SD-809-CLN-011).

The validation results of the bioanalytical assay SD-809.1 are acceptable.

APPEARS THIS WAY ON ORIGINAL

XI. SD-809-CLN-050 Validation method for the determination of d0-O-Desmethyl Metabolites (SD-971, SD-972, SD-973 and SD-974) of the Dihydrotetrabenazine metabolites from Tetrabenazine in Human Plasma containing lithium heparin as anticoagulant

The method involves extracting the analytes and the Internal Standards (IS) from human plasma using a liquid-liquid extraction procedure. The analytes were separated by HPLC on a PFP phase column and the eluates monitored by an API4000 MS/MS detector in positive MRM mode.
Analytes: SD-971 = 9-O-desmethyl-α-dihydrotetrabenazine
SD-972 = 10-O-desmethyl-α-dihydrotetrabenazine
SD-973 = 9-O-desmethyl-β-dihydrotetrabenazine
SD-974 = 10-O-desmethyl-β-dihydrotetrabenazine
Internal Std: SD-975 = 9-O-desmethyl-d3-α-dihydrotetrabenazine
SD-976 = 10-O-desmethyl-d3-α-dihydrotetrabenazine
SD-977 = 9-O-desmethyl-d3-β-dihydrotetrabenazine
SD-978 = 10-O-desmethyl-d3-β-dihydrotetrabenazine

Notes: Same as in the previous 2 methods, the internal standards for method SD-809-CLN-050 were the analytes for method SD-809-CLN-051 and vice versa.
Also, the analytes α- and β- desmethyl metabolites were used within the assay only as mixed working solutions (see figures under method SD-809-CLN-051).

The method was validated in the range from 0.500 to 50.0 ng/mL for all analytes using 100 µL aliquot of human plasma.
The validation results are presented in the table below.

Document Control Number: Report Type	Analyte	Standard Curve Range (ng/mL)	Precision[a] (%CV)		Accuracy[b] over Assay Range (%)		Stability
			Intra	Inter	Intra	Inter	
SD-809-CLN-050: method validation report; SD-809-CLN-074: stability report	Nondeuterated 9-O-desmethyl α-HTBZ	0.5 to 50	2.3 to 3.3	2.5 to 6.2	-3.7 to 0.8	-8.3 to -3.3	Room temperature: 24 h Freeze/thaw: 4 cycles Long-term stability: up to 440 days @ -80°C
	Nondeuterated 10-O-desmethyl α-HTBZ		2.1 to 3.1	3.4 to 4.8	-5.4 to 0.8	-6.5 to -3.6	
	Nondeuterated 9-O-desmethyl β-HTBZ		0.9 to 2.4	2.6 to 5.4	-5.5 to 1.4	-7.6 to -4.2	
	Nondeuterated 10-O-desmethyl β-HTBZ		2.0 to 5.2	3.1 to 10.3	-6.6 to 4.2	-5.0 to -3.5	

Recovery:
The overall recovery of SD-971 was 91.4%
The overall recovery of SD-972 was 89.9%
The overall recovery of SD-973 was 94.7%
The overall recovery of SD-974 was 93.9%
Specificity: SD-971, SD-972, SD-973 and SD-974 showed no significant interference at the retention time of the IS and the IS showed no significant interference at the retention time of SD-971, SD-972, SD-973 and SD-974. Specificity was tested with no significant interference observed in the 6 individual plasma sources tested.
The validation results of the bioanalytical method SD-809-CLN-050 are acceptable.

XII. SD-809-CLN-051 Validation method for the determination of d3-O-desmethyl metabolites (SD-975, SD-976, SD-977 and SD-978) of the d6-dihydrotetrabenazine metabolites from SD-809 (d6-Tetrabenazine) in human plasma containing lithium heparin as anticoagulant

The method involves extracting the analytes and the Internal Standards (IS) from human plasma using a liquid-liquid extraction procedure. The analytes were separated by HPLC on a PFP phase column and the eluates monitored by an API4000 MS/MS detector in positive MRM mode.
Analytes: SD-975 = 9-O-desmethyl-d3-α-dihydrotetrabenazine
SD-976 = 10-O-desmethyl-d3-α-dihydrotetrabenazine
SD-977 = 9-O-desmethyl-d3-β-dihydrotetrabenazine
SD-978 = 10-O-desmethyl-d3-β-dihydrotetrabenazine
Internal Std: SD-971 = 9-O-desmethyl-α-dihydrotetrabenazine
SD-972 = 10-O-desmethyl-α-dihydrotetrabenazine
SD-973 = 9-O-desmethyl-β-dihydrotetrabenazine
SD-974 = 10-O-desmethyl-β-dihydrotetrabenazine

The method was validated in the range from 0.500 to 50.0 ng/mL for all analytes using 100 µL aliquot of human plasma.

The validation results are presented in the table below.

Document Control Number: Report Type	Analyte	Standard Curve Range (ng/mL)	Precision[a] (%CV)		Accuracy[b] over Assay Range (%)		Stability
SD-809-CLN-051: method validation report; SD-809-CLN-074: stability report	Deuterated 9-O-desmethyl α-HTBZ	0.5 to 50	1.0 to 2.5	2.7 to 3.9	-8.6 to -0.8	-4.6 to -2.2	Room temperature: 24 h Freeze/thaw: 3 cycles Long-term stability: up to 441 days @ -80°C
	Deuterated 10-O-desmethyl α-HTBZ		1.7 to 3.4	2.9 to 3.5	-9.2 to -1.7	-5.1 to -0.8	
	Deuterated 9-O-desmethyl β-HTBZ		1.7 to 2.6	3.0 to 3.7	-6.8 to 0.2	-5.4 to -2.3	
	Deuterated 10-O-desmethyl β-HTBZ		1.8 to 7.1	3.9 to 6.9	-12.9 to 2.4	-5.8 to -2.9	

Abbreviations: CV, coefficient of variation; HTBZ, dihydrotetrabenazine; SD, standard deviation.
[a] Precision: (SD/Mean Measured Concentration) x 100
[b] Accuracy: [(Mean Measured Concentration – Nominal Concentration) x 100]/ Nominal Concentration

Recovery:
The overall recovery of SD-975 was 78.2%
The overall recovery of SD-976 was 76.3 %
The overall recovery of SD-977 was 78.5 %
The overall recovery of SD-978 was 73.8 %

Specificity: SD-975, SD-976, SD-977 and SD-978 showed no significant interference at the retention time of the IS and the IS showed no significant interference at the retention time of SD-975, SD-976, SD-977 and SD-978. Specificity was tested with no significant interference observed in the 6 individual plasma sources tested.
Matrix effect was tested by analyzing 6 individual blank plasma sources spiked at PQCL level with each analyte.

FIGURE 5: SD-975 REPRESENTATIVE CHROMATOGRAM OF EXTRACTED STANDARD 1 (0.500 NG/ML)

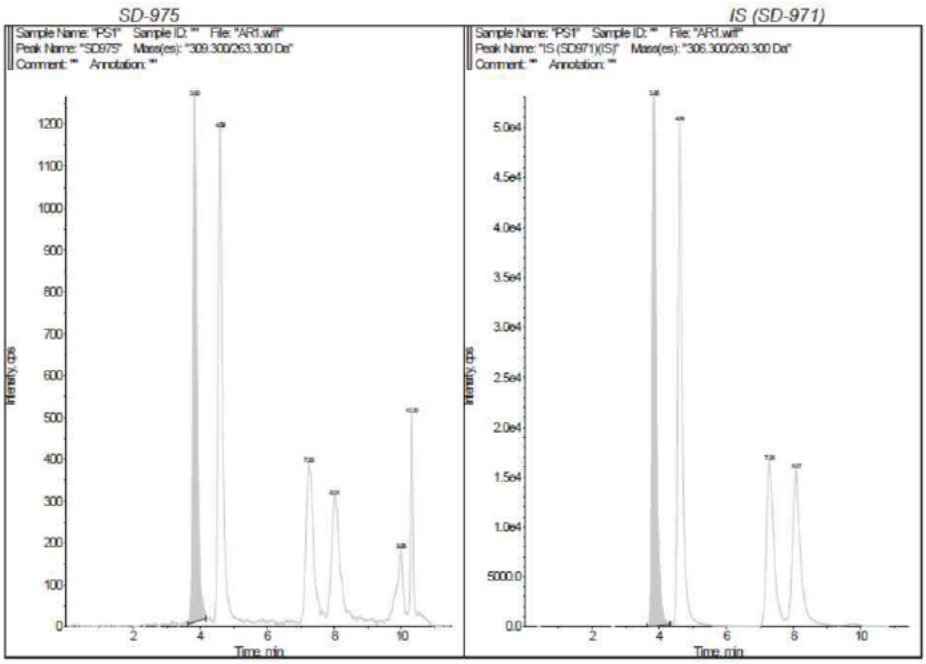
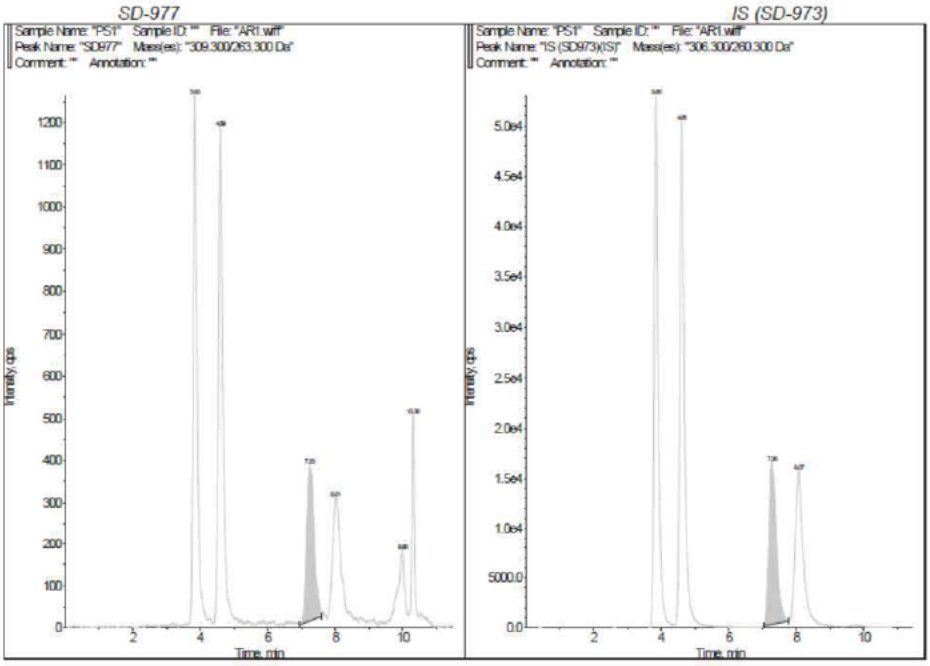


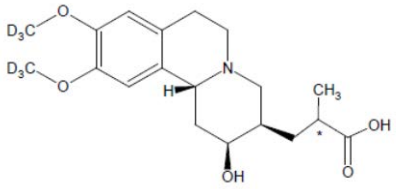
FIGURE 23: SD-977 REPRESENTATIVE CHROMATOGRAM OF EXTRACTED STANDARD 1 (0.500 NG/ML)



The validation results of the bioanalytical method SD-809-CLN-051 are acceptable.

XIII. SD-809-NC-053 LC-MS/MS analysis of Tetrabenazine reference standards

Results from [redacted] (b) (4) study ASX/04 confirmed that the early eluting component (M1) in human plasma was a 2-methylpropanoic acid metabolite of d6-β-HTBZ.



* One of 2 possible diastereoisomers

A reference standard SD-1020 analyzed as part of the clinical study consisted of two closely eluting diastereoisomers; with plasma metabolite M1 appearing to be coincident with the 1st diastereoisomer of SD-1020.

The Sponsor has synthesized, separated and purified each of the two diastereoisomers of SD-1020 which have been designated SD-1021 and SD-1022.

The aim of this study was to confirm by means of LC-MS/MS which of the two reference standards (SD-1021or SD-1022) was coincident with the M1 metabolite observed in human plasma in study ASX/04.

An over-spiking experiment was performed in pooled human plasma extract in order to find out which of the two supplied reference standards was consistent with metabolite M1. The sample was first run untreated (i.e. no spike) before being separately spiked with either SD-1021 or SD-1022 reference standard at a higher concentration (based on peak height) and re-run a second time (SD-1021) and a third time (SD-1022). The retention times and change in peak height was used to confirm whether the candidate reference standards SD-1021 or SD-1022 correspond to the plasma metabolite designated M1.

Human plasma extracts (n=3) from the related study ASX/04 were used for this analysis. The extracts were pooled to generate a pool of sufficient volume (ca. 600 µL) to perform the over-spiking experiment.

Pooled human plasma extract, Subject 002, 2-12 hours
Pooled human plasma extract, Subject 005, 2-12 hours
Pooled human plasma extract, Subject 006, 2-12 hours

A pooled human plasma extract was prepared by combining aliquots of the duplicate B plasma extract samples for subjects 002, 005 and 006 into a single tube.

For SD-1021/ SD-1022 over-spiking, an aliquot (190 µL) of the pooled human plasma extract was transferred to a 1.5 mL Eppendorf tube; to the tube was added 10 µL of SD-1021/ SD-1022 reference standard at 5 µg/mL.

Sample (100 µL) was injected for LC-MS/MS analysis using an accurate mass full scan at a mass resolution of 30,000 with a targeted product ion for m/z 356.

In addition, a mixed reference standard containing both SD-1021 and SD-1022 was analyzed prior to and after the samples and used as retention time markers.

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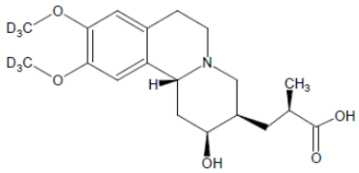
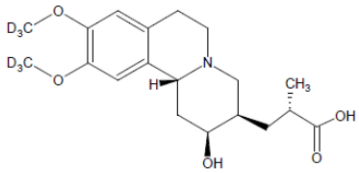
Reference standard of SD-1021 (retention time 20.0 minutes) and SD-1022 (retention time 20.7 minutes)



SD-1021



SD-1022

	SD-1021 m/z 356 $[M+H]^+$	SD-1022 m/z 356 $[M+H]^+$
Molecular formula:	$C_{19}H_{22}{}^{2}H_6O_5N$	$C_{19}H_{22}{}^{2}H_6O_5N$
Observed accurate mass:	356.2339	356.2338
Theoretical accurate mass:	356.2339	356.2339
Deviation from theoretical accurate mass (ppm):	0 ppm	-0.07 ppm

The figure below shows the accurate mass extracted ion chromatograms for M1 (m/z 356) in the non-spiked (untreated) plasma extract (top trace), in the SD-1021 over-spiked plasma extract (middle trace) and in the SD-1022 over-spiked plasma extract (bottom trace). The figure clearly shows that the SD-1021 reference standard coincides with metabolite M1; with the peak height increasing approximately 3-fold on addition of the SD-1021 reference standard spike (middle trace).

Accurate mass extracted ion chromatogram for m/z 356 in pooled human plasma extract (2-12 hour, AUC) untreated and over-spiked with SD-1021 or SD-1022

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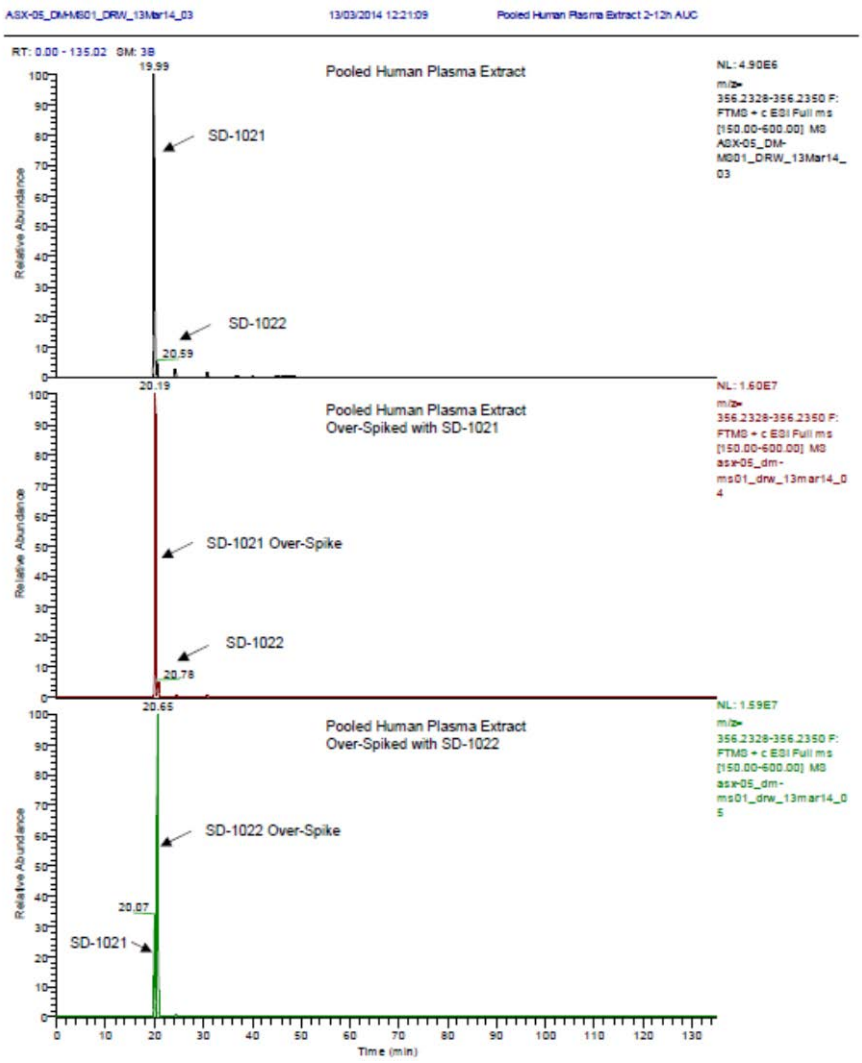
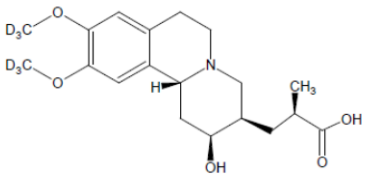


Conclusion: The over-spiking experiment performed in this study confirmed that the early eluting component M1 in human plasma was SD-1021 (figure below).



In Vitro Studies

XIV. 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

Objectives:
1) Investigate whether the Phase 1 metabolism of tetrabenazine (TBZ) is similar to or different than that of its deuterated analog SD-809 in in vitro liver microsomes of multiple species.
2) Investigate whether the Phase 1 metabolism of the metabolites of TBZ (i.e. alpha-HTBZ and beta-HTBZ) are similar to or different than those of their deuterated analogs d6-alpha-HTBZ and d6-beta-HTBZ in in vitro liver microsomes of multiple species..
The in vitro evaluation was performed by Auspex.

Methods: TBZ, alpha-HTBZ, beta-HTBZ, SD-809, d6-alpha-HTBZ, d6-beta-HTBZ were incubated with liver microsomes from rat, mouse, monkey, dog, and human. The respective test article half-life ($t_{1/2}$) was determined. Test articles were analyzed with HPLC-MS/MS.

The results of this study will be summarized together with the results of studies SD-809-NC-002 and SD-809-NC-003 (under SD-809-NC-003 Results).

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XV. SD-809-NC-002: In Vitro Stability of Tetrabenazine, SD-809, alpha-dihydrotetrabenazine (HTBZ), beta-HTBZ, d6-alpha-HTBZ and d6-beta-HTBZ in Human S9 Liver Fraction

Objectives:
1) Investigate whether the Phase 1 metabolism of tetrabenazine (TBZ) is similar to or different than that of its deuterated analog SD-809 in human S9 or cytosol liver fraction.
2) Investigate whether the Phase 1 metabolism of the metabolites of TBZ (i.e. alpha-HTBZ and beta-HTBZ) are similar to or different than those of their deuterated analogs d6-alpha-HTBZ and d6-beta-HTBZ in human S9 or cytosol liver fraction.
The in vitro evaluation was performed by Auspex.

Methods: TBZ, alpha-HTBZ, beta-HTBZ, SD-809, d6-alpha-HTBZ, d6-beta-HTBZ were incubated with human S9 or cytosol liver fraction and the respective test article half-life ($t_{1/2}$) was determined if possible. Test articles were analyzed with HPLC-MS/MS.

The results of this study will be summarized together with the results of studies SD-809-NC-001 and SD-809-NC-003 (under SD-809-NC-003 Results).

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XVI. SD-809-NC-003: In Vitro Stability of Tetrabenazine, SD-809, alpha-dihydrotetrabenazine (HTBZ), beta- HTBZ, d6-alpha- HTBZ and d6-beta-HTBZ in Human CYP1A2, 2D6 and 3A4 isozymes

Objectives:
1) Investigate whether the Phase 1 metabolism of tetrabenazine (TBZ) is similar to or different than that of its deuterated analog SD-809 in human CYP1A2, CYP2D6, and CYP3A4 isozymes.
2) Investigate whether the Phase 1 metabolism of the metabolites of TBZ (i.e. alpha-HTBZ and beta-HTBZ) are similar to or different than those of their deuterated analogs d6-alpha-HTBZ and d6-beta-HTBZ in human CYP1A2, CYP2D6, and CYP3A4 isozymes.
The in vitro evaluation was performed by Auspex.

Methods: TBZ, alpha-HTBZ, beta-HTBZ, SD-809, d6-alpha-HTBZ, d6-beta-HTBZ were incubated with human CYP1A2, CYP2D6, and CYP3A4 isozymes and the respective test article half-life ($t_{1/2}$) was determined if possible. Test articles were analyzed with HPLC-MS/MS.

Results:
SD-809 and TBZ
In *in vitro* human liver test systems, SD-809 and TBZ were metabolized rapidly; half-lives could not be calculated in S9. The half-lives of SD-809 and TBZ in human liver microsomes were twelve minutes or less under the test conditions and were similar (i.e., within 10% of each other) (see Table below).
Both TBZ and SD-809 were rapidly metabolized in the presence of CYP3A4, with relatively little metabolism in the presence of CYP1A2 (half-life: 135 and 164 minutes, respectively) or CYP2D6 (half-life: 178 and 204 minutes, respectively). In the three tested CYP enzymes, the stability of SD-809 was similar to that of TBZ, indicating that the substitution of deuterium for hydrogen in the O-linked methyl groups of SD-809 did not alter the CYP-dependent metabolism of SD-809 relative to tetrabenazine.

Half-lives of SD-809 and Tetrabenazine after Incubation with Human S9, Human Liver Microsomes, or Recombinant CYP1A2, CYP2D6, and CYP3A4

	Half-life (Minutes)	
	Substrate: SD-809	Substrate: Tetrabenazine
Human Liver Microsomes [a]	12.1 (2.33)	11.2 (2.03)
CYP1A2 [b]	164	135
CYP2D6 [b]	204	178
CYP3A4 [b]	5.93	5.32

Data are expressed as mean (standard deviation).
[a] Section 2.6.5.10.3; Reference: SD-809-NC-001, n = 6.
[b] Section 2.6.5.10.3; Reference: SD-809-NC-003, n = 1 (CYP1A2 and CYP3A4) or n = 2 (CYP2D6).

α-HTBZ and β-HTBZ:
The rates of metabolism, measured as substrate loss of deuterated α- and β-HTBZ, were compared to the corresponding nondeuterated forms after incubation with human liver S9

fraction (SD-809-NC-002), with human liver microsomes (SD-809-NC-001), and with CYP enzymes (SD-809-NC-003).
In in vitro human liver test systems, the metabolic half-life of deuterated α-HTBZ was greater than that of nondeuterated α-HTBZ by 48.5%. Across the two assays, the metabolic half-life of deuterated β-HTBZ was greater than that of nondeuterated β-HTBZ by 105% to 138% (SD-809-NC-001, SD-809-NC 002).
The half-lives of nondeuterated α-HTBZ and β-HTBZ were shortest in the presence of CYP2D6 isozymes (SD-809-NC-003), consistent with this enzyme's predominant role in HTBZ metabolism (per the Xenazine label).
In the presence of CYP2D6, the half-life of deuterated α-HTBZ was greater than that of nondeuterated α-HTBZ by 226%, while the metabolic half-life of deuterated β-HTBZ was greater than that of nondeuterated α-HTBZ by 138%. There was measurable loss of α-HTBZ and, to a lesser degree, β-HTBZ in the presence of CYP3A4 isozymes with similar (within 31%) rates comparing deuterated and nondeuterated forms.

Half-lives of Deuterated and Nondeuterated α-HTBZ and β-HTBZ after Incubation with Human S9, Human Liver Microsomes, or Recombinant CYP1A2, CYP2D6, and CYP3A4

	Half-life (Minutes)					
	α-HTBZ			β-HTBZ		
	Deuterated	Non-deuterated	% Change	Deuterated	Non-deuterated	% Change
Human S9 [a]	454 (176)	305 (107)	48.5 (11.5)	227 (58)	111 (27)	105 (19)
Human Liver Microsomes [b]	132 (41.6)	87.5 (20.7)	48.5 (14.8)	91.8 (32.0)	37.7 (6.93)	139 (36)
CYP1A2 [c]	NC	NC	NA	NC	NC	NA
CYP2D6 [c]	91.6 (9.20)	28.1 (3.47)	226 (18.0)	55.4 (4.68)	23.2 (1.01)	138 (13.1)
CYP3A4 [c]	76.6	71.1	7.74	231	176	31.3

NA: not applicable; NC: not calculated due to insufficient substrate loss.
Results are expressed as mean (standard deviation) half-life in minutes.
% Change: (Deuterated / nondeuterated)*100)-100.
[a] Section 2.6.5.10.3; Reference: SD-809-NC-002, n = 4.
[b] Section 2.6.5.10.3; Reference: SD-809-NC-001, n = 4.
[c] Section 2.6.5.10.3: Reference: SD-809-NC-003. n = 1 for CYP1A2 and CYP3A4. n = 3 for CYP2D6.

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XVII. SD-809-NC-041: 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

Objective: to evaluate the contribution of selected CYP enzymes (CYP1A2, CYP2D6 and CYP3A4/5) to the in vitro metabolism of d6- and d0-α-HTBZ and d0- and d6-β-HTBZ.

Methods: The O-desmethyl metabolites of deuterated or nondeuterated α-HTBZ and β-HTBZ (1 μM) were quantified after incubation with human liver microsomes (0.5 mg protein/mL) in the presence of selective CYP inhibitors (10 μM furafylline [a CYP1A2 metabolism-dependent inhibitor], 1 μM quinidine [a CYP2D6 direct inhibitor] and 50 μM troleandomycin [a CYP3A4/5 metabolism-dependent inhibitor]) or appropriate solvent and positive controls in the presence of an NADPH-regenerating system. Analytes were analyzed with HPLC-MS/MS.
Positive control incubations with marker substrates (phenacetin, a CYP1A2 substrate; dextromethorphan, a CYP2D6 substrate; and midazolam, a CYP3A4/5 substrate) in the presence and absence of furafylline (10 μM), quinidine (1 μM) or troleandomycin (50 μM), respectively, were performed concurrently with the test article incubations to determine if the test system was metabolically competent and to confirm the inhibition of CYP enzymes. The contribution of CYP1A2, CYP2D6 and CYP3A4/5 to the metabolism of phenacetin, dextromethorphan and midazolam were determined to be 81, 74 and 93%, respectively.

Results:
The 9- and 10-O-desmethyl metabolites were detected in the incubates of nondeuterated α-HTBZ, nondeuterated β-HTBZ, and deuterated β-HTBZ in the presence and absence of CYP inhibitors. The 10-O-desmethyl metabolite of deuterated α-HTBZ was below level of detection. The impact of the individual CYP enzymes was assessed by comparing the rate of O-desmethyl metabolite formation in the presence versus the absence of selective CYP inhibitors (see Table below).
CYP2D6 was responsible for 69% to 89% of the formation of 9-and 10-O-desmethyl HTBZ from both deuterated and nondeuterated substrates, where measurable; the formation of 10-O-desmethyl HTBZ from deuterated substrates was too low for calculation of CYP2D6 contribution. The selective inhibitors of CYP1A2 and CYP3A4/5 had less impact on the formation of the O-desmethyl metabolites of HTBZ, with neither enzyme contributing more than 29%.
These results confirm that CYP2D6 is the CYP isozyme primarily responsible for the O-demethylation of deuterated and nondeuterated α- and β- HTBZ substrates.

Contribution of CYP2D6, CYP1A2, CYP3A4/5 on the Formation of the 9- and 10-O-desmethyl Metabolites of Nondeuterated or Deuterated α-HTBZ and β-HTBZ in Human Liver Microsomes

Contributing CYP Isozyme	% Contribution of Individual CYP Isozymes on O-desmethyl Metabolite Production					
	α-HTBZ Substrate	9-O-desmethyl α-HTBZ	10-O-desmethyl α-HTBZ	β-HTBZ Substrate	9-O-desmethyl β-HTBZ	10-O-desmethyl β-HTBZ
CYP2D6	Deuterated	69%	NC	Deuterated	89%	NC
	Nondeuterated	83%	85%	Nondeuterated	89%	92%
CYP1A2	Deuterated	15%	NC	Deuterated	12%	29%
	Nondeuterated	13%	5.6%	Nondeuterated	NC	NC
CYP3A4/5	Deuterated	NC	NC	Deuterated	9.6%	NC
	Nondeuterated	23%	11%	Nondeuterated	NC	NC

Section 2.6.5.10.4; Reference: SD-809-NC-041.
NC: Not calculated due to inadequate metabolite concentrations.
HTBZ: dihydrotetrabenazine
% contribution = ((y)-($y_{inhibitor}$) / (y))*100, where y is the slope of the linear regression of metabolite formation over time in the solvent control, and $y_{inhibitor}$ is the slope of the linear regression of metabolite formation in the presence of inhibitor.

Comment: There seems to be a shift in the metabolism from CYP2D6 to CYP1A2 and 3A4/5, esp. in the 9- and 10-O-desmethyl β-HTBZ production. However, the % contribution of these enzymes is less than 29% and CYP2D6 is still the major enzyme responsible. Also, 10-O-desmethyl β-HTBZ is a minor metabolite for both TBZ and SD-809.

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XVIII. SD-809-NC-071: In Vitro Evaluation of SD-1021 (M1) as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes

Objective: to evaluate in vitro (in human liver microsomes) the inhibition potential of the SD-809 major metabolite M1 (SD-1021) on major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.
The in vitro evaluation was performed by [redacted] (b) (4).

Methods: To evaluate M1 as a direct, time-dependent and metabolism-dependent inhibitor of CYP enzymes, pooled human liver microsomes were incubated with marker substrates at concentrations approximately equal to their K_m or S_{50} in the presence or absence of M1. A mixed-gender pool of 200 individual human liver microsomal samples was used for this study (see table below).

XTreme 200 Human Liver Microsomes
Lot No. 1210347
Human Liver Microsomes
Pool of 200 (100 Male and 100 Female)
Suspension medium: 250 mM sucrose

H2610	0.5 mL at 20 mg/mL
H2620	1.0 mL at 20 mg/mL
H2630	5.0 mL at 20 mg/mL
H2640	50.0 mL at 20 mg/mL

Kinetic constants for enzyme activities in human liver microsomes (pool of 200)

Enzyme	Marker Substrate	Kinetic Constants	
		K_m (µM)	V_{max} (pmol/mg protein/min)
CYP1A2	Phenacetin	96.0 ± 12.7	913 ± 6
CYP2A6	Coumarin	0.603 ± 0.110	1180 ± 100
CYP2B6	Bupropion	95.6 ± 4.3	660 ± 10
CYP2B6	Efavirenz	5.45 ± 0.98	154 ± 8
CYP2C8	Amodiaquine	2.44 ± 0.19	2820 ± 90
CYP2C9	Diclofenac	12.4 ± 1.1	2640 ± 300
CYP2C19	S-Mephenytoin	64.5 ± 2.7	67.6 ± 3.6
CYP2D6	Dextromethorphan	10.0 ± 1.0	261 ± 16
CYP2E1	Chlorzoxazone	45.1 ± 3.4	2420 ± 300
CYP3A4/5	Testosterone	61.0 ± 2.9 [1]	4080 ± 780
CYP3A4/5	Midazolam	2.72 ± 0.25	1240 ± 90
CYP3A4/5	Nifedipine	13.6 ± 1.9	2840 ± 20
CYP3A4/5	Atorvastatin	81.8 ± 2.0	816 ± 6
UGT1A1	17β-Estradiol	12.6 ± 0.4 [2]	886 ± 75
UGT1A3	Chenodeoxycholic acid	169 ± 34	110 ± 10
UGT1A4	Trifluoperazine	19.1 ± 0.1	906 ± 78
UGT1A6	1-Naphthol	1.90 ± 0.20	1640 ± 60
UGT1A9	Propofol	16.8 ± 0.7	6470 ± 110
UGT2B7	Morphine	519 ± 43	3990 ± 450
UGT2B17	Testosterone	4.70 ± 0.41	733 ± 8

[1] For this assay, the K_m column represents S_{50} (Hill coefficient = 1.4).
[2] For this assay, the K_m column represents S_{50} (Hill coefficient = 1.7).
Kinetic constants are mean ± standard deviation of two or more determinations

To assess M1 ability to act as a direct inhibitor of CYP enzymes, M1 (at concentrations ranging from 0.1 to 100 µM) was incubated with marker substrate (at concentrations near the K_m or S_{50}, see table below) in duplicate 200-µL incubation mixtures as indicated in the table below.

IC_{50} determinations: Summary of assay conditions – Direct, time-dependent and metabolism-dependent inhibition of enzymes by M1

Enzyme	Substrate	Substrate concentration (µM)	Incubation volume (µL)	Protein [a] (µg/mL)	Incubation time (min)	Pre-incubation time (min)	SD-1021	
							Target concentrations (µM)	Solvent volume [b] (µL)
CYP1A2	Phenacetin	90	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP2B6	Efavirenz	5	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP2C8	Amodiaquine	2	200	12.5	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP2C9	Diclofenac	12	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP2C19	*S*-Mephenytoin	60	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP2D6	Dextromethorphan	10	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP3A4/5	Testosterone	60	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5
CYP3A4/5	Midazolam	3	200	50	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	0.5

a The human liver microsomal sample used for these experiments was a pool of 200 individuals.
b The vehicle used to dissolve the test article was 80:20 v/v DMSO:water containing 50 mM NaOH.

Note: Metabolism-dependent inhibition is often synonymous with time-dependent inhibition. In the case of inhibitory metabolites, all metabolism-dependent inhibitors are time-dependent inhibitors since the formation of metabolites takes time. However, the converse is not true; not all time-dependent inhibitors are metabolism-dependent inhibitors. To distinguish between time-dependent and metabolism-dependent inhibition, SD-1021 was pre-incubated with human liver microsomes for 30 minutes without and with an NADPH-generating system, respectively, prior to the incubation with the marker substrate. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls in all experiments.
All metabolite analyses were performed with LC-MS/MS methods. Authentic metabolite standards were used, and deuterated metabolites were used as internal standards in all assays.

The following direct inhibitors were included as positive controls and incubated for the normal incubation time and with the normal microsomal protein concentration in the presence of the marker substrate.

Enzyme	Positive control	Vehicle (v/v, final incubation concentration)	Concentration studied
CYP1A2	α-Naphthoflavone	Methanol (0.1%)	0.5 µM
CYP2B6	Orphenadrine	DMSO (0.2%)	750 µM
CYP2C8	Montelukast	Methanol (0.1%)	0.05 µM
CYP2C9	Sulfaphenazole	Methanol (0.1%)	2.0 µM
CYP2C19	Modafinil	DMSO (0.1%)	400 µM
CYP2D6	Quinidine	Water	5.0 µM
CYP3A4/5	Ketoconazole	Methanol (0.1%)	0.075 µM

The following metabolism-dependent inhibitors were preincubated with human liver microsomes for zero and 30 minutes followed by incubation with marker substrate for the normal pre-incubation time and with the normal microsomal protein concentration.

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Enzyme	Positive control	Vehicle (v/v, final incubation concentration)	Concentration studied
CYP1A2	Furafylline	DMSO (0.1%)	2.0 µM
CYP2B6	Phencyclidine	Water	30 µM
CYP2C8	Gemfibrozil glucuronide	Acetonitrile with 0.1% v/v formic acid (0.5%)	5.0 µM
CYP2C9	Tienilic acid	Tris base (0.002 mg/mL)	0.25 µM
CYP2C19	*S*-Fluoxetine	Methanol (1%)	40 µM
CYP2D6	Paroxetine	Water	1.0 µM
CYP3A4/5	Troleandomycin	Acetonitrile (0.1%)	7.5 µM

Results: Under the experimental conditions examined, there was no evidence that SD-1021 was a direct, time-dependent (NADPH-independent) or metabolism-dependent (time-dependent and NADPH-dependent) inhibitor of any CYP enzyme examined (i.e., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) as any isolated IC_{50} values are reported as > 100 µM and less than 7.2% inhibition was observed for any CYP enzymes at the highest test article concentration (100 µM).

Summary of results: In vitro evaluation of SD-1021(M1) as an inhibitor of human CYP enzymes

Enzyme	Substrate	Direct inhibition		Time-dependent inhibition			Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		Potential for time-dependent inhibition [c]	30-minute preincubation with NADPH		Potential for metabolism-dependent inhibition [d]
		IC_{50} (µM) [a]	Inhibition observed at 100 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 100 µM (%) [b]		IC_{50} (µM) [a]	Inhibition observed at 100 µM (%) [b]	
CYP1A2	Phenacetin	> 100	NA	> 100	NA	No	> 100	NA	No
CYP2B6	Efavirenz	> 100	NA	> 100	NA	No	> 100	NA	No
CYP2C8	Amodiaquine	> 100	7.2	> 100	4.4	No	> 100	NA	No
CYP2C9	Diclofenac	> 100	NA	> 100	NA	No	> 100	NA	No
CYP2C19	*S*-Mephenytoin	> 100	NA	> 100	NA	No	> 100	7.0	No
CYP2D6	Dextromethorphan	> 100	NA	> 100	NA	No	> 100	NA	No
CYP3A4/5	Testosterone	> 100	NA	> 100	NA	No	> 100	3.6	No
CYP3A4/5	Midazolam	> 100	NA	> 100	1.4	No	> 100	NA	No

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values.

b Inhibition observed (%) is calculated with the following formula (results are rounded to two significant figures):
Inhibition observed (%) = 100% − Percent solvent control.

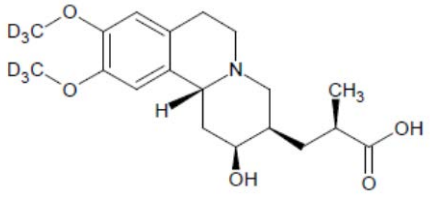
c When IC_{50} values were calculated, time-dependent (i.e., NADPH-independent) inhibition was determined by comparison of IC_{50} values for zero-minute preincubation and 30-minute preincubation without NADPH samples and by visual inspection of the IC_{50} plot. If the inhibition observed was insufficient to calculation IC_{50} values, percent remaining activities for each concentration were compared.

d When IC_{50} values were calculated, metabolism-dependent (i.e., time-dependent and NADPH-dependent) inhibition was determined by comparison of IC_{50} values for 30-minute preincubation with NADPH and 30-minute preincubation without NADPH samples and by visual inspection of the IC_{50} plot. If the inhibition observed was insufficient to calculation IC_{50} values, percent remaining activities for each concentration were compared.

NA Not applicable. Inhibition was not observed since the rates at the highest concentration of SD-1021 evaluated (100 µM) were equal to or higher than the control rates.

M1

Chemical structure



Reviewer's Comment: The experimental conditions and the results of this study are acceptable.

XIX. SD-809-NC-072: In Vitro Evaluation of SD-1021 (M1) as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

Objective: to evaluate in vitro (in human hepatocytes) the induction potential of the SD-809 major metabolite M1 (SD-1021) on major CYP enzymes.
The in vitro evaluation was performed by (b) (4).

Methods: This study was designed to allow any inductive effects of M1 to be assessed relative to three clinically relevant CYP inducers: omeprazole (an AhR activator and CYP1A2 inducer), phenobarbital (a CAR activator and CYP2B6 inducer) and rifampin (a PXR agonist and inducer of CYP3A4).
Three preparations of cultured human hepatocytes from three separate livers were treated once daily for three consecutive days with DMSO (0.1% v/v, vehicle control), flumazenil (25 µM, negative control), one of seven concentrations of M1 (0.01, 0.1, 1, 6, 10, 30 or 100 µM) or one of three known human CYP enzyme inducers, omeprazole (50 µM), phenobarbital (750 µM) and rifampin (20 µM).
The stock solutions of SD-1021 were prepared fresh prior to use on each day of treatment.
After treatment, the cells were harvested with Buffer RLT to isolate RNA, which was analyzed by qRT-PCR to assess the effect of SD-1021 on mRNA levels.
Quantitative RT-PCR was conducted according to SOP L6160.06 and the Applied Biosystems protocol. Each PCR was performed in triplicate. A Primer Mix was prepared for each Gene Expression assay.

Results:

CYP1A2 mRNA percent positive control: The effect of treating cultured human hepatocytes with SD-1021 (M1) on CYP1A2 mRNA levels

Percent Positive Control mRNA Fold	CYP1A2			Mean ± Std Dev	n
	HC10-8	HC4-18	HC7-5		
0.1% DMSO	0	0	0	0 ± 0	3
0.01 µM SD-1021	1.53	0.860	-0.00422	0.796 ± 0.770	3
0.1 µM SD-1021	0.149	0.516	-0.184	0.160 ± 0.350	3
1 µM SD-1021	0.866	0.250	0.0604	0.392 ± 0.421	3
6 µM SD-1021	0.479	0.0560	0.188	0.241 ± 0.216	3
10 µM SD-1021	0.979	0.333	0.0787	0.464 ± 0.464	3
30 µM SD-1021	0.124	0.0995	0.270	0.164 ± 0.092	3
100 µM SD-1021	0.495	0.118	0.337	0.317 ± 0.189	3
25 µM Flumazenil	0.105	-0.0746	0.135	0.0550 ± 0.1132	3
50 µM Omeprazole	100	100	100	100 ± 0	3

Treatment of cultured human hepatocytes with up to 100 µM of M1 caused little or no change in CYP1A2 mRNA levels.

CYP2B6 mRNA percent positive control: The effect of treating cultured human hepatocytes with SD-1021 (M1) on CYP2B6 mRNA levels

Percent Positive Control mRNA Fold	CYP2B6			Mean ± Std Dev	n
	HC10-8	HC4-18	HC7-5		
0.1% DMSO	0	0	0	0 ± 0	3
0.01 µM SD-1021	0.977	5.73	0.139	2.28 ± 3.01	3
0.1 µM SD-1021	-0.0387	4.04	-0.166	1.28 ± 2.39	3
1 µM SD-1021	0.542	5.66	0.810	2.34 ± 2.88	3
6 µM SD-1021	1.62	7.47	-0.332	2.92 ± 4.06	3
10 µM SD-1021	4.60	8.54	-0.657	4.16 ± 4.62	3
30 µM SD-1021	1.76	8.53	1.33	3.88 ± 4.04	3
100 µM SD-1021	0.609	6.32	1.52	2.82 ± 3.07	3
25 µM Flumazenil	0.851	3.36	-0.00664	1.40 ± 1.75	3
750 µM Phenobarbital	100	100	100	100 ± 0	3

SD-1021 caused little or no change in CYP2B6 mRNA levels in hepatocyte cultures HC10-8 and HC7-5. In hepatocyte culture HC4-18, however, SD-1021 caused > 2-fold change increases in CYP2B6 mRNA levels. However, these increases were < 20% of the positive control, phenobarbital, up to 8.5%.

CYP3A4 mRNA percent positive control: The effect of treating cultured human hepatocytes with SD-1021 (M1) on CYP3A4 mRNA levels

Percent Positive Control mRNA Fold	CYP3A4			Mean ± Std Dev	n
	HC10-8	HC4-18	HC7-5		
0.1% DMSO	0	0	0	0 ± 0	3
0.01 µM SD-1021	0.483	5.38	0.626	2.16 ± 2.79	3
0.1 µM SD-1021	-0.221	1.81	0.299	0.631 ± 1.057	3
1 µM SD-1021	1.37	5.09	0.633	2.36 ± 2.39	3
6 µM SD-1021	0.0745	3.42	0.257	1.25 ± 1.88	3
10 µM SD-1021	1.11	4.03	0.906	2.01 ± 1.75	3
30 µM SD-1021	0.352	3.21	1.27	1.61 ± 1.46	3
100 µM SD-1021	1.19	3.55	2.15	2.30 ± 1.19	3
25 µM Flumazenil	-0.116	2.65	0.622	1.05 ± 1.43	3
20 µM Rifampin	100	100	100	100 ± 0	3

M1 (SD-1021) at up to 100 µM had little or no effect on CYP3A4 mRNA levels in all three hepatocyte cultures except for slight elevations in hepatocyte culture HC4-18. These elevations were not concentration-dependent and were < 20% of the positive control, rifampin.

Conclusion: under the conditions of this study where the CYP positive controls, omeprazole, phenobarbital and rifampin caused appropriate increases in CYP1A2, CYP2B6 and CYP3A4 mRNA, treatment with up to 100 µM M1 (SD-1021) had little or no effect on CYP1A2 mRNA levels in all three hepatocyte cultures.

Reviewer's Comment: The experimental conditions and the results of this study are acceptable.

APPEARS THIS WAY ON ORIGINAL

XX. SD-809-NC-073: In Vitro Evaluation of SD-1021 (M1) as an Inhibitor and Substrate of Human P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 Transporters

Objective: to evaluate in vitro M1 (SD-1021) as an inhibitor and a substrate of human transporters. The in vitro evaluation was performed by (b) (4).

Methods: The ability of M1 (0.01, 0.03, 0.1, 0.3, 1 and 3 µM) to inhibit human ABC transporters (efflux transporters: P-gp and BCRP) was evaluated by measuring the bidirectional permeability of a probe substrate (digoxin or prazosin) across a monolayer of Caco-2 and MDCKII-BCRP cells in the presence of SD-1021.
The ability of M1 (0.003, 0.01, 0.03, 0.1, 0.3, 1 and 3 µM) to inhibit human uptake transporters (OATP1B1, OATP1B3, OCT2, OAT1 and OAT3) was evaluated by measuring the accumulation of probe substrates (see table below).
To determine if M1 (0.3, 1 and 3 µM) is a substrate of human ABC transporters (P-gp and BCRP), the bidirectional permeability of SD-1021 across MDCKII-MDR1 and MDCKII-BCRP cells was measured. To determine if M1 (0.3, 1 and 3 µM) is a substrate of human SLC transporters (OATP1B1, OATP1B3, OCT2, OAT1 and OAT3), the accumulation of M1 (0.3, 1 and 3 µM) in transporter-expressing and control HEK293 cells was measured.
Comment: The (M1) concentrations tested are adequate, since they cover the estimated max plasma concentrations of M1 (0.126 µM).
Estimate the max conc for M1 (MW 356.2):
The steady state (α+β) HTBZ Cmax following 24 mg b.i.d. is 112 ng/ml according to SD-809-CLN-078, Population PK Modeling, Table 7.
According to Table 11 in the sponsor response to IR (Sept 24, 2015), M1 is 40% of (a+β)-HTBZ (e.g. 44.8 ng/ml [µg/L] or 0.125 µM) and M4 is 56% of (a+β)-HTBZ.

SD-1021 was evaluated for its ability to inhibit human efflux and uptake transporters as summarized in the table below:

Transporter	Test system	Probe substrate	Experimental design
P-gp	Caco-2	Digoxin	Bidirectional transport of the probe substrate across Caco-2 cells
BCRP	MDCKII-BCRP	Prazosin	Bidirectional transport of the probe substrate across MDCKII-BCRP and control MDCKII cells
OATP1B1	HEK293	Estradiol-17β-glucuronide	Uptake of the probe substrate into OATP1B1 and control cells
OATP1B3	HEK293	Estradiol-17β-glucuronide	Uptake of the probe substrate into OATP1B3 and control cells
OCT2	HEK293	Metformin	Uptake of the probe substrate into OCT2 and control cells
OAT1	HEK293	p-Aminohippurate	Uptake of the probe substrate into OAT1 and control cells
OAT3	HEK293	Estrone-3-sulfate	Uptake of the probe substrate into OAT3 and control cells

The potential of SD-1021 to be a substrate of human efflux and uptake transporters was evaluated as outlined below.

Transporter	Test system	Experimental design
P-gp	MDCKII-MDR1	Bidirectional permeability of test article in MDCKII-MDR1 and control cells
BCRP	MDCKII-BCRP	Bidirectional permeability of the test article in MDCKII-BCRP and control cells
OATP1B1	HEK293	Accumulation of the test article in OATP1B1 and control cells
OATP1B3	HEK293	Accumulation of the test article in OATP1B3 and control cells
OCT2	HEK293	Accumulation of the test article in OCT2 and control cells
OAT1	HEK293	Accumulation of the test article in OAT3 and control cells
OAT3	HEK293	Accumulation of the test article in OAT3 and control cells

Results:

P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 were not inhibited more than 23% in the presence of SD-1021 at the concentrations tested, indicating that SD-1021 is not an inhibitor of the tested efflux and uptake transporters.

P-gp inhibition: Bidirectional permeability of digoxin across Caco-2 cells in the presence of SD-1021, valspodar and verapamil

Substrate	Inhibitor	[Inhibitor] (μM)	P_{app} ($\times 10^{-6}$ cm/sec)		Net flux	Percent of control (%)	Percent inhibition (%)	IC_{50} parameters
			Apical to basal	Basal to apical				
Digoxin (10 μM)	Solvent control	0	2.07 ± 0.75	20.9 ± 2.1	18.82	100.00	NA	IC_{50}: > 3 μM
	SD-1021	0.01	1.46 ± 0.05	25.3 ± 2.2	23.88	128	NC	
		0.03	1.52 ± 0.22	21.6 ± 0.7	20.04	107	NC	
		0.1	1.38 ± 0.45	23.1 ± 1.5	21.74	116	NC	
		0.3	1.38 ± 0.11	27.5 ± 0.5	26.12	141	NC	
		1	1.57 ± 0.19	23.1 ± 1.6	21.55	115	NC	
		3	1.89 ± 0.11	18.4 ± 3.2	16.53	87.2	12.8	
	Valspodar	1 μM	6.45 ± 0.59	7.64 ± 0.42	1.20	1.10	98.9	NA
	Verapamil	10 μM	13.3 ± 5.2	6.14 ± 1.31	−7.16	−45.8	Complete	

Substrate	Inhibitor	[Inhibitor] (μM)	Control cells recovery (%)	
			Apical to basal	Basal to apical
Digoxin (10 μM)	SD-1021	0	88.5	92.7
		3	88.1	103

NA Not applicable
NC Not calculated

BCRP inhibition: Bidirectional permeability of prazosin across MDCKII-BCRP cells in the presence of SD-1021, Ko143 and ritonavir

Substrate	Inhibitor	[Inhibitor] (μM)	Control cells			BCRP cells			Net efflux ratio	Relative transport (Percent of control [%])	Percent Inhibition (%)	IC_{50} parameters
			P_{app} ($\times 10^{-6}$ cm/sec)		Efflux ratio	P_{app} ($\times 10^{-6}$ cm/sec)		Efflux ratio				
			Apical to basal	Basal to apical		Apical to basal	Basal to apical					
Prazosin (1 μM)	Solvent control	0	19.7 ± 2.3	30.3 ± 1.9	1.54	6.09 ± 1.29	59.3 ± 2.7	9.74	6.33	100	NA	IC_{50}: > 3 μM
	SD-1021	0.01	21.9 ± 1.3	32.4 ± 2.7	1.48	5.05 ± 0.51	59.0 ± 2.7	11.7	7.92	130	NC	
		0.03	20.4 ± 4.2	31.3 ± 2.3	1.53	4.90 ± 0.38	54.8 ± 5.2	11.2	7.30	118	NC	
		0.1	18.6 ± 0.7	32.5 ± 2.2	1.75	4.89 ± 0.48	58.1 ± 1.5	11.9	6.79	108	NC	
		0.3	23.2 ± 1.5	34.0 ± 1.4	1.46	5.51 ± 0.56	62.7 ± 3.7	11.4	7.78	127	NC	
		1	20.4 ± 1.4	29.8 ± 1.2	1.46	5.83 ± 0.30	60.5 ± 7.7	10.4	7.09	114	NC	
		3	18.9 ± 1.2	29.6 ± 2.9	1.57	5.67 ± 1.06	57.6 ± 1.6	10.2	6.48	103	NC	
	Ko143	1	19.1 ± 1.6	29.7 ± 2.4	1.56	25.5 ± 2.1	30.7 ± 1.1	1.20	0.773	−4.3	Complete	NA
	Ritonavir	50	19.0 ± 2.7	17.4 ± 3.5	0.915	18.3 ± 0.8	29.9 ± 1.8	1.63	1.78	14.7	85.3	

Substrate	Inhibitor	[Inhibitor] (μM)	Control cells recovery (%)		BCRP cells recovery (%)	
			Apical to basal	Basal to apical	Apical to basal	Basal to apical
Prazosin (1 μM)	SD-1021	0	69.9	91.6	93.3	89.5
		3	73.1	89.4	83.2	93.6

OATP1B1 inhibition: Uptake of estradiol-17β-glucuronide into OATP1B1 cells in the presence of SD-1021, rifampin and cyclosporine

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	Percent Inhibition (%)	IC_{50} parameters
			Control	OATP1B1				
Estradiol-17β-glucuronide (50 nM)	Solvent control	0	0.0249 ± 0.0127	2.19 ± 0.23	1.08	100	NA	IC_{50}: > 3 μM
	SD-1021	0.003	0.0318 ± 0.0020	2.19 ± 0.14	1.08	99.7	NC	
		0.01	0.0142 (n = 2)	1.98 ± 0.19	0.984	90.8	9.2	
		0.03	0.0184 ± 0.0062	2.38 ± 0.79	1.18	109	NC	
		0.1	0.0299 ± 0.0238	2.34 ± 0.37	1.15	106	NC	
		0.3	0.0207 ± 0.0098	2.49 ± 0.16	1.23	114	NC	
		1	0.0123 ± 0.0056	2.27 ± 0.10	1.13	104	NC	
		3	0.0148 ± 0.0046	2.48 ± 0.23	1.23	114	NC	
	Rifampin	10	0.0262 ± 0.0046	0.248 ± 0.018	0.111	10.2	89.8	NA
	Cyclosporin	1	0.0451 ± 0.0033	0.126 ± 0.025	0.0404	3.7	96.3	

OATP1B3 inhibition: Uptake of estradiol-17β-glucuronide into OATP1B3 cells in the presence of SD-1021, rifampin and cyclosporine

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	Percent Inhibition (%)	IC_{50} parameters
			Control	OATP1B3				
Estradiol-17β-glucuronide (50 nM)	Solvent control	0	0.0613 (n = 3)	0.638 ± 0.036	0.289	100	NA	IC_{50}: > 3 μM
	SD-1021	0.003	0.0661 ± 0.0352	0.643 ± 0.049	0.288	99.9	NC	
		0.01	0.0459 (n = 2)	0.682 ± 0.052	0.318	110	NC	
		0.03	0.0688 ± 0.0509	0.691 ± 0.100	0.311	108	NC	
		0.1	0.0931 (n = 2)	0.690 ± 0.087	0.298	103	NC	
		0.3	0.0810 (n = 2)	0.660 ± 0.035	0.290	100	NC	
		1	0.0349 ± 0.0304	0.676 ± 0.013	0.320	111	NC	
		3	0.0270 ± 0.0162	0.613 ± 0.051	0.293	102	NC	
	Rifampin	10	0.195 ± 0.095	0.125 ± 0.053	−0.0352	−12.2	Complete	NA
	Cyclosporin	1	0.168 ± 0.015	0.0903 ± 0.0169	−0.0390	−13.5	Complete	

OCT2 inhibition: Uptake of metformin into OCT2 cells in the presence of SD-1021, quinidine and cimetidine

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	Percent Inhibition (%)	IC_{50} parameters
			Control	OCT2				
Metformin (10 μM)	Solvent control	0	13.3 ± 5.6	90.0 ± 17.6	38.4	100	NA	IC_{50}: > 3 μM
	SD-1021	0.003	11.2 ± 4.4	78.5 ± 8.6	33.6	87.6	12.4	
		0.01	8.27 ± 2.26	76.5 ± 4.7	34.1	88.9	11.1	
		0.03	6.44 ± 0.39	78.7 ± 5.9	36.1	94.2	5.8	
		0.1	6.97 ± 1.47	98.3 ± 15.7	45.6	119	NC	
		0.3	7.67 ± 0.20	82.1 ± 7.0	37.2	97.0	3.0	
		1	5.16 ± 0.86	64.2 ± 6.5	29.5	77.0	23.0	
		3	7.92 ± 2.45	69.0 ± 5.3	30.6	79.6	20.4	
	Quinidine	300	2.16 ± 0.82	9.17 ± 2.07	3.51	9.1	90.9	NA
	Cimetidine	1000	9.67 ± 4.93	12.5 (n = 2)	1.42	3.7	96.3	

OAT1 inhibition: Uptake of p-aminohippurate into OAT1 cells in the presence of SD-1021, probenecid and novobiocin

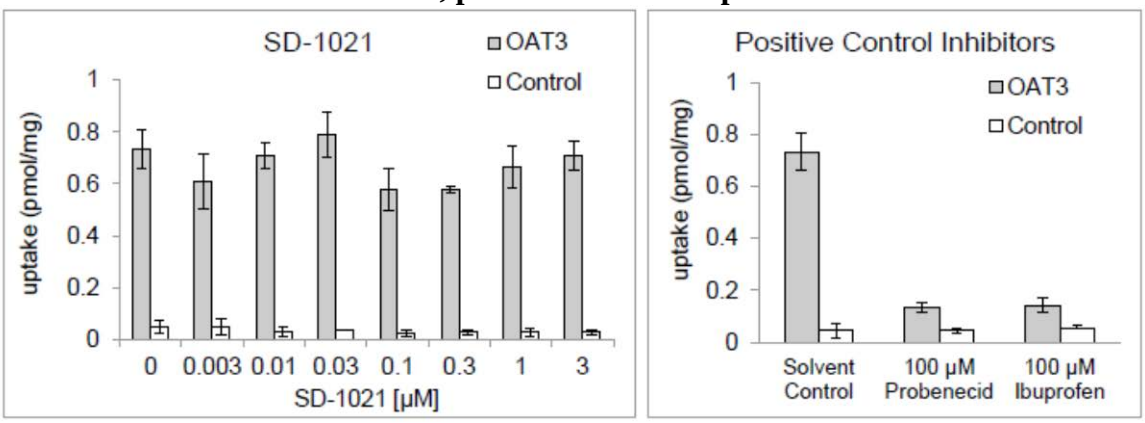
Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	Percent Inhibition (%)	IC_{50} parameters
			Control	OAT1				
p-Aminohippurate (1 μM)	Solvent control	0	0.721 ± 0.255	10.3 ± 1.2	9.60	100	NA	IC_{50}: > 3 μM
	SD-1021	0.003	0.758 ± 0.289	11.9 ± 2.7	11.2	116	NC	
		0.01	0.296 ± 0.202	10.3 ± 1.7	9.96	104	NC	
		0.03	0.620 ± 0.546	11.8 ± 1.5	11.2	117	NC	
		0.1	0.449 ± 0.220	9.76 ± 0.72	9.31	97.0	3.0	
		0.3	0.348 ± 0.340	8.35 ± 1.23	8.01	83.4	16.6	
		1	0.361 ± 0.219	8.94 ± 0.44	8.58	89.4	10.6	
		3	0.217 ± 0.175	9.35 ± 1.13	9.13	95.1	4.9	
	Probenecid	100	0.517 ± 0.103	2.57 ± 0.75	2.05	21.4	78.6	NA
	Novobiocin	300	0.830 ± 0.198	1.17 ± 0.11	0.341	3.6	96.4	

OAT3 inhibition: Uptake of estrone-3-sulfate into OAT3 cells in the presence of SD-1021, probenecid and ibuprofen

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	Percent Inhibition (%)	IC_{50} parameters
			Control	OAT3				
Estrone-3-sulfate (50 nM)	Solvent control	0	0.0453 ± 0.0256	0.735 ± 0.074	0.345	100	NA	IC_{50}: > 3 μM
	SD-1021	0.003	0.0472 ± 0.0284	0.610 ± 0.104	0.281	81.6	18.4	
		0.01	0.0289 ± 0.0181	0.710 ± 0.052	0.340	98.7	1.3	
		0.03	0.0357 (n = 2)	0.791 ± 0.087	0.378	110	NC	
		0.1	0.0231 ± 0.0105	0.576 ± 0.080	0.277	80.2	19.8	
		0.3	0.0275 ± 0.0097	0.575 ± 0.013	0.274	79.5	20.5	
		1	0.0261 ± 0.0172	0.665 ± 0.080	0.319	92.6	7.4	
		3	0.0280 ± 0.0093	0.709 ± 0.058	0.341	98.8	1.2	
	Probenecid	100	0.0458 ± 0.0104	0.133 ± 0.019	0.0434	12.6	87.4	NA
	Ibuprofen	100	0.0536 ± 0.0114	0.143 ± 0.029	0.0446	12.9	87.1	

The efflux ratio of SD-1021 in MDR1- and BCRP-expressing cells was below two in the presence and absence of appropriate inhibitors, suggesting that SD-1021 is not a substrate of the efflux transporters P-gp and BCRP.
The accumulation of SD-1021 in OATP1B1, OATP1B3, OCT2 and OAT1 cells was less than two at the majority of conditions and was not affected by the appropriate positive control inhibitors, suggesting SD-1021 is not a substrate of OATP1B1, OATP1B3, OCT2 or OAT1.The accumulation of SD-1021 in OAT3 cells was time and concentration dependent and was more than 2 fold higher than in control cells in the majority of test conditions. The uptake into OAT3 cells was reduced in the presence of the positive control inhibitor suggesting that SD-1021 is a substrate of OAT3.

OAT3 inhibition: Uptake of estrone-3-sulfate into OAT3 cells in the presence of SD-1021, probenecid and ibuprofen



Conclusions:
SD-1021 is not an inhibitor of the tested efflux and uptake transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3).
SD-1021 is not a substrate of the efflux transporters P-gp and BCRP.
SD-1021 is not a substrate of OATP1B1, OATP1B3, OCT2 or OAT1.
The uptake into OAT3 cells was reduced in the presence of the positive control inhibitor suggesting that SD-1021 is a substrate of OAT3.

XXI. 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

Objective: to evaluate in vitro M4 (SD-1018) as an inhibitor of the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) in human liver microsomes.
The in vitro evaluation was performed by (b) (4)

Methods: To evaluate SD-1018 as a direct, time-dependent and metabolism-dependent inhibitor of CYP enzymes, human liver microsomes from a pool of 200 individuals were incubated with marker substrates in the presence or absence of SD-1018. SD-1018 was evaluated for its ability to inhibit the following human CYP enzymes using the conditions specified:

IC_{50} determinations: Summary of assay conditions to measure microsomal CYP enzyme activity –Direct, time-dependent and metabolism-dependent inhibition of enzymes by SD-1018

Enzyme	Substrate	Substrate concentration (µM)	Incubation volume (µL)	Protein [a] (µg/mL)	Incubation time (min)	Pre-incubation time (min)	SD-1018 Target concentrations (µM)
CYP1A2	Phenacetin	90	200	100	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP2B6	Efavirenz	5	200	100	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP2C8	Amodiaquine	2	200	12.5	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP2C9	Diclofenac	12	200	100	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP2C19	*S*-Mephenytoin	60	200	100	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP2D6	Dextromethorphan	10	200	100	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP3A4/5	Midazolam	3	200	50	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10
CYP3A4/5	Testosterone	60	200	100	5	30	0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10

a The human liver microsomal sample used for these experiments was a pool of 200 individuals (catalog number: H2600, lot number: 1210347).
b Acetonitrile was the vehicle used to dissolve the test article.

To distinguish between time-dependent and metabolism-dependent inhibition, SD-1018 was pre-incubated with human liver microsomes for 30 min without and with an NADPH-generating system, respectively, prior to the incubation with the marker substrate.
Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls in all experiments.
The following direct inhibitors were included as positive controls and incubated for the normal incubation time and with the normal microsomal protein concentration in the presence of the marker substrate:

Enzyme	Positive control	Vehicle (v/v, final incubation concentration)	Concentration studied
CYP1A2	α-Naphthoflavone	Methanol (0.1%)	0.5 µM
CYP2B6	Orphenadrine	DMSO (0.2%)	750 µM
CYP2C8	Montelukast	Methanol (0.1%)	0.05 µM
CYP2C9	Sulfaphenazole	Methanol (0.1%)	2.0 µM
CYP2C19	Modafinil	DMSO (0.1%)	400 µM
CYP2D6	Quinidine	Water	5.0 µM
CYP3A4/5	Ketoconazole	Methanol (0.1%)	0.075 µM

The following metabolism-dependent inhibitors were pre-incubated with human liver microsomes for zero and 30 min followed by incubation with marker substrate for the normal preincubation time and with the normal microsomal protein concentration:

Enzyme	Positive control	Vehicle (v/v, final incubation concentration)	Concentration studied
CYP1A2	Furafylline	DMSO (0.1%)	2.0 µM
CYP2B6	Phencyclidine	Water	30 µM
CYP2C8	Gemfibrozil glucuronide	Acetonitrile with 0.1% v/v formic acid (0.5%)	5.0 µM
CYP2C9	Tienilic acid	Tris base (0.002 mg/mL)	0.25 µM
CYP2C19	Esomeprazole	DMSO (0.1%)	10 µM
CYP2D6	Paroxetine	Water	1.0 µM
CYP3A4/5	Troleandomycin	Acetonitrile (0.1%)	7.5 µM

All metabolite analyses were performed with LC-MS/MS methods.

Results: The evaluation of SD-1018 as a direct, time-dependent and metabolism-dependent inhibitor of human CYP enzymes is summarized in the table below:

Enzyme	Substrate	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-min preincubation		30-min preincubation without NADPH		30-min preincubation with NADPH		Potential for metabolism-dependent inhibition [c]
		IC_{50} (µM) [a]	Inhibition observed at 10 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 10 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 10 µM (%) [b]	
CYP1A2	Phenacetin	> 10.0	1.5	> 10.0	0.0	> 10.0	4.4	Little or no
CYP2B6	Efavirenz	> 10.0	NA	> 10.0	NA	> 10.0	4.2	Little or no
CYP2C8	Amodiaquine	> 10.0	NA	> 10.0	0.0	> 10.0	1.4	Little or no
CYP2C9	Diclofenac	> 10.0	NA	> 10.0	0.0	> 10.0	NA	Little or no
CYP2C19	*S*-Mephenytoin	> 10.0	1.9	> 10.0	11	> 10.0	6.1	Little or no
CYP2D6	Dextromethorphan	> 10.0	NA	> 10.0	1.3	> 10.0	7.8	Little or no
CYP3A4/5	Midazolam	> 10.0	NA	> 10.0	4.2	> 10.0	7.7	Little or no
CYP3A4/5	Testosterone	> 10.0	1.0	> 10.0	NA	> 10.0	4.6	Little or no

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values.

b Inhibition observed (%) is calculated with the following formula (results are rounded to two significant figures):
Inhibition observed (%) = 100% − Percent solvent control.

c Metabolism-dependent inhibition was determined by comparison of IC_{50} values both with and without preincubation and with and without NADPH-generating system present in the preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC_{50} plots.

NA Not applicable. Inhibition was not observed as the rates at the highest concentration of SD-1018 evaluated (10 µM) were higher than the control rates.

Conclusions: there was little or no evidence that SD-1018 caused direct, time-dependent or metabolism-dependent inhibition of any of the CYP enzymes evaluated.

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XXII. DP-2016-002: In Vitro Evaluation of SD-1018 (SD-809 Metabolite M4) as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

Objective: to evaluate in vitro M4 (SD-1018) as an inducer of major CYP enzymes in human liver hepatocytes.
The in vitro evaluation was performed by (b) (4)

Methods: SD-1018 was evaluated for its effect on the following human CYP mRNA levels: CYP1A2, CYP2B6 and CYP3A4.
Three cryopreserved preparations of cultured human hepatocytes from three separate livers (referred to as HC10-10, HC10-8 and HC7-8) were treated once daily for three consecutive days with methanol (1% v/v, vehicle control), flumazenil (25 μM, negative control), one of seven concentrations of SD-1018 (0.1, 0.3, 1, 3, 5, 10 or 20 μM) or one of three known human CYP inducers, omeprazole (50 μM), phenobarbital (750 μM) and rifampin (20 μM). After treatment, the cells were harvested with Buffer RLT to isolate RNA, which was analyzed by qRT-PCR to assess the effect of SD-1018 on CYP1A2, CYP2B6 and CYP3A4 mRNA levels.
The potential of SD-1018 to cause cytotoxicity was assessed based on the release of lactate dehydrogenase (LDH) into the culture medium (a measure of cell membrane integrity) and by daily microscopic evaluation.

Results: Treatment of cultured human hepatocytes with positive control CYP inducers caused appropriate increases in CYP mRNA expression. Omeprazole (50 μM) caused increases from 38.6- to 163-fold in CYP1A2 mRNA levels. Phenobarbital (750 μM) caused increases from 9.57- to 20.1-fold in CYP2B6 mRNA levels. Rifampin (20 μM) caused increases from 17.4- to 71.5-fold in CYP3A4 mRNA levels.
Treatment of cultured human hepatocytes with up to 20 μM SD-1018 had little or no effect on CYP1A2 mRNA levels (range of 0.996- to 2.14-fold change) or CYP2B6 mRNA levels (range of 1.13- to 2.33-fold change). The increases above 2.0-fold were only up to 0.703 and 13.0% as effective as the positive controls, omeprazole and phenobarbital (respectively), at inducing CYP mRNA expression.

CYP1A2 mRNA percent positive control: The effect of treating cultured human hepatocytes with SD-1018 on CYP1A2 mRNA levels

Percent Positive Control mRNA Fold	CYP1A2				
	HC10-10	HC10-8	HC7-8	Mean ± Std Dev	n
Vehicle Control	0	0	0	0 ± 0	3
0.1 μM SD-1018	0.0723	0.152	0.128	0.117 ± 0.041	3
0.3 μM SD-1018	-0.00407	0.287	0.604	0.295 ± 0.304	3
1 μM SD-1018	0.148	0.168	1.63	0.650 ± 0.852	3
3 μM SD-1018	0.326	0.267	0.742	0.445 ± 0.259	3
5 μM SD-1018	0.287	0.362	0.644	0.431 ± 0.188	3
10 μM SD-1018	0.283	0.254	0.758	0.432 ± 0.283	3
20 μM SD-1018	0.448	0.703	1.03	0.728 ± 0.293	3
25 μM Flumazenil	0.127	0.129	0.120	0.125 ± 0.005	3
50 μM Omeprazole	100	100	100	100 ± 0	3

CYP2B6 mRNA fold increase: The effect of treating cultured human hepatocytes with SD-1018 on CYP2B6 mRNA levels

mRNA Fold Increase		HC10-10	HC10-8	HC7-8
CYP2B6	Vehicle Control	0	0	0
	0.1 µM SD-1018	0.308	0.462	0.134
	0.3 µM SD-1018	0.317	0.350	0.436
	1 µM SD-1018	0.503	0.437	0.631
	3 µM SD-1018	0.677	0.478	0.530
	5 µM SD-1018	0.653	0.759	0.531
	10 µM SD-1018	0.779	0.854	0.695
	20 µM SD-1018	0.538	1.33	0.783
	25 µM Flumazenil	0.329	0.653	0.0940
	750 µM Phenobarbital	19.1	10.3	8.57

mRNA Fold increase = Fold change − 1

Treatment of hepatocyte cultures HC10-10, HC10-8 and HC7-8 with up to 20 µM SD-1018 caused concentration-dependent increases up to 2.86-, 3.95- and 4.27-fold change (respectively) in CYP3A4 mRNA levels. However, the maximal increases were only 11.3, 16.4 and 4.64% (respectively) as effective as the positive control, rifampin, at inducing CYP3A4 mRNA expression.

CYP3A4 mRNA fold increase: The effect of treating cultured human hepatocytes with SD-1018 on CYP3A4 mRNA levels

mRNA Fold Increase		HC10-10	HC10-8	HC7-8
CYP3A4	Vehicle Control	0	0	0
	0.1 µM SD-1018	0.258	0.682	0.135
	0.3 µM SD-1018	0.333	0.475	0.308
	1 µM SD-1018	0.378	0.593	0.657
	3 µM SD-1018	0.925	0.834	0.665
	5 µM SD-1018	1.20	1.32	1.13
	10 µM SD-1018	1.68	1.66	1.81
	20 µM SD-1018	1.86	2.95	3.27
	25 µM Flumazenil	0.184	0.581	0.213
	20 µM Rifampin	16.4	17.9	70.5

mRNA Fold increase = Fold change − 1

Conclusion: treatment of cultured human hepatocytes with up to 20 µM SD-1018 had little or no effect (i.e. < 2.0-fold change and/or < 20% of the positive control) on CYP1A2 and CYP2B6 mRNA levels.
Treatment with up to 20 µM SD-1018 caused concentration-dependent increases > 2.0-fold in CYP3A4 mRNA levels in all three preparations tested; however, these increases were < 20% as effective as the positive control rifampin at inducing CYP3A4 mRNA expression.

XXIII. 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

Objective: to evaluate SD-1018 (SD-809 metabolite M4) as an inhibitor and a substrate of human transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2). The in vitro evaluation was performed by (b) (4)

Methods:
SD-1018 (0.1, 0.3, 1, 3, 10 and 20 μM) was evaluated as an inhibitor of human ABC and SLC transporters as outlined in the following table.

Transporter	Test system	Probe substrate	Experimental design
P-gp	Caco-2	Digoxin	Bidirectional transport of the probe substrate across MDCKII transporter-expressing and control MDCKII cells and Caco-2 cells
BCRP	MDCKII-BCRP	Prazosin	
OATP1B1	HEK293	[^{3}H]-Estradiol-17β-glucuronide	Accumulation of the probe substrate into transporter-expressing and control cells
OATP1B3	HEK293	[^{3}H]-Estradiol-17β-glucuronide	
OAT1	HEK293	[^{3}H]-*p*-Aminohippurate	
OAT3	HEK293	[^{3}H]-Estrone-3-sulfate	
OCT2	HEK293	[^{14}C]-Metformin	

Known inhibitors were included as positive controls in all experiments.

SD-1018 (0.3, 1 and 4 μM) was evaluated as a substrate of human ABC and SLC transporters as summarized in the table below.

Transporter	Test system	Experimental design
P-gp	MDCKII-MDR1	Bidirectional permeability of test article in MDCKII transporter-expressing and control cells
BCRP	MDCKII-BCRP	
OATP1B1	HEK293	Accumulation of the test article in transporter-expressing and control cells
OATP1B3	HEK293	
OAT1	HEK293	
OAT3	HEK293	
OCT2	HEK293	

Known substrates and inhibitors were included as positive controls in all experiments.

Results:
Evaluation of M4 as an inhibitor:
Under the conditions tested, SD-1018 was not an inhibitor of the P-gp, BCRP, OATP1B1, OATP1B3 and OAT3 transporters.

P-gp inhibition: Bidirectional permeability of digoxin across Caco-2 cells in the presence of SD-1018, valspodar and verapamil

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Substrate	Inhibitor	[Inhibitor] (μM)	P_{app} ($\times 10^{-6}$ cm/sec)		Net flux	Percent of control (%)	IC_{50} parameters
			Apical to basal	Basal to apical			
Digoxin (10 μM)	Solvent control	0	0.657 ± 0.512	25.8 ± 7.9	25.2	100	IC_{50}: >20 μM
	SD-1018	0.1	0.706 ± 0.287	23.4 ± 5.0	22.7	90.3	
		0.3	0.665 ± 0.454	21.1 ± 3.1	20.4	81.2	
		1	0.547 ± 0.388	22.3 ± 3.1	21.8	86.5	
		3	1.23 ± 0.15	30.7 ± 2.5	29.5	117	
		10	0.732 ± 0.292	29.7 ± 2.7	28.9	115	
		20	0.834 ± 0.538	25.6 ± 4.9	24.8	98.4	
	Valspodar	1	9.51 ± 1.02	12.3 ± 0.6	2.82	11.2	NA
	Verapamil	60	9.61 ± 1.21	11.5 ± 0.3	1.91	7.6	

Substrate	Inhibitor	[Inhibitor] (μM)	Recovery (%)	
			Apical to basal	Basal to apical
Digoxin (10 μM)	SD-1018	0	96.3	100
		20	97.5	105

NA Not applicable

Values are triplicate determinations rounded to three significant figures with standard deviations rounded to the same degree of accuracy.

Percentages are rounded to one decimal place except percentages ≥ 100, which are rounded to the nearest whole number.

BCRP inhibition: Bidirectional permeability of prazosin across MDCKII-BCRP cells in the presence of SD-1018, Ko143 and lopinavir

Substrate	Inhibitor	[Inhibitor] (μM)	Control cells			BCRP Cells			Corrected efflux ratio	Relative transport (Percent of control [%])	IC_{50} parameters
			P_{app} ($\times 10^{-6}$ cm/sec)		Efflux ratio	P_{app} ($\times 10^{-6}$ cm/sec)		Efflux ratio			
			A to B	B to A		A to B	B to A				
Prazosin (1 μM)	Solvent control	0	5.29 ± 0.87	7.34 ± 0.87	1.39	1.22 ± 0.42	14.0 ± 1.3	11.5	8.30	100	IC_{50} (μM): > 20
	SD-1018	0.1	6.16 ± 0.21	7.33 ± 0.98	1.19	1.54 ± 0.22	13.2 ± 0.4	8.61	7.24	85.5	
		0.3	5.80 ± 0.71	7.44 ± 0.17	1.28	1.21 ± 0.23	12.2 ± 0.5	10.1	7.84	93.7	
		1	6.06 ± 0.35	6.67 ± 0.55	1.10	1.21 ± 0.24	13.3 ± 0.4	11.0	9.98	123	
		3	6.83 ± 0.58	7.35 ± 0.35	1.08	1.05	13.8 ± 1.3	13.2	12.2	154	
		10	5.72 ± 0.41	7.08 ± 0.99	1.24	1.15 ± 0.07	12.2 ± 1.6	10.6	8.54	103	
		20	4.96 ± 1.01	6.65 ± 0.76	1.34	1.18 ± 0.04	12.7 ± 0.8	10.7	7.98	95.6	
	Ko143	1	6.34 ± 0.55	6.69 ± 0.98	1.06	4.88 ± 0.63	7.92 ± 0.47	1.62	1.54	7.4	NA
	Lopinavir	30	6.24 ± 0.25	6.65 ± 0.17	1.06	4.52 ± 0.59	6.99 ± 0.75	1.55	1.45	6.2	

Substrate	Inhibitor	[Inhibitor] (μM)	Control cells recovery (%)		BCRP Cells recovery (%)	
			Apical to basal	Basal to apical	Apical to basal	Basal to apical
Prazosin (1 μM)	SD-1018	0	66.0	97.7	88.9	83.6
		20	68.0	89.8	93.6	80.7

A Apical

B Basal

NA Not applicable

OATP1B1 inhibition: Accumulation of [3H]-estradiol-17β-glucuronide into OATP1B1 cells in the presence of SD-1018, cyclosporin and rifampin

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OATP1B1			
[^{3}H]-Estradiol-17β-glucuronide (50 nM)	Solvent control	0	0.0219 (n = 2)	4.75 ± 0.13	2.36	100	IC_{50}: > 20 μM
	SD-1018	0.1	0.0197 ± 0.0066	4.58 ± 0.26	2.28	96.4	
		0.3	0.0213 ± 0.0026	4.48 ± 0.19	2.23	94.2	
		1	0.0182 ± 0.0040	4.40 ± 0.21	2.19	92.6	
		3	0.0186 ± 0.0021	4.67 ± 0.15	2.32	98.3	
		10	0.0237 (n = 2)	4.50 ± 0.03	2.24	94.6	
		15	0.0203 ± 0.0094	4.43 ± 0.14	2.20	93.2	
		20	0.0165 ± 0.0059	4.30 ± 0.21	2.14	90.7	
	Rifampin	10	0.0219 ± 0.0064	0.350 ± 0.011	0.164	6.9	NA
	Cyclosporine	1	0.0194 ± 0.0032	0.183 ± 0.028	0.0818	3.5	

n Number of replicates

OATP1B3 inhibition: Accumulation of [3H]-estradiol-17β-glucuronide into OATP1B3 cells in the presence of SD-1018, cyclosporin and rifampin

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OATP1B3			
[^{3}H]-Estradiol-17β-glucuronide (50 nM)	Solvent control	0	0.0259 (n = 2)	0.901 ± 0.047	0.437	100	IC_{50}: > 20 μM
	SD-1018	0.1	0.0237 ± 0.0066	0.890 ± 0.049	0.433	99.0	
		0.3	0.0253 ± 0.0026	0.862 ± 0.028	0.418	95.7	
		1	0.0221 ± 0.0040	0.842 ± 0.021	0.410	93.7	
		3	0.0225 ± 0.0021	0.902 ± 0.018	0.440	101	
		10	0.0276 (n = 2)	0.890 ± 0.032	0.431	98.6	
		15	0.0243 ± 0.0094	0.895 ± 0.027	0.435	99.6	
		20	0.0205 ± 0.0059	0.836 ± 0.030	0.408	93.2	
	Rifampin	10	0.0259 ± 0.0064	0.0456 ± 0.0041	0.00986	2.3	NA
	Cyclosporine	1	0.0233 ± 0.0032	0.0373 ± 0.0008	0.00699	1.6	

OAT3 inhibition: Accumulation of [^{3}H]-estrone-3-sulfate into OAT3 cells in the presence of SD-1018, ibuprofen and probenecid

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OAT3			
[^{3}H]-Estrone-3-sulfate (50 nM)	Solvent control	0	0.0528 ± 0.0032	1.48 ± 0.25	0.712	100	IC_{50}: > 20 μM
	SD-1018	0.1	0.0586 ± 0.0288	1.21 ± 0.19	0.574	80.6	
		0.3	0.0467 (n = 2)	1.24 ± 0.12	0.596	83.7	
		1	0.115 ± 0.089	1.22 ± 0.19	0.554	77.8	
		3	0.0452 ± 0.0317	1.70 ± 0.22	0.828	116	
		10	0.0621 ± 0.0043	1.35 (n = 2)	0.645	90.5	
		15	0.0490 ± 0.0285	1.36 ± 0.41	0.657	92.3	
		20	0.0248 ± 0.0078	1.31 ± 0.43	0.641	90.0	
	Probenecid	100	0.0445 ± 0.0151	0.112 ± 0.019	0.0336	4.7	NA
	Ibuprofen	100	0.0524 ± 0.0440	0.164 ± 0.007	0.0559	7.8	

SD-1018 at the highest concentration evaluated inhibited the OAT1 and OCT2 transporters by 26 and 16%, respectively. IC_{50} values were not calculated as the inhibition of these transporters was less than 50%.

OAT1 inhibition: Accumulation of [^{3}H]-p-aminohippurate into OAT1 cells in the presence of SD-1018, novobiocin and probenecid

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OAT1			
[^{3}H]-*p*-Aminohippurate (1 μM)	Solvent control	0	0.238 (n = 2)	22.3 ± 1.2	22.0	100	IC_{50}: > 20 μM
	SD-1018	0.1	0.0913 ± 0.0069	22.1 ± 4.2	22.0	99.7	
		0.3	0.0993 ± 0.1025	18.6 ± 0.9	18.5	83.8	
		1	0.0596 ± 0.0391	18.7 ± 1.1	18.7	84.8	
		3	0.0774 ± 0.0450	17.0 ± 0.5	16.9	76.7	
		10	0.0417 (n = 2)	17.2 ± 0.6	17.1	77.8	
		15	0.165 ± 0.054	15.4 ± 1.9	15.2	69.0	
		20	0.0913 ± 0.0069	16.4 ± 1.4	16.4	74.2	
	Probenecid	100	0.206 (n = 2)	1.17 ± 0.26	0.966	4.4	NA
	Novobiocin	300	0.0457 ± 0.0339	0.678 ± 0.122	0.632	2.9	

OCT2 inhibition: Accumulation of [^{14}C]-metformin into OCT2 cells in the presence of SD-1018, cimetidine and quinidine

Probe substrate	Inhibitor	[Inhibitor] (μM)	Uptake (pmol/mg)		Background corrected uptake rate (pmol/mg/min)	Percent of control (%)	IC_{50} parameters
			Control	OCT2			
[^{14}C]-Metformin (10 μM)	Solvent control	0	5.27 ± 0.42	225 ± 1	110	100	IC_{50}: > 20 μM
	SD-1018	0.1	4.07 ± 0.32	203 ± 5	99.4	90.5	
		0.3	4.98 ± 0.51	200 ± 4	97.5	88.7	
		1	4.45 ± 0.51	198 ± 9	96.7	88.0	
		3	4.39 ± 0.62	198 ± 9	96.6	87.9	
		10	6.00 ± 2.34	191 ± 8	92.3	84.0	
		15	6.18 ± 0.84	185 ± 7	89.3	81.3	
		20	5.74 ± 0.18	190 ± 8	92.0	83.7	
	Quinidine	300	1.55 ± 0.57	12.6 ± 1.6	5.54	5.0	NA
	Cimetidine	1000	1.79 ± 0.49	17.5 ± 1.1	7.86	7.2	

Substrate determination:

The efflux ratio of SD-1018 (0.3, 1 and 4 μM) across MDCKII-MDR1 cells was less than two in the absence and presence of the P-gp inhibitor valspodar (10 μM), indicating SD-1018 is not a substrate of the P-gp transporter.
The efflux ratio of SD-1018 (0.3, 1 and 4 μM) across MDCKII-BCRP cells was less than two in the absence and presence of the BCRP inhibitor Ko143 (1 μM).
The uptake ratio of SD-1018 (0.3, 1 and 4 μM) into OATP1B1-expressing cells was greater than two in the absence of inhibitor, but was not reduced in the presence of OATP1B1 inhibitor rifampin (10 μM), indicating that the uptake of SD-1018 was not OATP1B1-mediated and consequently, is not a substrate of the OATP1B1 transporter.
The uptake ratio of SD-1018 (0.3, 1 and 4 μM) into OATP1B3-expressing cells was less than two in the absence of inhibitor with the exception of each tested concentration at the 3-min time point where the uptake ratios were approximately four. At these same conditions in the presence of OATP1B3 inhibitor rifampin (10 μM), the uptake ratios were not reduced to below two, indicating that the uptake of SD-1018 was not OATP1B3-mediated and consequently, is not a substrate of the OATP1B3 transporter.
The uptake ratio of SD-1018 (0.3, 1 and 4 μM) into OAT1-expressing cells was less than two in the absence and presence of the OAT1 inhibitor probenecid (100 μM), indicating SD-1018 is not a substrate of the OAT1 transporter.
The uptake ratio of SD-1018 (0.3, 1 and 4 μM) into OAT3-expressing cells was less than two in the absence and presence of the OAT3 inhibitor probenecid (100 μM), indicating SD-1018 is not a substrate of the OAT3 transporter.
The uptake ratio of SD-1018 (0.3, 1 and 4 μM) into OCT2-expressing cells was less than two in the absence and presence of the OCT2 inhibitor quinidine (300 μM), indicating SD-1018 is not a substrate of the OCT2 transporter.

Conclusions:

Under the conditions tested, SD-1018 was not an inhibitor of the P-gp, BCRP, OATP1B1, OATP1B3 and OAT3 transporters. SD-1018 at the highest concentration evaluated inhibited the OAT1 and OCT2 transporters by 26 and 16%, respectively. IC_{50} values were not calculated as the inhibition of the transporters was less than 50%.
SD-1018 was not a substrate of the P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 transporters under the conditions tested (net efflux ratio or uptake ratio was less than two and/or was not reduced in the presence of a known inhibitor).

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Appendix

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Sponsor Response to 15 Sep 2015, 16 Sep 2015 and 18 Sep 2015 Information Requests

QUESTION/COMMENTS TO 1.11.3 CLINICAL INFORMATION AMENDMENT (0008)

Please refer to 1.11.3 Clinical Information Amendment (0008) submitted Sept 14, 2015.

You state that: Current draft labeling does not refer to the 9-O-desmethyl β-HTBZ metabolite of tetrabenazine.

Please note that per the current (June 2015) Xenazine label, α-HTBZ, βHTBZ and 9-desmethyl-β-DHTBZ, are the major circulating metabolites.

We believe that the confusion is due to inconsistency in the name assigned to the same metabolite in your reports: 9-O-desmethyl β-HTBZ is sometimes referred to as 9-O-desmethyl β-DHTBZ.

For example, in 16.1.12.3 Analytical Phase Report of Study AUS-SD-809-CTP-07, page 31, SD-973 = 9-O-desmethyl-β-dihydrotetrabenazine (9-O-desmethyl-β-DHTBZ), however in the main report of Study AUS-SD-809-CTP-07, page 70, the same metabolite is referred to as 9-O-desmethyl β-HTBZ. This metabolite appears to be a major metabolite at steady state according to tables 15 and 16 in Study AUS-SD-809-CTP-07.

The same applies to the mass balance study: some of the major/minor metabolites have been referred to differently in the (b) (4) report vs. the (b) (4) report.

When addressing the questions in our Sept 15 Request for information, please be consistent in naming metabolites, if necessary, provide formulas.

Teva Response:

Teva acknowledges that during the course of this development program, multiple metabolite names have been used. Please refer to Table 1 for the list of names used in the 2015 Xenazine prescribing information in relationship to names used in New Drug application (NDA) 208082. The relationship of these metabolites to the metabolic pathway is shown in Figure 1 (Section 2.7.2, Summary of Clinical Pharmacology Studies, Figure 7).

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Table 1. Listing of Terms Used for the Same Metabolite

Metabolite as per Xenazine Prescribing Information	Nomenclature for Metabolite fromSD-809 in NDA 208082	Nomenclature for Metabolite from Tetrabenazine in NDA 208082
α-HTBZ*	• α-dihydrotetrabenazine • α-HTBZ • d_6-α-HTBZ • SD-948 • M6	• α-dihydrotetrabenazine • α-HTBZ • d_6-α-HTBZ • SD-946 • M6
β-HTBZ *	• β-dihydrotetrabenazine • β-HTBZ • d_6-β-HTBZ • SD-949 • M5	• β-dihydrotetrabenazine • β-HTBZ • d_6-β-HTBZ • SD-947 • M5
9-desmethyl-α-DHTBZ ** (2015 XENAZINE label)	• 9-O-α-desmethyl dihydrotetrabenazine • d_3-9-O-α-desmethyl DHTBZ • d_3-9-O-α-desmethyl HTBZ • d_4-9-ODM-α-HTBZ • SD-975	• 9-O-α-desmethyl dihydrotetrabenazine • d_6-9-O-α-desmethyl DHTBZ • d_6-9-O-α-desmethyl HTBZ • d_6-9-ODM-α-HTBZ • SD-971
9-desmethyl-β-DHTBZ ** (2015 XENAZINE label) [1-O-dealkylated dihydrotetrabenazine (initial tetrabenazine ADME study in NDA 021894 cited by FDA in Sequence 0008, Section 1.11.3 Clinical Information Amendment Information Request)]	• 9-O-β-desmethyl dihydrotetrabenazine • d_3-9-O-β-desmethyl DHTBZ • d_3-9-O-β-desmethyl HTBZ • d_3-9-ODM-β-HTBZ • SD-977	• 9-O-β-desmethyl dihydrotetrabenazine • d_6-9-O-β-desmethyl DHTBZ • d_6-9-O-β-desmethyl HTBZ • d_6-9-ODM-β-HTBZ • SD-973
10-desmethyl-α-DHTBZ ** (not mentioned in label)	• 10-O-α-desmethyl dihydrotetrabenazine • d_3-10-O-α-desmethyl DHTBZ • d_3-10-O-α-desmethyl HTBZ • d_3-10-ODM-α- HTBZ • SD-976	• 10-O-α-desmethyl dihydrotetrabenazine • d_6-10-O-α-desmethyl DHTBZ • d_6-10-O-α-desmethyl HTBZ • d_6-10-ODM-α- HTBZ • SD-972
10-desmethyl-β-DHTBZ ** (not mentioned in label)	• 10-O-β-desmethyl dihydrotetrabenazine • d_3-10-O-β-desmethyl DHTBZ • d_3-10-O-β-desmethyl HTBZ • d_3-10-ODM-β-HTBZ • SD-978	• 10-O-β-desmethyl dihydrotetrabenazine • d_6-10-O β-desmethyl DHTBZ • d_6-10-O-β-desmethyl HTBZ • d_6-10-ODM-β-HTBZ • SD-974

* HTBZ = dihydrotetrabenazine
** DHTBZ = dihydrotetrabenazine

QUESTION 1: PLASMA SAMPLES FOR MASS BALANCE STUDY

1. **We note that the analysis of plasma samples for the mass balance study was done by two different CROs: (b) (4) and (b) (4) performed Metabolite Profiling and Identification, summarized in 16.1.13.3 Metabolite Profiling and Identification Report. In addition to metabolite identification, they also performed semi-quantitative analysis of plasma samples. Using this assay (Table 10, Sect. 2.7.2 Summary of Clinical Pharmacology Studies, p. 58), 9-O-desmethyl-β-DHTBZ appears to be a minor metabolite for both SD-809 and tetrabenazine since it is not listed as M1-M6 or under "metabolites between 1 and 10% of total radioactivity".**

Teva Response:

Based on results from Study SD-809-C-12, metabolite 9-O-desmethyl-β-DHTBZ is a minor metabolite for both SD-809 and tetrabenazine. It is listed in footnote 'e' of Section 2.7.2 Summary of Clinical Pharmacology Studies, Table 10 (reproduced herein as Table 2 ; footnote in **bold** font) as one of the "metabolites between 1 and 10% of total radioactivity" using the nomenclature identification for the metabolite of '9 ODM β HTBZ.'

Table 2. 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.

(b) (4) analyzed the plasma samples using a validated LC-MS/MS assay; this analysis is summarized in 16.1.13.1 Bioanalytical Report. The individual plasma concentrations for parent/metabolites are in Tables 54 -59 in 16.1.13.1 Bioanalytical Report.

- **Please provide the individual and summary PK results (AUC, Cmax and t1/2) using the (b) (4) analysis for each quantified metabolite.**

Teva's Response:

The LC-MS/MS assay performed by (b) (4) was used to quantify parent drug (i.e., SD-809 and tetrabenazine) and 6 of their respective metabolites: these are shown in the red circled areas in Figure 2 (modified from Section 2.7.2, Summary of Clinical Pharmacology Studies, Figure 7).

Individual subject and summary pharmacokinetic data from the LC-MS/MS assays with the addition of total (α+β)-HTBZ are in Table 3 through Table 10. The test article dosed, the analyte (including the most common aliases in parentheses), the pharmacokinetic parameters, and data sources (from the Study SD-809-C-12 clinical study report) are identified in each table.

The structures circled in blue in Figure 2 depict the analytes identified by the semiquantitative radioactivity assay shown in Table 11.

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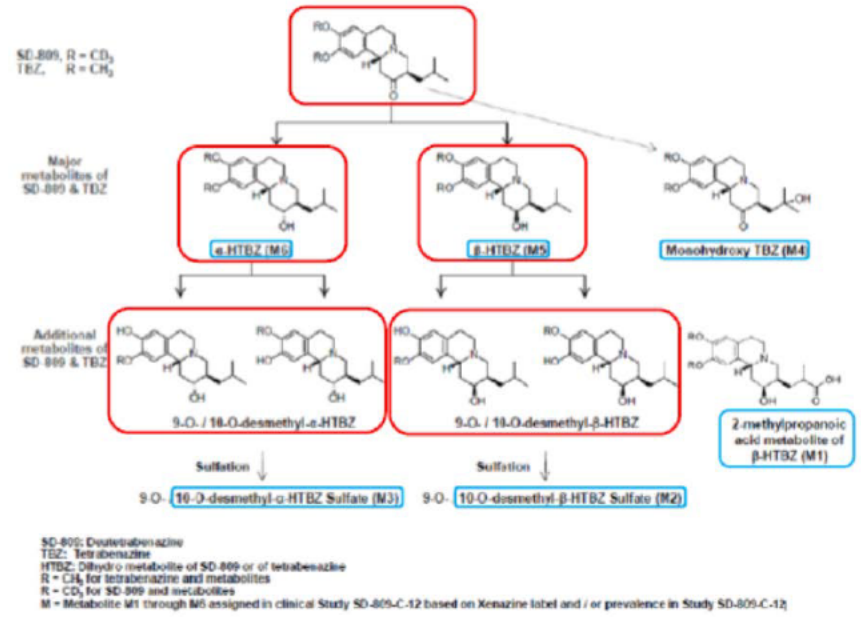
Figure 2. Metabolic Pathway of SD-809 and Tetrabenazine



Source: Section 2.7.2, Summary of Clinical Pharmacology Studies, Figure 7.
Red circles: Parent drug and 6 metabolites quantified by LC-MS/MS assay performed by (b) (4)
Blue circles: Analytes identified by the semiquantitative radioactivity assay shown in Table 11.

Table 3. SD-809 and Tetrabenazine Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: SD-809				Treatment: Tetrabenazine (Cohort 2) Analyte: Tetrabenazine (SD-808)			
Parameter Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	0.375	0.219	2.49	7	0	0	NC
2	0.0824	0.184	NC	8	1.33	2.1	0.76
3	0	0	NC	9	0.128	0.186	NC
4	0.128	0.294	NC	10	0	0	NC
5	1.41	0.283	17.62	11	1.87	2.17	1.06
6	0	0	NC	12	0	0	NC
n	4	4	ND	n	3	3	ND
Geometric Mean	0.273	0.241	ND	Geometric Mean	0.683	0.946	ND
Geometric CV%	199.0	22.4	ND	Geometric CV%	273.0	251.0	ND
Source: Study SD-809-C-12, Table 9 (AUC and C_{max}); Listing 16.2.6.4.1 (Page 1 of 10); Table 14.2.8.4.1 (Page 1 of 9).				Source: Study SD-809-C-12, Table 9 (AUC and C_{max}); Listing 16.2.6.4.2 (Page 1 of 10); Table 14.2.8.4.3 (Page 1 of 11).			
Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done.							

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Table 4. α-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: α-HTBZ (d_5-α-HTBZ; d_5-alpha-HTBZ; SD-948; M6)				Treatment: Tetrabenazine (Cohort 2) Analyte: α-HTBZ (alpha-HTBZ; SD-946; M6)			
Parameter / Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	424	23.6	10.58	7	115	7.71	18.68*
2	316	23.6	9.47	8	116	20.5	8.02
3	701	25.1	NC	9	88.0	13.9	8.87*
4	240	35.7	10.09	10	101	18.1	3.78
5	617	21.3	15.41	11	80.2	31.1	4.14
6	629	40.3	17.19	12	177	24.3	8.31
n	6	6	5	n	6	6	4
Geometric Mean	454	27.5	12.177	Geometric Mean	109	17.6	5.682
Geometric CV%	45.3	26.3	27.6	Geometric CV%	28.3	51.8	44.0
Source: Study SD-809-C-12, Table 10; Listing 16.2.6.4.1 (Page 2 of 10); Table 14.2.8.4.1 (Page 2 and 3 of 9).				Source: Study SD-809-C-12, Table 10; Listing 16.2.6.4.2 (Page 2 of 10); Table 14.2.8.4.3 (Page 2 and 3 of 11).			

Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done.
* = Period used for regression analysis < 2-fold the calculated $t_{1/2}$. Estimate reported but not included in summary statistics.

Table 5. β-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: β-HTBZ (d_5-β-HTBZ; d_5-beta-HTBZ; SD-949; M5)				Treatment: Tetrabenazine (Cohort 2) Analyte: β-HTBZ (beta-HTBZ; SD-947; M5)			
Parameter / Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	178	14.8	7.42	7	15.3	2.04	4.34*
2	68.3	10.8	4.40	8	34.3	10.2	3.57
3	427	22.7	11.19	9	15.8	4.57	2.38*
4	57.5	13.5	7.55	10	24.6	6.54	2.31*
5	204	12.3	14.81	11	19.4	11.6	2.84*
6	508	37.0	14.84	12	51.0	11.7	2.87
n	6	6	6	n	6	6	2
Geometric Mean	177	16.8	9.201	Geometric Mean	24.2	6.62	3.198
Geometric CV%	112.0	48.9	50.2	Geometric CV%	50.1	77.4	15.6
Source: Study SD-809-C-12, Table 10; Listing 16.2.6.4.1 (Page 3 of 10); Table 14.2.8.4.1 (Page 4 and 5 of 9).				Source: Study SD-809-C-12, Table 10; Listing 16.2.6.4.2 (Page 3 of 10); Table 14.2.8.4.3 (Page 4 and 5 of 11).			

Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done.
* = Period used for regression analysis < 2-fold the calculated $t_{1/2}$. Estimate reported but not included in summary statistics.

Table 6. Total (α+β)-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: total (α+β)-HTBZ [Total d_5 (α + β) HTBZ; d_5-alpha-HTBZ+d_5-beta-HTBZ]				Treatment: Tetrabenazine (Cohort 2) Analyte: total (α+β)-HTBZ [alpha-HTBZ+ beta-HTBZ]			
Parameter / Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	606	38.4	9.53	7	133	9.73	18.68*
2	387	34.4	8.92	8	152	30.7	6.12
3	1150	47.8	NC	9	105	18.5	8.87*
4	301	48.2	9.40	10	128	24.6	3.35
5	834	33.6	14.87	11	101	42.7	3.63
6	1140	77.3	16.29	12	231	36.0	8.31
n	6	6	5	n	6	6	4
Geometric Mean	652	44.6	11.411	Geometric Mean	136	24.4	4.987
Geometric CV%	60.7	31.9	29.2	Geometric CV%	30.8	57.8	45.4
Source: Study SD-809-C-12, Table 10; Listing 16.2.6.4.1 (Page 4 of 10); Table 14.2.8.4.1 (Page 6 and 7 of 9).				Source: Study SD-809-C-12, Table 10; Listing 16.2.6.4.2 (Page 4 of 10); Table 14.2.8.4.3 (Page 6 and 7 of 11).			

Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done.
* = Period used for regression analysis < 2-fold the calculated $t_{1/2}$. Estimate reported but not included in summary statistics.

Table 7. 9-ODM-α-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: 9-ODM-α-HTBZ (d_3-9-O-desmethyl-α-HTBZ ; d_3-9-Odesmethyl-alpha-HTBZ; SD-975)				Treatment: Tetrabenazine (Cohort 2) Analyte: 9-ODM-α-HTBZ (9-O-desmethyl-α-HTBZ; 9-Odesmethyl-alpha-HTBZ ; SD-971)			
Parameter Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	12.3	0.86	16.83*	7	21.2	1.42	27.49*
2	12.4	0.949	19.3*	8	43.7	2.61	20.08*
3	8.03	0.679	NC	9	41.7	3.43	9.41*
4	18.4	1.09	14.25*	10	22.5	2.53	8.31*
5	15.7	0.804	NC	11	39.5	5.18	8.26*
6	11.4	0.769	19.35*	12	34.1	2.48	12.25*
n	6	6	ND	n	6	6	ND
Geometric Mean	12.6	0.849	ND	Geometric Mean	32.5	2.73	ND
Geometric CV%	29.0	16.7	ND	Geometric CV%	32.7	44.6	ND
Source: Study SD-809-C-12, Table 12; Listing 16.2.6.4.1 (Page 5 of 10); Table 14.2.8.4.1 (Page 8 of 9).				Source: Study SD-809-C-12, Table 12; Listing 16.2.6.4.2 (Page 5 of 10); Table 14.2.8.4.3 (Page 8 of 11).			
Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done. * = Period used for regression analysis < 2-fold the calculated $t_{1/2}$. Estimate reported but not included in summary statistics.							

Table 8. 9-ODM-β-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: 9-ODM-β-HTBZ (d_3-9-O-desmethyl-β-HTBZ ; d_3-9-Odesmethyl-beta-HTBZ; SD-977)				Treatment: Tetrabenazine (Cohort 2) Analyte: 9-ODM-β-HTBZ (9-O-desmethyl-β-HTBZ; 9-Odesmethyl-beta-HTBZ ; SD-973)			
Parameter Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	87.6	2.98	20.09*	7	157	3.39	31.64*
2	77.0	3.33	16.68	8	203	8.98	23.24
3	81.2	2.33	22.71*	9	143	8.45	17.22
4	63.9	2.26	19.41*	10	131	8.29	17.37*
5	102	2.06	31.25*	11	154	15.5	15.75
6	92.0	2.14	32.16*	12	183	8.10	22.16*
n	6	6	ND	n	6	6	3
Geometric Mean	83.1	2.48	ND	Geometric Mean	160	8.03	18.474
Geometric CV%	16.2	19.6	ND	Geometric CV%	16.1	51.9	20.6
Source: Study SD-809-C-12, Table 13; Listing 16.2.6.4.1 (Page 6 of 10); Table 14.2.8.4.1 (Page 9 of 9).				Source: Study SD-809-C-12, Table 13; Listing 16.2.6.4.2 (Page 6 of 10); Table 14.2.8.4.3 (Page 9 and 10 of 11).			
Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done. * = Period used for regression analysis < 2-fold the calculated t1/2. Estimate reported but not included in summary statistics.							

Table 9. 10-ODM-α-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: 10-ODM-α-HTBZ (d_3-10-O-desmethyl-α-HTBZ ; d_3-10-Odesmethyl-alpha-HTBZ; SD-976)				Treatment: Tetrabenazine (Cohort 2) Analyte: 10-ODM-α-HTBZ (10-O-desmethyl-α-HTBZ; 10-Odesmethyl-alpha-HTBZ; SD-972)			
Parameter Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	0.00	0.00	NC	7	0.00	0.00	NC
2	0.00	0.00	NC	8	0.00	0.00	NC
3	0.00	0.00	NC	9	0.00	0.00	NC
4	0.00	0.00	NC	10	0.00	0.00	NC
5	0.00	0.00	NC	11	0.00	0.00	NC
6	0.00	0.00	NC	12	0.00	0.00	NC
n	ND	ND	ND	n	ND	ND	ND
Geometric Mean	ND	ND	ND	Geometric Mean	ND	ND	ND
Geometric CV%	ND	ND	ND	Geometric CV%	ND	ND	ND
Source: Study SD-809-C-12, Section 11.4.3.3; Listing 16.2.6.4.1 (Page 7 of 10); Table 14.2.8.4.1 (Page 9 of 9).				Source: Study SD-809-C-12, Section 11.4.3.3; Listing 16.2.6.4.2 (Page 7 of 10); Table 14.2.8.4.3 (Page 9 and 10 of 11).			
Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done.							

Table 10. 10-ODM-β-HTBZ Pharmacokinetic Parameters from Study SD-809-C-12

Treatment: SD-809 (Cohort 1) Analyte: 10-ODM-β-HTBZ (d_3-10-O-desmethyl-β-HTBZ ; d_3-10-Odesmethyl-beta-HTBZ; SD-978)				Treatment: Tetrabenazine (Cohort 2) Analyte: 10-ODM-β-HTBZ (10-O-desmethyl-β-HTBZ; 10-Odesmethyl-beta-HTBZ ; SD-974)			
Parameter / Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	Subject	$AUC_{(0\text{-last})}$ (ng•h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)
1	0.00	0.00	NC	7	0.00	0.00	NC
2	0.00	0.00	NC	8	1.32	1.01	2.29*
3	0.00	0.00	NC	9	0.162	0.649	NC
4	0.00	0.00	NC	10	1.88	0.858	3.86*
5	0.00	0.00	NC	11	2.97	2.09	1.31*
6	0.00	0.00	NC	12	2.13	0.839	8.07*
n	ND	ND	ND	n	5	5	ND
Geometric Mean	ND	ND	ND	Geometric Mean	1.2	0.997	ND
Geometric CV%	ND	ND	ND	Geometric CV%	168.0	46.6	ND
Source: Study SD-809-C-12, Section 11.4.3.4; Listing 16.2.6.4.1 (Page 8 of 10).				Source: Study SD-809-C-12, Table 13; Listing 16.2.6.4.2 (Page 8 of 10); Table 14.2.8.4.3 (Page 11 of 11).			
Abbreviations: $AUC_{(0\text{-last})}$ = AUC from time 0 to the last quantifiable time point; NC = not calculated; ND = not done. * = Period used for regression analysis < 2-fold the calculated $t_{1/2}$. Estimate reported but not included in summary statistics.							

- **Please provide site by site summary of the result for each metabolite using (b) (4) assay and the semi-quantitative analysis (b) (4) (b) (4)**

Teva's Response:

Table 11 provides a side by side presentation of pharmacokinetic parameters from the bioanalytical assay and the semi-quantitative assay for % sample radioactivity (also referred to as drug-related material). For reference, the analytes quantified with the bioanalytical assay are shown in Figure 2 circled with a red line. The analytes presented as percent of plasma sample radioactivity (% total drug-related material) are circled with a blue line in Figure 2.

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

		PK parameters from LC-MS/MS assay from (b) (4) geometric mean (%CV) [a]				Semi-quantitative analysis of radioactivity in plasma samples from (b) (4) mean (SD) [b]	
Test article	Metabolite	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)

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Test article	Metabolite	PK parameters from LC-MS/MS assay from (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.

QUESTION 2: SD-809-C-12 – TABLES 14 AND 15

2. In Tables 14 and 15 (SD-809-C-12 report, p. 80 and 81) "Grand total" seems to represent the % of the plasma radiochromatograms from the [^{14}C]-SD-809/TBZ cohorts which was characterized (not % of total circulating drug-related material). Please clarify how the percentage of each metabolite was calculated in these tables.

Teva's Response:

The percentage values cited in the tables, which are described as "percentage of total sample radioactivity", do refer to the % of total circulating drug-related material in plasma. The values for individual metabolites represent the radioactivity associated with the respective peaks in the plasma radiochromatograms, expressed as a fraction of the total radioactivity in the sample. The reason that metabolites M1-M6 were singled out in the tables is that these were the circulating metabolites that, in at least one subject dosed with either ^{14}C-SD-809 or with ^{14}C-tetrabenazine, represented 10% or more of total circulating drug-related material. The contribution of minor metabolites (each accounting for approximately 1-10% of total drug-related material in plasma not already accounted for in M1-M6) is expressed as a sum of these individual components. Collectively, a total of ~80% of circulating drug-related material in plasma was accounted for in this way, both in the cohort dosed with ^{14}C-SD-809 and the cohort dosed with ^{14}C-tetrabenazine. The remaining ~20% of radioactivity was not identified, but consisted of numerous trace components, each of which was present in plasma at a level of <1% of total drug-related material.

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QUESTION 3: SD-809-C-12 – METABOLITE PROFILING AND IDENTIFICATION REPORT

3. Please refer to Report SD-809-C-12 (16.1.13.3 Metabolite Profiling and Identification Report).

4.1 Sample pooling

4.1.1 Plasma

One plasma pool was created for each of the twelve subjects, across the 2 – 12 hours sampling interval. The pooling strategy was undertaken to create an AUC (area under the curve) plasma pool, as detailed in Hamilton et al [3].

In addition four further AUC plasma pools were created. A preliminary cohort pool was constructed from the 2-12 hour sampling interval from each subject, one for the [^{14}C]-SD-809 and one for the [^{14}C]-tetrabenazine. In addition, one for the six [^{14}C]-SD-809 dosed subjects and a second for the six [^{14}C]-tetrabenazine dosed subjects, by pooling a fixed volume of each of the six individual pools. As these two pools were not time proportional, these analyses were not presented.

Please clarify which of these plasma pools were analyzed using the LC-MS/MS Analysis procedure described in Sect 4.4 of the Metabolite Profiling and Identification Report.

Teva's Response:

Each plasma pool was analyzed using the LC-MS/MS method detailed in Study SD-809-C-12, Appendix 16.1.13.3, Metabolite Profiling and Identification, Section 4.4.1. The LC-MS/MS method was only used to verify identity of the radiochromatogram peak in instances in which reference standards were available. Quantification of metabolites in the radiochromatogram was performed by assessing peak area in the radiochromatogram. The following plasma pools were analyzed using the LC-MS/MS procedure described in Study SD-809-C-12, Appendix 16.1.13.3, Metabolite Profiling and Identification Report, Section 4.4:

Per subject AUC pools. The % sample radioactivity (% total drug related material) in each subject's chromatogram are reported in Study SD-809-C-12, Appendix 16.1.13.3 Table 1 and depicted in Figure 2 through Figure 7 (SD-809 cohort) and Figure 9 through Figure 14 (Tetrabenazine cohort) of the same report.

Time-proportional AUC pool for SD-809 cohort. The % sample radioactivity (% of total circulating drug-related material) in the pooled cohort chromatogram is depicted in of the Study SD-809-C-12, Appendix 16.1.13.3, Figure 15.

Time-proportional AUC pool for tetrabenazine cohort. The % sample radioactivity (% of total circulating drug-related material) in the pooled cohort chromatogram is depicted in of the Study SD-809-C-12, Appendix 16.1.13.3, Figure 16.

Fixed-volume AUC pool for SD-809 and tetrabenazine cohort pools. The remaining two pools were analyzed, but not reported in the clinical study report or appendices, as they were incorrectly constructed.

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QUESTION 4: SD-809-C-12 – CLARIFICATION FOR RADIOCHROMATOGRAM OF AUC POOLED PLASMA

4. **Please refer to Report SD-809-C-12 (16.1.13.3 Metabolite Profiling and Identification Report), Figure 15: Radiochromatogram of an AUC pooled plasma extract obtained from subjects 001 – 006. Please clarify whether the peak between M2 and M3 in the radiochromatogram (with retention time approximately 45 min) has been characterized.**

Teva's Response:

For both SD-809 and tetrabenazine, this component represented greater than 1% but less than 10% of the total circulating radioactivity and was identified as co-elution of the following components:

- For dosing with SD-809: sulphate of O-desmethyl d_3-HTBZ; glucuronide of d_6-α-HTBZ and mono-hydroxy d_6-α-HTBZ
- For dosing with tetrabenazine: sulphate of O-desmethyl d_0-HTBZ; glucuronide of d_0-α-HTBZ and mono-hydroxy d_0-α-HTBZ

Please note that the data for these components are presented in the Study SD-809-C-12, Appendix 16.1.13.3, Metabolite Profiling and Identification Report, Table 7 and Table 8 – the retention time is approximately 44 minutes. The supporting mass spectrometry information is also available in the report (Figure 41 through Figure 43 and Figure 52 through Figure 54). It should be noted that these components were observed in the urine pools, as the co-eluting component, U4 (see Study SD-809-C-12, Appendix 16.1.13.3, Metabolite Profiling and Identification Report, Table 2 in addition to Table 7 through Table 8).

Teva also notes that Stacy Metz conveyed the following by e-mail on 18 September 2015: "**This metabolite [referring to 9-O-desmethyl β-DHTBZ] appears to be a major metabolite at steady state according to Tables 15 and 16 in Study AUS-SD-809-CTP-07**". Please refer to the Sequence 0008, Section 1.11.3, Clinical Information Amendment in which we provided our methodology for determining major metabolites. As per the 27 March 2012 correspondence, the sponsor used total circulating drug material as the denominator when classifying metabolites as major. The bioanalytical information in Study AUS-SD-809-CTP-07, Table 15 and Table 16, does not provide information about total circulating drug-related material. Therefore this study was not used to define major metabolites. Instead quantification of metabolites as a percentage of total drug-related material was conducted with radiochromatograms obtained in SD-809-C-12 as this is the most appropriate and rigorous technique to assess all metabolites, not just those for which there were previously existing reference standards.

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Memo of Teleconference

Teleconference Date: September 25, 2015
Application Number: NDA 208082
Product Name: AustedoTM (deutetrabenazine)
Sponsor/Applicant Name: Teva Pharmaceuticals
Subject: Clinical Pharmacology Discussion with Sponsor

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1.0 DISCUSSION BACKGROUND:
The Clinical Pharmacology review team requested additional information regarding the classification of metabolites of SD-908 as potential major metabolites.

> 1. We note that the analysis of plasma samples from the mass balance study was done by two different CROs: (b) (4) (b) (4) performed Metabolite Profiling and Identification, summarized in 16.1.13.3 Metabolite Profiling and Identification Report. In addition to metabolite identification, they also performed semi-quantitative analysis of plasma samples. Using this assay (Table 10, Sect. 2.7.2 Summary of Clinical Pharmacology Studies, p.58), 9-O-desmethyl-β-DHTBZ appears to be a minor metabolite for both SD-809 and tetrabenazine since it is not listed as M1-M6 or under "metabolites between 1 and 10% of total radioactivity".

Teva Response:
Based on results from Study SD-809-C-12, metabolite 9-O-desmethyl-β-DHTBZ is a minor metabolite for both SD-809 and tetrabenazine. It is listed in footnote 'e' of Section 2.7.2 Summary of Clinical Pharmacology Studies, Table 10 (reproduced herein as Table 2; footnote in bold font) as one of the "metabolites between 1 and 10% of total radioactivity" using the nomenclature identification for the metabolite of '9 ODM β HTBZ.'

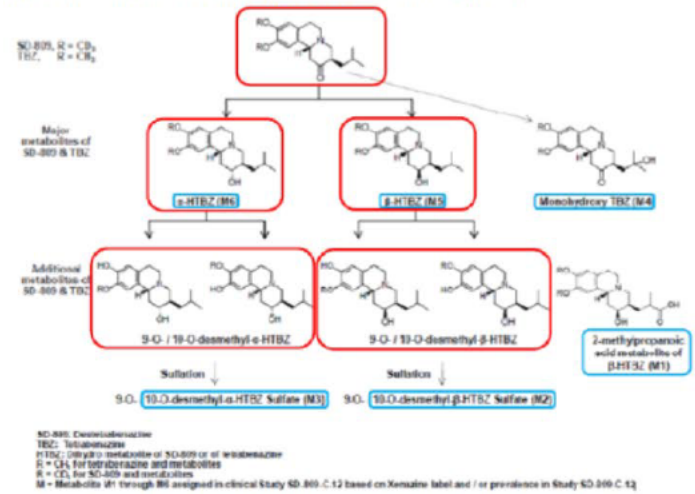
Teleconference Discussion:
The Clinical Pharmacology review team noted that the result showing 9-O-desmethyl-β-DHTBZ is a minor metabolite for both SD-809 and tetrabenazine is based on semi-quantitative testing performed by (b) (4) however, based on the validated analysis performed by (b) (4) (b) (4) LC-MS/MS analysis, 9-O-desmethyl-β-DHTBZ is a major metabolite. The latter conclusion is supported by the results of Study AUS-SD-809-CTP-07 (using SD-809) showing 9-O-desmethyl-β-DHTBZ is a major metabolite.

Although we understand that there could be differences based on different assays (semi-quantitative vs. quantitative), we are concerned that the conclusions about 9-O-desmethyl-β-DHTBZ and all other metabolites are based only on semi-quantitative analyses. It appears that no attempt was made to quantify M1 and M4 using validated methods of analysis with a comparison of the results for SD-809 to those of tetrabenazine. The Agency clarified there is no concern regarding 9-O-desmethyl-β-DHTBZ; but it is an example of how the two different assays can provide different results.

During the EOP2 meeting with Auspex Pharmaceuticals (Dec, 2012), we recommended that the sponsor provide strong evidence in the NDA that justifies the claim that actual exposures to SD-809 metabolites, are similar for both tetrabenazine and SD-809 at steady state , and that any metabolites are not expected to represent an increased safety risk to patients after dose adjustment. Therefore, it is not clear why the (b) (4) LC-MS/MS assay quantified the six metabolites shown in the red circled in Figure 2 but why the metabolites circled in blue were not identified as metabolites (Figure 2).

In addition, the percentage of total sample radioactivity for the parent compound and the individual metabolites are based on plasma pools constructed from the 2 to 12 hour sampling interval (even though plasma samples were collected for >48h). We are concerned that the majority of the AUC for metabolites with longer half-lives (longer than 12 hours), might not be included in the sampling interval, therefore the percentage of total for these metabolites might be underestimated.

Figure 2. Metabolic Pathway of SD-809 and Tetrabenazine



Source: Section 2.7.2, Summary of Clinical Pharmacology Studies, Figure 7.
Red circles: Parent drug and 6 metabolites quantified by LC-MS/MS assay performed by (b) (4)
Blue circles: Analytes identified by the semiquantitative radioactivity assay shown in Table 11.

The sponsor defined major metabolites as a percentage of total circulating drug-related material consistent with the ICH M3(R2) guidance; therefore the most appropriate technique for assessment was to use the semi-quantitative (b) (4) method. However, the Clinical Pharmacology Drug-Drug Interaction (DDI) Guidance, defines a major metabolite as having exposure >25% of parent. In this case, we can consider (a+β)-HTBZ as parent (since they are active and tetrabenazine (TBZ) levels are so low, that comparison to TBZ would show that almost all of the metabolites are greater than 25% of TBZ.

The sponsor pointed out that in vitro DDI studies were conducted with M1 and the report was submitted in the NDA.

Comment: According to Table 11 (see the sponsor response to IR Sept 24, 2015), both M1 and M4 are greater than 25% of (a+β)-HTBZ (M1 is 40% of (a+β)-HTBZ and M4 is 56% of (a+β)-HTBZ) In vitro DDI study results were submitted for M1 but not for M4.

Although the percentage of M4 associated with TBZ and SD-809 are similar, this similarity does not eliminate the need to submit results of DDI studies for M4. The M4 metabolite associated with Xenazine was identified years after the approval of the NDA. In 2011, the FDA required the Xenazine sponsor to conduct DDI studies with 9-O-desmethyl-β-DHTBZ , which was soon after the Xenazine sponsor identified 9-O-desmethyl-β-DHTBZ as a major metabolite of TBZ.

TEVA's representatives argued that the level of M1 after administration SD-809 is approximately 2-fold higher than the level observed with tetrabenazine but there is no increased safety risk because SD-809 is administered at approximately half the dose of tetrabenazine. The clinical review team expressed concern that labeling text does not ensure patients will not exceed 48 mg, the maximum recommended daily dose of SD-809. The clinical review team also noted that patients in the open label studies received doses up to 72 mg daily.

Response to FDA Telcon Request for information regarding Metabolite - 20 Oct 2015

The Division's Memorandum of Teleconference, dated 09 October 2015, summarizing the content of a teleconference between the Teva Pharmaceuticals, Inc. (Teva) and FDA on 25 September 2015, is presented in Section 1.6.3. Provided below is additional clarification regarding classification of the metabolites of SD-809 and tetrabenazine as well as Teva's proposal for additional studies to address the concerns raised by FDA in the Memorandum.

Teva's Response:

Teva appreciates the clarification provided by FDA during the 25 September 2015 teleconference and in the 09 October 2015 Memorandum with regard to the need to evaluate the metabolites M1 and M4 for potential drug interactions as per draft guidance "Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012".

Table 1 clarifies how Teva has classified each metabolite with respect to the guidance for safety testing and the potential for drug interactions and also includes the studies that were conducted as a consequence of those classifications.

Table 1. Summary of SD-809 and Tetrabenazine Metabolite Characterization

Metabolite in Figure 2 (Sequence 0009; Section 1.11.3)	Percentage of Total Circulating Drug-Related Material [Mean (SD)] [a]		Classification of Major vs Minor Metabolite Based on Requirement for Safety Testing [b] and Subsequent Studies		Percentage of α-HTBZ plus β-HTBZ ([α+β]-HTBZ or total active) Based on Plasma Radioactivity or Traditional Bioanalysis (Mean)		Classification of Major vs Minor Metabolites Based on Requirement for DDI Evaluation [c] and Subsequent Studies	
Test article	SD-809	TBZ	SD-809	TBZ	SD-809	TBZ	SD-809	TBZ
α-HTBZ (M6)* (active)	13.0 (4.6)	4.0 (1.4)	Major	Minor	n/a	n/a	n/a	n/a
β-HTBZ (M5) * (active)	8.3 (4.2)	1.8 (1.5)	Minor	Minor	n/a	n/a	n/a	n/a
2-methylpropanoic acid β-HTBZ (M1)	9.2 (3.6)	4.1 (2.0)	Minor; evaluated in in vitro genotoxicity studies	Minor	52 [d]	79 [d]	Major; evaluated in in vitro DDI studies (Section 2.6.4.8)	Major
Sulfate of O-desmethyl-β-HTBZ (M2)	2.5 (1.1)	6.4 (2.9)	Minor	Minor	15 [d]	126 [d]	Minor	Major
Sulfate of O-desmethyl-α-HTBZ (M3)	4.0 (1.5)	16.4 (5.6)	Minor	Major	24 [d]	310 [d]	Minor	Major
Monohydroxy tetrabenazine (M4)	12.9 (3.2)	15.6 (4.9)	Major [e]	Major	69 [d]	291 [d]	Major; to be evaluated in in vitro DDI studies	Major
9-desmethyl-β-DHTBZ **	< 10%	< 10%	Minor	Minor	14 [f]	65 [f]	Minor	Major
9-desmethyl-α-DHTBZ **	< 10%	< 10%	Minor	Minor	3 [f]	15 [f]	Minor	Minor

Abbreviations: AUC = area under concentration time curve; DDI = drug drug interaction; DPM = disintegrations per minute; h = hour; n/a = not applicable; * HTBZ = dihydrotetrabenazine; ** DHTBZ = dihydrotetrabenazine

a: Percentage plasma sample radioactivity in AUC 2-12 h plasma pools; References: SD-809-C-12, Section 16.1.13.4; Appendix 16.1.13.3, Table 9 and Table 10.

b: ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

c: Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012, draft guidance.

d: The mean DPM attributed to metabolites M1, M2, M3, and M4 expressed as a percentage of the DPM attributed to M5+M6 (total [α+β] HTBZ), calculated for each individual. Reference: calculated from SD-809-C-12, Section 16.1.13.4.

e: M4 is also a metabolite in rat.

f: The mean AUC_{tau} for the metabolites 9-desmethyl-α-DHTBZ and 9-desmethyl-β-DHTBZ at steady state expressed as the AUC_{tau} of total [α+β] HTBZ. Reference: calculated from AUS-SD-809-CTP-07, Table 14.2.5.4.

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As noted in the Memorandum, M1 has been evaluated in a panel of in vitro drug interaction studies; these data, which indicate that M1 is not expected to cause clinically relevant drug interactions, are provided in Section 2.6.4.8 in the NDA submission. As we are unable to reference the drug-interaction potential of M4 from past experience with Xenazine, we are evaluating M4 in the following in vitro studies:

- Direct and time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 in human liver microsomes
- Induction of CYP1A2, CYP2B6 and CYP3A4 mRNA levels in primary cultures of cryopreserved human hepatocytes
- Inhibition of efflux transporters P-gp (MDR1/ABCB1) in Caco-2 cells, BCRP (ABCG2) in MDCKII cells and OATP1B1 (OATP2/OATP-C/SLCO1B1), OATP1B3 (OATP8/SLCO1B3), OAT1 (SLC22A6), OAT3 (SLC22A8), or OCT2 (SLC22A2) in HEK-293 cells
- Substrate determination for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2

The probes, inhibitors, and positive controls in these studies will conform to "Drug Interaction Studies —Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012" draft guidance.

Reports summarizing the results of these studies will be submitted to the NDA no later than 01 February 2016.

Teva proposes that these in vitro studies will sufficiently characterize the drug-interaction potential of M4. Should M4 prove to be positive for drug interactions in these studies then, per the draft guidance criteria, consideration will be given to the design of appropriate in vivo drug-interaction studies.

Response to IR about plasma pooling

The Division's original Request for Information (e-mail from Stacy Metz dated 09 November 2015) is presented below in **bold**, followed by Teva's response.

Please refer to Report SD-809-C-12 (16.1.13.4 Metabolite Profiling and Identification Report – Bridging).

I. Plasma Pooling Methodology

Pooling was performed in plasma to generate an "AUC pool" for each subject across the following time points – 2, 2.5, 6, and 12 hours in the following proportions:

2 hour: 0.57 mL

2.5 hour: 0.91 mL

6 hour: 2.16 mL

12 hour: 1.36 mL

Total: 5.00 mL

Please clarify how were the time points for pooling selected? We note that the following plasma samples were collected in the mass balance study: 0 (pre-dose), 20 and 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192 and 216 hour.

Teva's Response:

In Study SD-809-C-12, multiple sets of blood samples were collected. The samples related to the question posed by FDA include:

- Blood samples for metabolite profiling and identification (20 mL), referred to in this document as the "metabolite profile samples," with the volume collected based on requirements for metabolite profiling

  As per protocol, these plasma samples were collected at 0 (pre-dose), 2, 2.5, 6, 12, 24, and 48 hours after dose administration.

- Blood samples to assess total radioactivity in blood and in plasma as part of the mass balance recovery (up to 4 mL), referred to in this document as the "mass balance recovery samples"

  These samples were collected at 0 (pre-dose), 20 and 40 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours and were specifically allocated for measurement of total radioactivity. Based on the years of experience of the vendor, the 4 mL volumes of these samples were insufficient for metabolite profiling in plasma. However, these samples were used to describe the time course of radioactivity over 120 hours and used to determine a course of action for the "metabolite profile" samples (see below).

- Blood samples for pharmacokinetic analyses (4 mL)

  These samples were collected at 0 (pre-dose), 20 and 40 minutes, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours and were specifically allocated for analysis of parent compound and metabolites for which there were validated LC/MS methods.

The vendor and sponsor reviewed the concentrations of radioactivity in the mass balance recovery samples and aligned this with the vendor's prior experience on the amount of radioactivity required in each sample for successful metabolite profiling. Based on this evaluation, the samples collected at 2, 2.5, 6, and 12 hours post dose were considered to have sufficient radioactivity for the intended chromatographic analyses. The 24-hour and 48-hour samples, which contained lower levels of radioactivity (Study SD-809-C-12 Clinical Study Report, Table 14.2.7.2.2), were omitted from the AUC pool, as they would have diluted the concentration of radioactivity in the pool, thus reducing the possibility of identifying and performing semi-quantification of identified metabolites. As a comparison, in the mass-balance and metabolite-identification study conducted with tetrabenazine in NDA 21894 (see table from the Xenazine development program, reproduced as Figure 1), metabolite identification and semi-quantification was performed on samples that were collected out to 8 hours post dose.

The semi-quantitative analyses of metabolites by radioactivity were conducted on the metabolite profile samples from 2 to 12 hours via a per-subject "AUC pool" approach (Hamilton, 1981).

Figure 1. Reproduction from Xenazine (NDA 21894) Summary Basis of Approval, Referencing: "A Phase 1 Open-Label Study to Assess th Absorption, Metabolism, and Elimination of [^{14}C]-Tetrabenazine"

Component	0.25 – 1.5 hours	2 – 3 hours	4 – 8 hours	Mean
P1	ND	ND	ND	NC
P2	ND	ND	ND	NC
P3	ND	ND	ND	NC
P4	ND	ND	ND	NC
P5	ND	ND	ND	NC
P6	ND	ND	4.10 (4.65)	NC
P7	ND	ND	ND	NC
P8	ND	ND	8.23 (9.14)	NC
P9	ND	ND	ND	NC
P10	ND	ND	ND	NC
P11	23.44 (19.67)	29.52 (20.41)	15.20 (16.90)	22.73 (17.99)
P12	ND	ND	ND	NC
P13	26.73 (19.01)	41.77 (25.68)	24.22 (20.86)	30.91 (24.92)
P14	ND	ND	ND	NC
P15	ND	ND	ND	NC
P16	49.54 (35.24)	50.11 (34.65)	19.77 (21.96)	39.81 (30.81)
P17	13.65 (9.71)	6.54 (4.52)	4.49 (4.97)	8.22 (6.40)
P18	25.73 (18.30)	16.78 (11.66)	14.05 (15.60)	18.83 (15.15)
Other	1.52 (1.08)	ND	ND	NC

Results expressed as ng equivalents/ml(Values in parentheses indicate % sample radioactivity)
ND Component not detected NC Not calculable

Source: Summary Basis of Approval for NDA 21894, Clinical Pharmacology Review, Part 3, page 111; accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021894s000TOC.cfm on 17 November 2015.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the PK bridging between SD-809(deutetrabenazine) and the reference product, Xenazine (tetrabenazine tablet), acceptable?

Yes, the PK bridging between SD-809 and Xenazine is acceptable if the recommend maximum daily dose of SD-809 is 48 mg (24 BID).

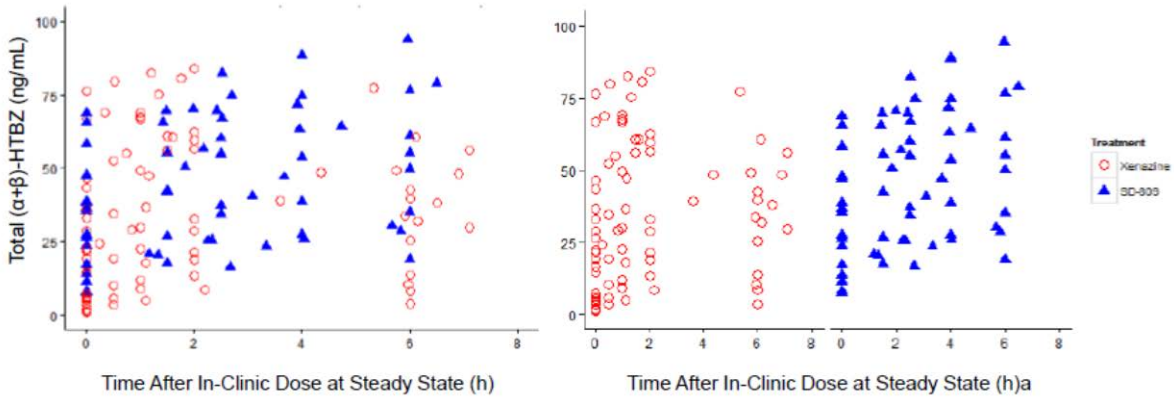
Since this NDA is a 505(b)(2) submission for SD-809 with Xenazine as the reference listed drug, PK bridging between SD-809 and Xenazine needs to be established. However, in the Phase 1stage, the Sponsor was not able to obtain US approved Xenazine tablets to conduct PK bridging studies. Instead, commercially available tetrabenazine tablets sourced from (b) (4) and unformulated tetrabenazine power in capsule were used in Phase 1 studies to evaluate the exposure to the active α-HTBZ and β-HTBZ metabolites following administration of SD-809 and tetrabenazine. Since the US approved Xenazine was not used in Phase 1 studies, data from Phase 1 studies cannot be used to establish the PK bridge between SD809 and its reference drug, Xenazine.

Xenazine was only available as a baseline treatment in the Switch Cohort of Study SD-809-C-16, which is an open-label, long-term safety study of SD-809 in subjects with chorea associated with Huntington's disease. There were two cohorts in Study SD-809-C-16, the Rollover Cohort and the Switch Cohort. The Rollover Cohort had successfully completed Study SD-809-C-15, including a 1-week washout; the Switch Cohort switched overnight from stable dosing (≥8 weeks) with Xenazine to SD-809. The objective of the Switch Cohort was to evaluate the safety and tolerability of switching subjects from Xenazine to SD-809 and to evaluate the pharmacokinetics of Xenazine, SD-809, and their respective α-HTBZ and β-HTBZ metabolites in subjects switching from Xenazine to SD-809. Patients in the Switch cohort (N=37) underwent PK sampling at Baseline (Day 0) while on stable doses of Xenazine. Patients were then switched overnight to an AUC-matched dose of SD-809 and were evaluated in the clinic at Week 1 to assess chorea control; dose adjustment was then permitted to optimize chorea control after week 1. Patients underwent PK sampling after approximately 8 weeks of repeated-dose administration with SD-809. For both treatments, stable doses were administered for at least one week prior to PK sampling. Rich PK data were collected in 12 subjects (5 samples/subject over 6 hours post-dose) and sparse PK data were collected in 24 subjects (2 samples/subject). (The initial switch was a simple 2:1 conversion based on the stable daily dose of Xenazine. This dose conversion ratio was derived from Phase 1 PK studies including study SD-809-CTP-07 and supported by population PK modeling and simulation analysis in the Phase 1 stage. However, the majority of subjects in the Switch

study experienced dose increase after week 1, suggesting that the 2:1 conversion ratio might not be optimal.)

To assess the overall comparability of exposure observed in the Switch Cohort, non-normalized plasma concentrations of total (α+β)-HTBZ observed over approximately 6 hours after administration of Xenazine (Day 0) or SD-809 (Week 8) at steady state were presented below (Figure 1), allowing comparison of Xenazine with SD-809.

Figure 1 Non-normalized total (α+β)-HTBZ plasma concentrations at Baseline (Xenazine) and at Week 8 (SD-809)



Source: Information amendment clinical 0047 page 7

However, the SD-809 dose for the same subject could be different from that at Week 0 due to permitted dose adjustment to optimize chorea control after Week 1. Therefore, to appropriately compare exposure following administration of Xenazine and SD-809 over the intended dose range, concentrations and parameters were normalized to the maximum single dose for each treatment, i.e. 37.5 mg for Xenazine and 24 mg for SD-809. Dose–normalized plasma concentrations of total (α+β)-HTBZ in the Switch Cohort following administration of Xenazine and SD-809 appears to be in similar range, as shown in Figure 2. In addition, dose-normalized observed Cmax were compared between Xenazine and SD-809 in the rich sampling subgroup in the Switch Cohort. The result shows that Cmax of SD-809 at highest proposed dose appears to be covered by Cmax of Xenazine at highest approved dose, as shown in Table 1. Therefore, the PK bridging between SD-809 and Xenazine is acceptable if the highest recommend daily dose of SD-809 is 48 mg (24 mg BID).

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Figure 2 Dose-normalized Plasma Concentrations of Total (α+β)-HTBZ in the Switch Cohort of Study SD-809-C-16 (dose normalized to the maximum single dose for each treatment)

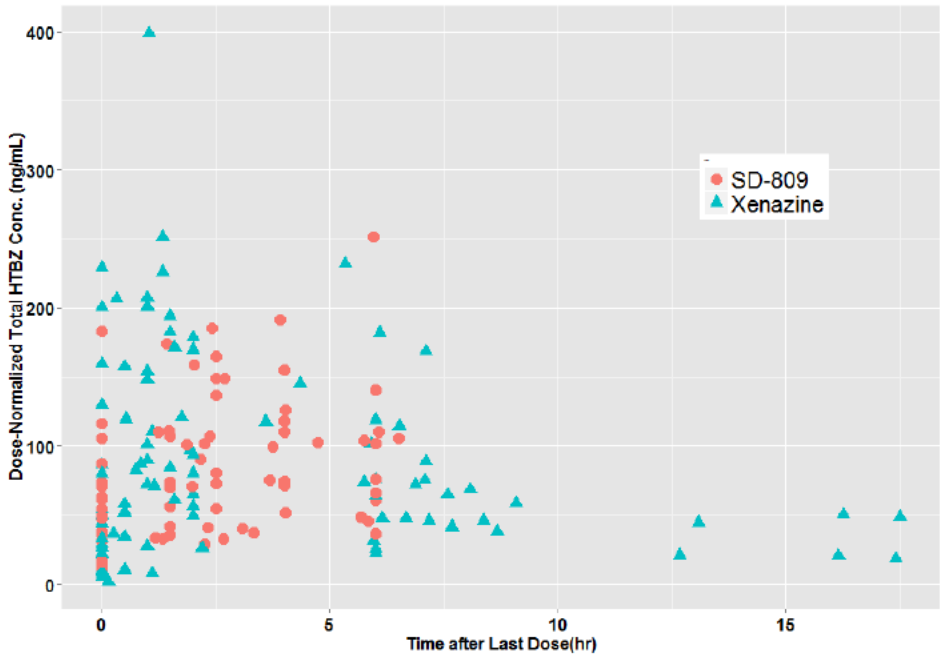

Table 1 Cmax Comparison between Xenazine and SD-809 in SWITCH Cohort (Dose-normalized)

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

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

1.1.2 Should the dose of SD-809 be adjusted in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809?

Yes, the SD-809 dose should be adjusted in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809. A maximum dose of 18 mg BID (36 mg daily) is recommended.

Results from study SD-809-C-08, a drug-drug interaction study with a potent CYP2D6 inhibitor paroxetine (N=24), showed that there was a 3-fold increase in mean AUC0–∞ for total (α+β)-HTBZ, from 624 ng hr/mL on Day 1 (SD-809 alone) to 1901 ng·hr/mL on Day 11 (SD-809 + paroxetine). And slower elimination was observed with concomitant administration of paroxetine (mean t1/2, 9.75 hours on Day 1 and 16.0 hours on Day 11).

To further evaluate the maximum daily dose in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809, predicted mean steady state PK profiles of total (α+β)-HTBZ at different doses of SD-809 with or without strong CYP2D6 inhibitor paroxetine were derived through nonparametric superposition using data from the dedicated DDI study (SD-809-C-08). Although the results show that total (α+β)-HTBZ exposure at 18 mg BID SD-809 dose in subjects with impaired CYP2D6 function is higher than that at 24 mg BID dose (the proposed maximum SD-809 dose for patients without impaired CYP2D6 function or CYP2D6 inhibition) in subjects with normal CYP2D6 function, such total (α+β)-HTBZ exposure is similar or lower than the total (α+β)-HTBZ exposure at approved maximum Xenazine dose (25 mg BID) in CYP2D6 PM subjects and subjects on concomitant strong CYP2D6 inhibitors. Therefore, SD-809 dose adjustment is bridged to the Xenazine dosing recommendations in subjects with impaired CYP2D6 function. The 18 mg BID SD-809 dose is considered to be acceptable in subjects with impaired CYP2D6 function. The predicted mean steady state PK profiles of total (α+β)-HTBZ are shown in Figure 3.

Moreover, in the pivotal efficacy study SD-809-C-15, maximum dose levels for subjects on strong CYP2D6 inhibitors were restricted to 18 BID, instead of 24 mg BID for subjects with normal CYP2D6 function. Table 2 shows the SD-809 dose levels for CYP2D6 PMs and subjects on strong 2D6 Inhibitors in Study SD-809-C-15.

Figure 3 Predicted Mean Steady-state PK Profiles of Total (α+β) HTBZ at Different Scenarios with or without Strong 2D6 Inhibitor Paroxetine

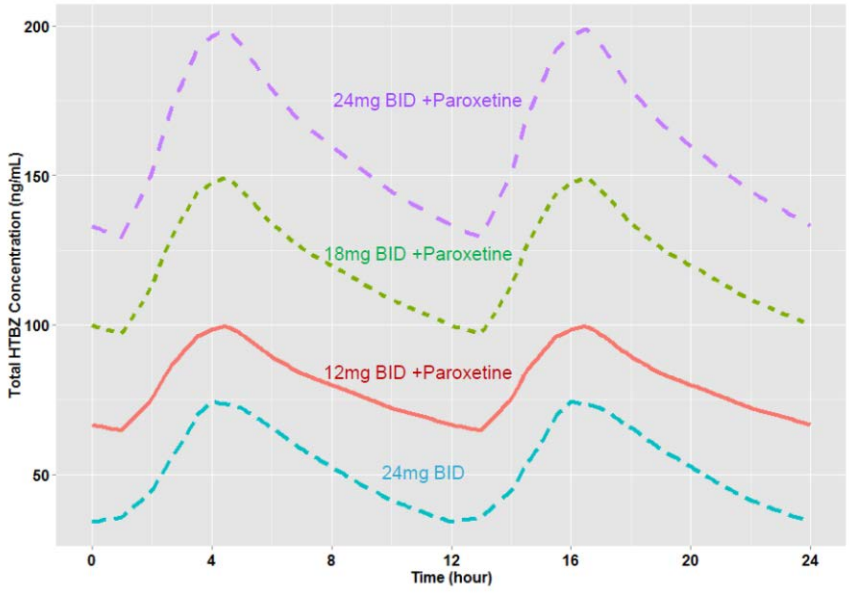

Table 2 SD-809 Dose Levels for 2D6 PMs and Subjects on Strong 2D6 Inhibitors in the Pivotal Efficacy Study (SD-809-C-15)

Patient ID	2D6 Status	Highest Dose	Maintenance Dose
1	Poor metabolizer	18 mg BID	15 mg BID
30	Poor metabolizer	18 mg BID	15 mg BID
39	Poor metabolizer	21 mg BID	21 mg BID
8	Strong inhibitor	18 mg BID	18 mg BID
19	Strong inhibitor	18 mg BID	18 mg BID
20	Strong inhibitor	18 mg BID	15 mg BID
22	Strong inhibitor	18 mg BID	18 mg BID
24	Strong inhibitor	18 mg BID	18 mg BID
25	Strong inhibitor	15 mg BID	15 mg BID

Therefore, based on the discussion above, dose adjustment by limiting the highest SD-809 dose to 18 mg BID (36 mg daily) is recommended for patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809.

1.2 Recommendations

The maximum dose of18 mg BID (36 mg daily) is recommended in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809.

1.3 Label Statements

The pharmacometrics reviewer recommends restricting the daily dose of SD-809 to 36 mg (18 mg BID) in patients taking strong CYP2D6 inhibitors or who are CYP2D6 poor metabolizers.

The pharmacometrics reviewer recommends presenting the dedicated DDI study results, *i.e.* 3-fold increase in total (α+β)-HTBZ exposures (1.9-folder and 6.5-fold increase for α-

HTBZ and β-HTBZ, respectively), rather than the popPK analysis results, *i.e.* 2-fold increase, for the effect of impaired CYP2D6 function on the systemic exposure to α-HTBZ and β-HTBZ of SD-809.

The pharmacometrics reviewer is OK with the sponsor's values for CL and V in the label.

2 PERTINENT REGULATORY BACKGROUND

SD-809 (deutetrabenazine) is developed as a treatment for chorea associated with Huntington's disease. SD-809 is a selectively deuterated form of tetrabenazine, which is a vesicular monoamine transporter (VMAT)-2 inhibitor approved in the US in August 2008 as Xenazine for the treatment of chorea associated with Huntington's disease (NDA 21894). (b) (4) (b) (4) (b) (4). SD-809 has been classified as a new molecular entity. This NDA is a 505(b)(2) NDA submission for SD-809 with Xenazine as the reference listed drug.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Summary of study report SD-809 CLN-078

3.1.1 Population Pharmacokinetic Modeling

A population pharmacokinetic analysis was performed to describe the disposition of α-HTBZ and β-HTBZ following dosing of SD-809. Specifically, the model was used to derive PK parameters as well as the peak (Cmax) and overall exposure (AUC) at steady-state for individual α-HTBZ and β-HTBZ as well as total (α+ β) -HTBZ in HD subjects administrated SD-809.

3.1.2 Data

PK concentration-time data collected in a Phase 3 study SD-809-C-15 [First-HD] was used for the population pharmacokinetic analysis. The dataset included 45 subjects with chorea associated with HD who received from 6 to 24 mg BID twice-daily dosing of SD-809. The study design is presented in Table 3. A maximum of 4 PK samples, 2 samples per visit (Weeks 9 and 12), were available per subject. The numbers of plasma α-HTBZ and β-HTBZ concentrations available for the population PK analysis are presented in Table 4.

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Table 3 Description of SD-809-C-15 Study Design

Protocol Number	Study Description	Dose regimens	Expected Number of Subjects	Planned PK Blood Sampling
SD-809-C-15 [First-HD]	A randomized, double blind, placebo-controlled study of SD-809 for the treatment of chorea associated with HD	• Ascending SD-809 doses: 6 mg QD and from 6 mg BID up to 24 mg BID or 18 mg BID if subject is receiving a potent CYP2D6 inhibitor • Placebo	90 adult subjects with HD (45 for SD-809 and 45 for placebo)	Week 9: • Sample 1 upon arrival at clinic • Sample 2 at least 2 hours after Sample 1 Week 12: • Sample 1 upon arrival in clinic • Sample 2 at least 3 hours after Sample 1

CYP2D6=Cytochrome P450 2D6 enzyme; BID=Twice daily dose; HD=Huntington's disease; QD=Once daily dose

Source: Study report SD-809-CLN-078 page 10

Table 4 Summary of α-HTBZ and β-HTBZ Samples

Analyte	Week	Nominal Sample	Number (% of Total)			Total Excluded
			Non BLQ	BLQ	Included	
α-HTBZ	Week 9	Sample 1	43 (100)	0 (0.0)	43 (100)	0 (0.0)
		Sample 2	42 (100)	0 (0.0)	42 (100)	0 (0.0)
	Week 12	Sample 1	42 (100)	0 (0.0)	42 (100)	0 (0.0)
		Sample 2	41 (100)	0 (0.0)	41 (100)	0 (0.0)
β-HTBZ	Week 9	Sample 1	42 (97.7)	1 (2.33)	42 (97.7)	1 (2.33)
		Sample 2	41 (97.6)	1 (2.38)	41 (97.6)	1 (2.38)
	Week 12	Sample 1	42 (100)	0 (0.0)	42 (100)	0 (0.0)
		Sample 2	41 (100)	0 (0.0)	41 (100)	0 (0.0)

BLQ=Below the limit of quantification; HTBZ=Dihydrotetrabenazine.
Note: Samples 1 were collected upon arrival at clinic and samples 2 were collected at least 2 hours after samples 1 at Week 9 and at least 3 hours after sample 1 at Week 12.

Source: Study report SD-809-CLN-078 page 19

3.1.3 Structural Model

The structure of the PK models describing the kinetics of α-HTBZ and β-HTBZ is illustrated in Figure 4. For both α-HTBZ and β-HTBZ, a two-compartment model with first order elimination and parallel first order and zero order absorption resulted in the best fit.

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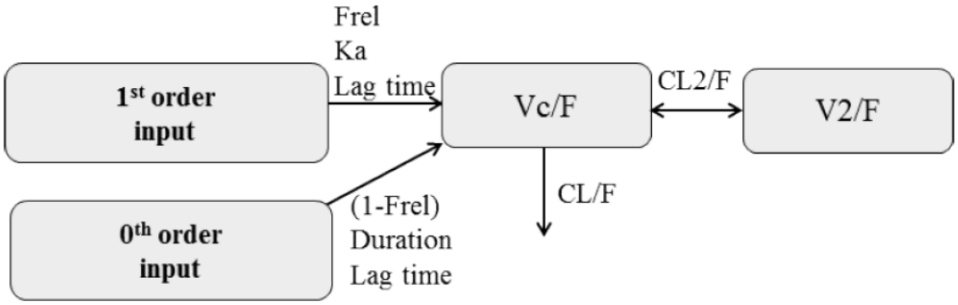
Figure 4 Schematic Representation of Population PK Models for α-HTBZ and β-HTBZ



CL/F=Apparent central clearance; CL2/F=Apparent inter-compartmental clearance; Frel=Relative fraction of input; HTBZ=Dihydrotetrabenazine; Ka=First order rate constant of input; Vc/F=Apparent central volume of distribution; V2/F=Apparent peripheral volume of distribution

Source: Study report SD-809-CLN-078 page 13

3.1.4 Covariate Model

Covariates were tested on clearance and volume of distribution parameters. Intrinsic covariates included age, sex, race, body weight, CYP2D6 phenotype, CRCL, and liver function test (BIL, PT). Extrinsic covariates included daily dose levels and CYP2D6 inhibitors (presence or absence of strong inhibitor). The final model included body weight as a covariate on clearance and volume of distribution terms, as well as impaired CYP2D6 function as a covariate on clearance.

3.1.5 Final Model Results

Parameter estimates of the final models are provided in Table 5.Due to the sparseness of data in study SD-809-C-15, structural PK models of α-HTBZ and β-HTBZ previously estimated from Phase 1 data were used to model concentration-time profiles. Absorption and distribution parameters were fixed based on a population PK model developed in the healthy volunteers using Phase 1 data form studies AUS-SD-809-CTP-07 Part 2, SD-809-C-08 and SD-809-C-11 CL/F and Vc/F as well as the corresponding random effects and covariate effects were estimated in the current model.

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Table 5 Final Population PK Parameters of α-HTBZ and β-HTBZ in Study SD-809-C-15

PK Parameters	α-HTBZ	β-HTBZ
Zero-Order Absorption		
Relative Fraction	0.780 (FIX)	0.701 (FIX)
Duration (h)	1.88 (FIX)	1.78 (FIX)
Lag (h)	1.16 (FIX)	1.69 (FIX)
First-Order Absorption		
Ka (h^{-1})	0.325 (FIX)	0.326 (FIX)
Lag (h)	0.610 (FIX)	0.794 (FIX)
CL/F (L/h) Reference population: functional CYP2D6	$46.1 \times (WT/70)^{0.359}$ × 0.776 for Impaired CYP2D6	$74.3 \times (WT/70)^{0.188}$ × 0.282 for Impaired CYP2D6
Vc/F (L)	464 (FIX) $\times (WT/70)^{1.02}$	681 (FIX) $\times (WT/70)^{1.10}$
CL2/F (L/F)	47.3 (FIX)	48.9 (FIX)
V2/F (L)	248 (FIX)	240 (FIX)
Between Subject-Variability	**α-HTBZ**	**β-HTBZ**
Zero-Order Absorption		
Duration (h)	34.2% (FIX)	50.7% (FIX)
Lag (h)	55.9% (FIX)	36.7% (FIX)
First-Order Absorption		
Ka (h-1)	89.6% (FIX)	71.6% (FIX)
Lag (h)	37.9% (FIX)	35.6% (FIX)
CL/F (L/h)	38.2%	67.3%
Vc/F (L)	12.8%	23.9%
Inter-Occasion Variability	**α-HTBZ**	**β-HTBZ**
CL/F	15.0%	8.91%
Vc/F	49.0%	26.2%
Error Model	**α-HTBZ**	**β-HTBZ**
Proportional Error (%)	17.4	18.4
Additional Error (ng/mL)	0.072	0.558

FIX=parameter values fixed from Phase 1 model[3]
CL/F=Apparent clearance; CL2/F=Apparent inter-compartmental clearance; CYP2D6=Cytochrome P450 2D6 enzyme; HTBZ=Dihydrotetrabenazine; Ka=First order rate constant of input; Lag=Lag time of input; PK=Pharmacokinetic; Vc/F=Apparent central volume of distribution; V2/F=Apparent peripheral volume of distribution; WT=Body weight (kg)

Source: Study report SD-809-CLN-078 page 27

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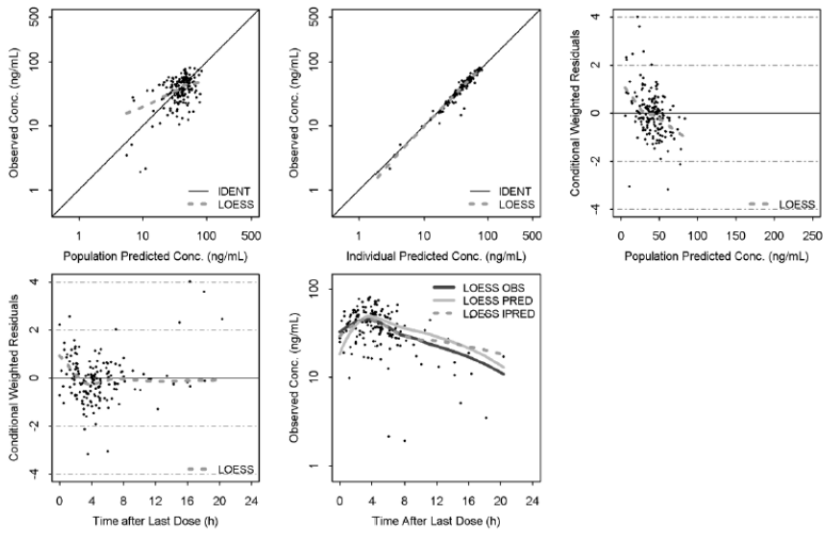
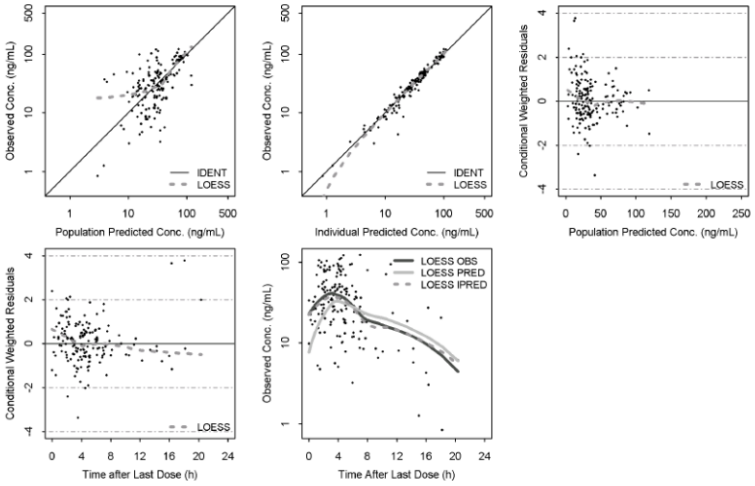
Diagnostic plots for the final model of α-HTBZ and β-HTBZ are presented in Figure 5 and Figure 6, respectively. Figure 5 Diagnostic Plots for the Final Population PK Model of α-HTBZ



Conc= Concentration; HTBZ= Dihydrotetrabenazine; IDENT= Identity line; IPRED= Individual prediction; LOESS= Locally weighted scatterplot smoothing; OBS= Observed; PRED= Population prediction

Source: Study report SD-809-CLN-078 page 63

Figure 6 Diagnostic Plots for the Final Population PK Model of β-HTBZ

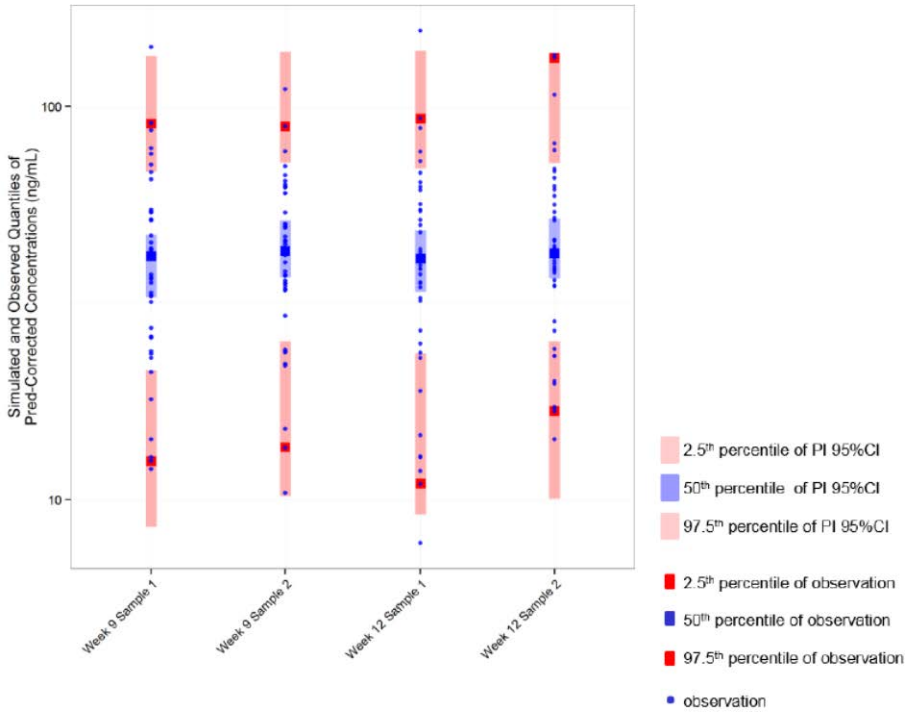


Conc= Concentration; HTBZ= Dihydrotetrabenazine; IDENT= Identity line; IPRED= Individual prediction; LOESS= Locally weighted scatterplot smoothing; OBS= Observed; PRED= Population prediction

Source: Study report SD-809-CLN-078 page 64

The prediction-corrected visual predictive check shows that the model was reasonably able to reproduce the observed data (Figure 7, Figure 8)

Figure 7 Prediction-Corrected Visual Predictive Checks of the Final Population PK Model of α-HTBZ



CI= Confidence interval; HTBZ= Dihydrotetrabenazine; PI= Percentile interval; Pred= Population prediction

Source: Study report SD-809-CLN-078 page 75

Figure 8 Prediction-Corrected Visual Predictive Checks of the Final Population PK Model of β-

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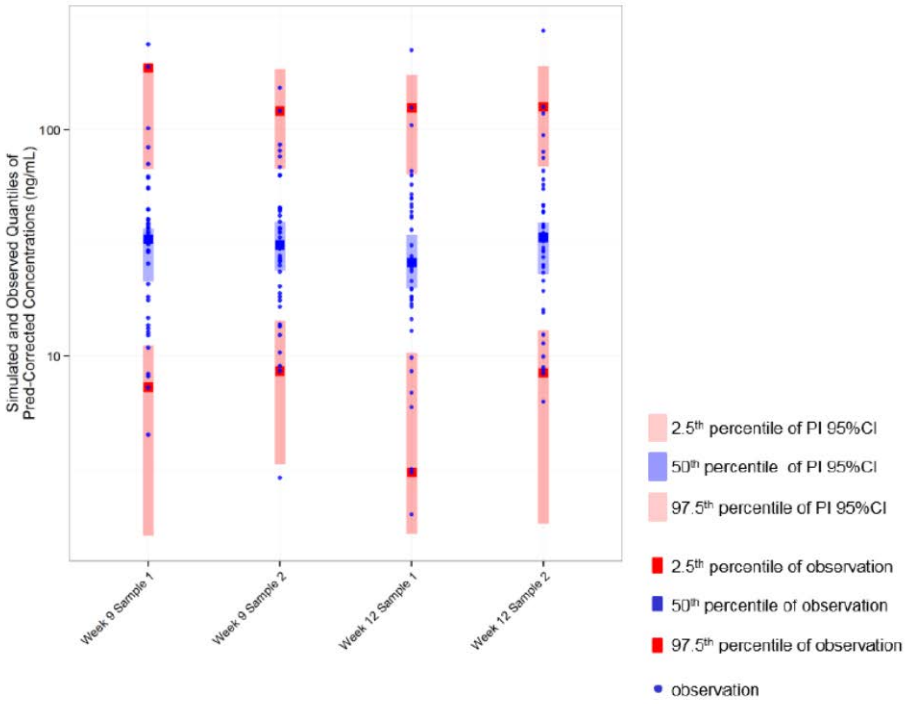
HTBZ



CI= Confidence interval; HTBZ= Dihydrotetrabenazine; PI= Percentile interval; Pred= Population prediction

Source: Study report SD-809-CLN-078 page 77

Bootstrap analysis results are shown in Table 6 and Table 7 for α-HTBZ and β –HTBZ, respectively, indicating acceptable parameter estimation.

Table 6 Bootstrap Values of the Full Population PK Model of α-HTBZ

PK Parameters	Origin	Median	Difference (%)	95% Confidence Interval
CL/F (L/h)	45.9	47.6	3.85%	[41.6, 55.3]
Effect of CYP2D6 inhibitors on CL/F Reference: Absence	0.775	0.777	0.26%	[0.651, 0.881]
Effect of body weight on Vc/F Reference: $(WT/70)^{effect}$	1.01	1.02	0.56%	[0.432, 1.67]
Effect of body weight on CL/F Reference: $(WT/70)^{effect}$	0.356	0.356	-0.06%	[-0.0720, 0.432]
BSV CL/F	37.9	37.8	-0.08%	[27.4, 47.3]
BSV Vc/F	12.6	13.0	3.28%	[11.8, 31.8]
IOV CL/F	14.9	14.7	-1.09%	[8.94, 17.8]
IOV Vc/F	48.1	48.7	1.25%	[23.3, 72.5]
Additive Error	0.0745	0.0729	-2.17%	[0.0445, 0.104]
Proportional Error	18.7	17.9	-4.35%	[9.57, 25.4]

BSV= Between subject variability; CL/F= Apparent clearance; CYP2D6= Cytochrome P450 2D6 enzyme; HTBZ = Dihydrotetrabenazine; IOV= Inter-occasion variability; PK= Pharmacokinetic; Vc/F= Apparent central volume of distribution; WT= Body weight (kg)
Note: Bootstrap results are based on 1000 runs stratified by presence or absence of CYP2D6 inhibitors.

Source: Study report SD-809-CLN-078 page 50

Table 7 Bootstrap Values of the Full Population PK Model of β -HTBZ

PK Parameters	Origin	Median	Difference (%)	95% Confidence Interval
CL/F (L/h)	75.5	70.7	-6.29%	[56.8, 87.4]
Effect of CYP2D6 inhibitors on CL/F Reference: Absence	0.294	0.296	0.68%	[0.227, 0.473]
Effect of CYP2D6 Phenotype on CL/F Reference: Non poor metabolizer	0.50	0.496	-0.92%	[0.348, 0.674]
Effect of body weight on Vc/F Reference: $(WT/70)^{effect}$	1.66	1.59	-4.32%	[0.230, 2.08]
Effect of body weight on CL/F Reference: $(WT/70)^{effect}$	0.417	0.406	-2.66%	[0.0977, 0.555]
BSV CL/F	71.5	69.1	-3.38%	[50.5, 85.4]
BSV Vc/F	27.2	26.1	-4.28%	[12.5, 32.1]
IOV CL/F	11.5	10.9	-5.41%	[6.61, 14.4]
IOV Vc/F	35.7	34.0	-4.81%	[20.4, 41.1]
Additive Error	0.541	0.556	2.69%	[0.391, 2.64]
Proportional Error	17.9	17.8	-0.41%	[8.34, 24.8]

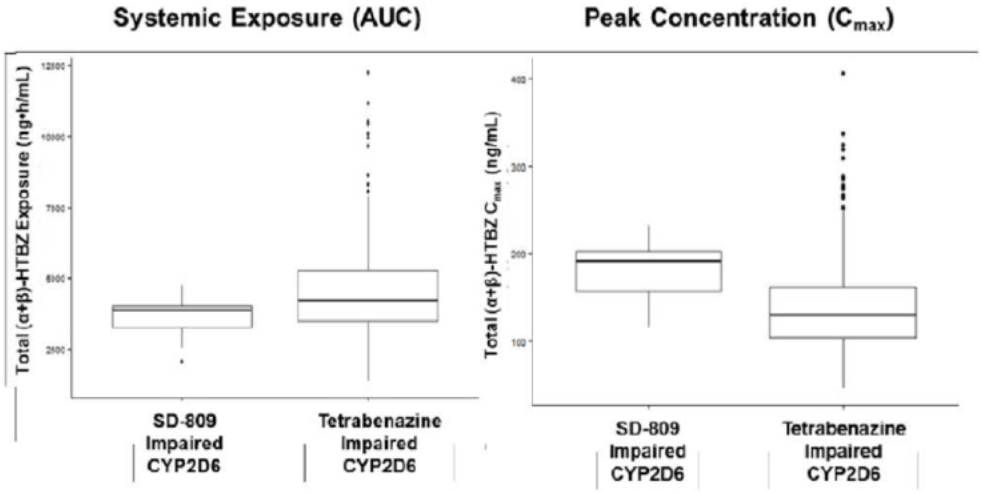
BSV= Between subject variability; CL/F= Apparent clearance; CYP2D6= Cytochrome P450 2D6 enzyme; HTBZ = Dihydrotetrabenazine; IOV= Inter-occasion variability; PK= Pharmacokinetic; Vc/F= Apparent central volume of distribution; WT= Body weight (kg)
Note: Bootstrap results are based on 1000 runs stratified by presence or absence of CYP2D6 inhibitors.

Source: Study report SD-809-CLN-078 page 51

Reviewer's comments: The goodness of fit and VPC show that the final models are able to reasonably describe the PK profiles of α-HTBZ and β-HTBZ in study SD-809-C-15. Bootstrap analysis results suggest acceptable parameter estimation from the final models. Due to the sparseness of data in study SD-809-C-15, absorption and distribution parameters were fixed based on a population PK model developed in the healthy volunteers using Phase 1 data, which is considered to be acceptable because the PK of SD-809 is similar between healthy subjects and HD patients. The modeling results show that impairment of CYP2D6 is expected to decrease the typical CL/F of α-HTBZ andβ-HTBZ by approximately 22% and 72%, respectively. The median Cmax and AUC0-24 values of total (α+β)-HTBZ in a subject with impaired CYP2D6 is expected to be approximately 2-fold higher than that expected in a subject with functional CYP2D6. However, the dedicated DDI study SD-809-C-08 shows that systemic exposure (AUCinf) of total (α+β)-HTBZ was 3-fold higher in the presence of paroxetine than that in the absence of paroxetine (1.9-folder higher for α-HTBZ and 6.5-fold higher for β-HTBZ, respectively). The pharmacometrics reviewer recommends reporting the dedicated DDI study results rather than the popPK analysis results regarding the CYP2D6 impairment effect on exposure based on the following considerations. The popPK was not pre-specified to evaluate the effect of impaired CYP2D6 function on SD-809 PK. Detailed information on the dose given, time of administration, and time of discontinuation for the co-administered strong CYP2D6 inhibitors is not available. .Moreover, the sample size of subject with impaired CYP2D6 function in the popPK analysi is relatively small (N=9; 3 CYP2D6 poor metabolizers and 7 subjects on strong CYP2D6 inhibitors including paroxetine, bupropion, and fluoxetine; with 1 subject who is both CYP2D6 PM and also on strong CYP2D6 inhibitor) and only sparse PK data is available from these 9 subjects (4 samples per subject).

(b) (4)

Figure 9 Total (α+β)-HTBZ AUC0-24 and Cmax in CYP2D6-Impaired Subjects: Simulations Following 25 mg BID Tetrabenazine and 24 mg BID SD-809 Dosing



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

Source: Summary of Clinical Pharmacology page 75

Reviewer's comments: Although in subjects with impaired CYP2D6 function, SD-809 at 24 mg BID is predicted to yield median AUC0-24 values that fall within the exposure range of tetrabenazine at 25 mg BID dose in subjects with impaired CYP2D6 function, the predicted median Cmax values at 24 mg BID SD-809 dose in subjects with impaired CYPD2D6 function are higher than the median and even 75% percentile of the predicted Cmax values at 25 mg BID tetrabenazine dose in subjects with impaired CYPD2D6 function, which raises the concern that the higher Cmax values may increase of the risk of AEs, especially QT prolongation given the positive exposure-QT prolongation relationship. Moreover, in the pivotal efficacy study SD-809-C-15, the SD-809 dose was adjusted in subjects on strong CYP2D6 inhibitors (maximum dose levels for subjects on strong CYP2D6 inhibitors were restricted to 18 BID, instead of 24 mg BID for subjects with normal CYP2D6 function). (b) (4)

(b) (4).

4 REVIEWER'S ANALYSIS

4.1 Introduction

The PM reviewer conducted analysis to evaluate the maximum daily dose in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809. Specifically, mean steady state PK profiles of total (α+β)-HTBZ at different doses of SD-809 with or without strong CYP2D6 inhibitor paroxetine were predicted through nonparametric superposition using data from the dedicated DDI study.

4.2 Objectives

The objective of the reviewer's analysis is to evaluate the impact of impaired CYP2D6 function on the PK profiles of total (α+β)-HTBZ and to facilitate the dose recommendation for subjects with impaired CYP2D6 function.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 8 Analysis Data Sets.

Table 8 Analysis Data Sets

Study Number	Name	Link to Sharedrive
SD-809-C-08	Study_c_08_PC.csv	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Deutetrabenzine_NDA208082_XW\PPK Analyses\Study C-08

4.3.2 Software

Phoenix 6.4 (Certara) andR 3.0.2 (R Foundation for Statistical Computing) were used for the analysis.

4.3.3 Models

Nonparametric superposition using data from the dedicated DDI study (SD-809-C-08) was performed to derive the predicted mean steady state PK profiles of total (α+β)-HTBZ at different doses of SD-809 with or without strong CYP2D6 inhibitor paroxetine. No model was used and no assumption was made.

4.3.4 Results

See Section 1 (Summary of Findings) of this report.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
superposition.csv	Simulated PK profile of total (α+β)-HTBZ in	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Deutetrabenzine_NDA208082_XW\FDA Reviews\Mid cycle\CYP2D6

	patients with and without impaired 2D6 function	

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/s/

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