

Supplemental Materials

Table S1. Pharmacokinetic parameters for deutetrabenazine and tetrabenazine and their active metabolites in Study AUS-SD-809-CTP-06 (secondary pharmacokinetic analysis including all evaluable subjects).

All Evaluable Subjects (n = 19)						
Analyte Name	Parameter Mean (%CV)	Deutetrabenazine (n = 19)	Tetrabenazine (n = 19)	Ratio of LS Means (%)	Lower 95% CL (%)	Upper 95% CL (%)
α -HTBZ	C_{max} (ng/mL)	46.1 (30.4)	41.2 (36.0)	113.7	100.0	129.3
	AUC_{0-t} (h*ng/mL)	362.0 (40.1)	161.9 (60.5)	214.8	195.1	236.7
	AUC_{0-inf} (h*ng/mL)	373 (39.3)	189 (59.2)	213.6	194.0	235.0
	$t_{1/2}$ (h)	8.97 (34.7)	5.47 (51.4)	174.7	156.5	195.0
β -HTBZ	C_{max} (ng/mL)	29.6 (49.4)	20.5 (51.5)	145.8	126.2	168.5
	AUC_{0-t} (h*ng/mL)	164.3 (94.7)	70.7 (101.3)	240.1	219.9	262.2
	AUC_{0-inf} (h*ng/mL)	171 (94.0)	74.0 (99.5)	235.8	216.7	256.5
	$t_{1/2}$ (h)	5.00 (79.7)	2.95 (57.2)	153.0	138.3	169.3
$(\alpha+\beta)$ -HTBZ	C_{max} (ng/mL)	74.6 (37.1)	61.6 (38.2)	121.7	106.3	139.2
	AUC_{0-t} (h*ng/mL)	529.5 (53.9)	254.7 (70.7)	222.5	206.0	240.3
	AUC_{0-inf} (h*ng/mL)	542 (53.8)	261 (69.6)	222.2	205.9	239.7
	$t_{1/2}$ (h)	8.62 (38.2)	4.82 (50.8)	188.0	167.4	211.1

Table S2. AUC_{0-t} values for inactive and active metabolites in Study AUS-SD-809-CTP-06

		Inactive metabolites				Total ODM	Active metabolites	Ratio ^a
		9-0-desmethyl- α -HTBZ	10-0-desmethyl- α -HTBZ	9-0-desmethyl- β -HTBZ	10-0-desmethyl- β -HTBZ		Total (α + β)HTBZ	
Deutetrabenazine-treated Subjects	N	14	14	14	14	14	14	14
	Mean	21.00	0	92.40	0.68	114.10	443.01	0.29
	CV (%)	37	0	30	111	29	49	34
Tetrabenazine-treated Subjects	N	14	14	14	14	14	14	14
	Mean	42.50	0	205	2.97	250.15	195.55	1.50
	CV (%)	47	0	33	46	34	55	39

^aRatio of inactive to active metabolites

Table S3. Geometric mean values (Geometric CV%) of pharmacokinetic parameters for deuterated and non-deuterated total ($\alpha + \beta$), α and β dihydrotetrabenazine metabolites and downstream O-desmethyl dihydrometabolites from Study SD-809 C12

PK Parameter ^a	Dihydrotetrabenazine Analytes			
	d6- α -HTBZ (n = 6)	α -HTBZ (n = 6)	d6- β -HTBZ (n = 6)	β -HTBZ (n = 6)
T _{lag} (h) ^b	0.33 (0.00-0.33)	0.33 (0.00-0.67)	0.33 (0.33-0.67)	0.50 (0.33-1.00)
T _{max} (h) ^b	1.50 (0.67-4.00)	1.50 (0.67-3.00)	1.50 (1.00-4.00)	1.50 (0.67-2.50)
C _{max} (ng/mL)	27.5 (26)	17.6 (52)	16.8 (49)	6.62 (77)
AUC _{0-t} (ng*h/mL)	454 (45)	109 (28)	177 (110)	24.2 (50)
t _{1/2} (h)	12.2 (28) [n = 5]	5.68 (44) [n = 4]	9.2 (50)	3.2 (16) [n = 2]
MRT _{0-t} (h)	17.4 (38)	7.14 (46)	10.4 (47)	3.69 (32)
O-Desmethyl Dihydrometabolites Analytes				
PK Parameter ^a	d3-9-O-desmethyl- α -HTBZ (n = 6)	9-O-desmethyl- α -HTBZ(n = 6)	d3-9-O-desmethyl- β -HTBZ (n = 6)	9-O-desmethyl- β -HTBZ (n = 6)
T _{lag} (h) ^b	1.25 (0.33-4.02)	0.50 (0.33-1.50)	0.84 (0.33-1.50)	0.50 (0.33-1.50)
T _{max} (h) ^b	5.00 (1.00-12.02)	2.50 (1.00-6.00)	7.00 (1.00-18.00)	2.25 (1.00-8.00)
C _{max} (ng/mL)	0.85 (17)	2.73 (45)	2.48 (20)	8.03 (52)
AUC _{0-t} (ng*h/mL)	12.6 (29)	32.5 (33)	83.1 (16)	160 (16)
MRT _{0-t} (h)	10.5 (16)	9.77 (23)	22.7 (23)	20.3 (35)

^aNon-radioactive bioanalytical assay results; ^bmedian (range)

Figure S1. AUC_{0-inf} and C_{max} following single dose administration of tetrabenazine (25 mg) and deutetrabenazine (25 mg) (all evaluable subjects, n = 19)

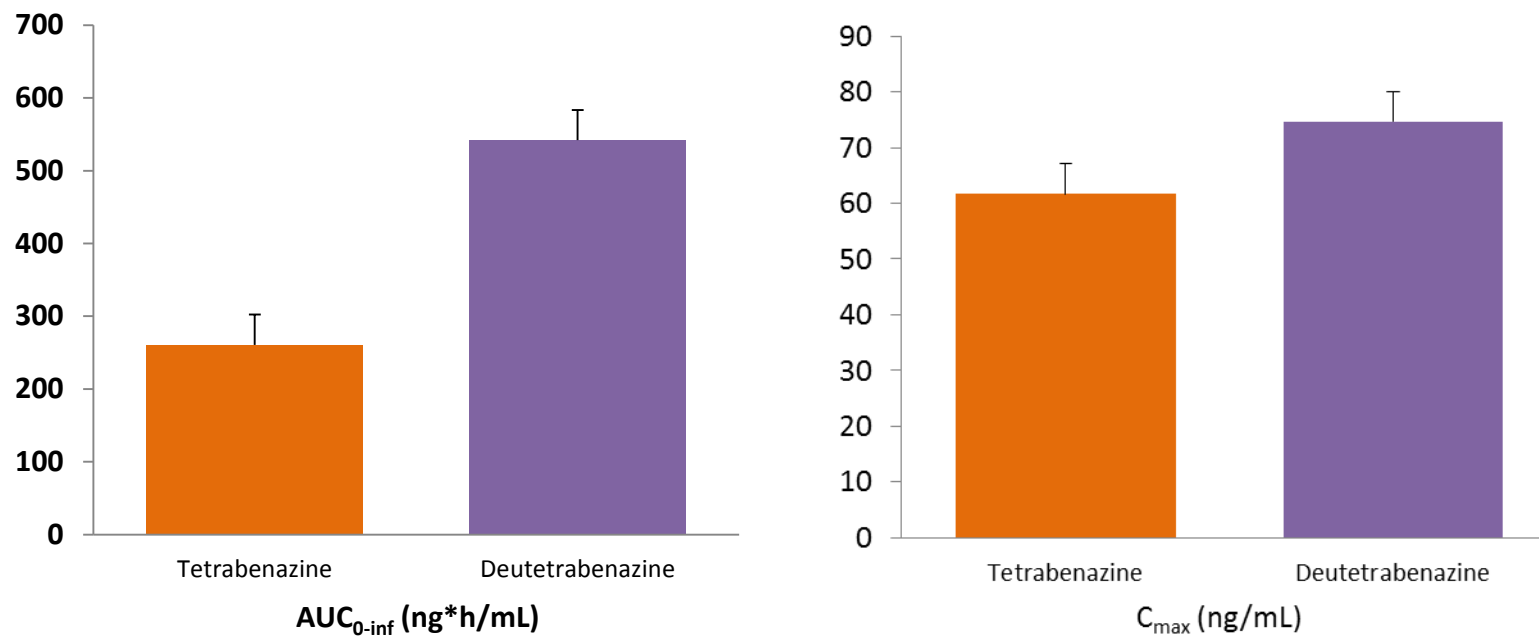


Figure S2. Radioactive chromatograms

Following administration of either [14C]-deutetrabenzazine or [14C]-tetrabenzazine, six metabolites were observed in the plasma samples analysed, each accounting for at least 10% of the sample radioactivity in at least one individual, or in the pooled samples during the course of the metabolite profiling analyses.

Figure S2A. Radiochromatogram of an AUC pooled plasma samples from subjects treated with [14C]-deutetrabenzazine

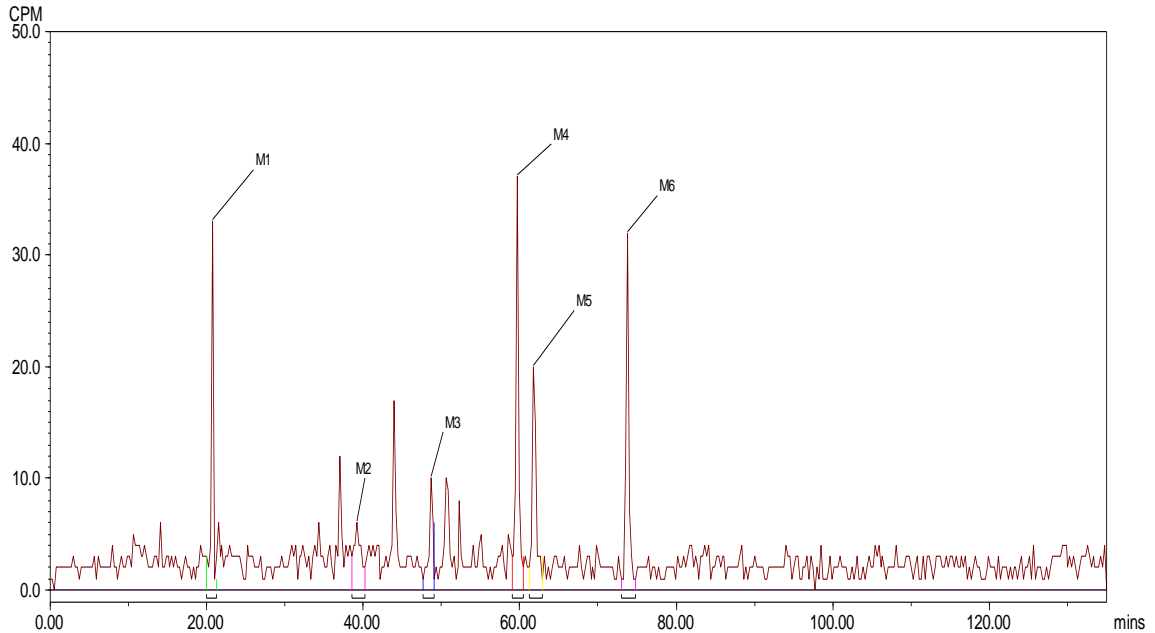
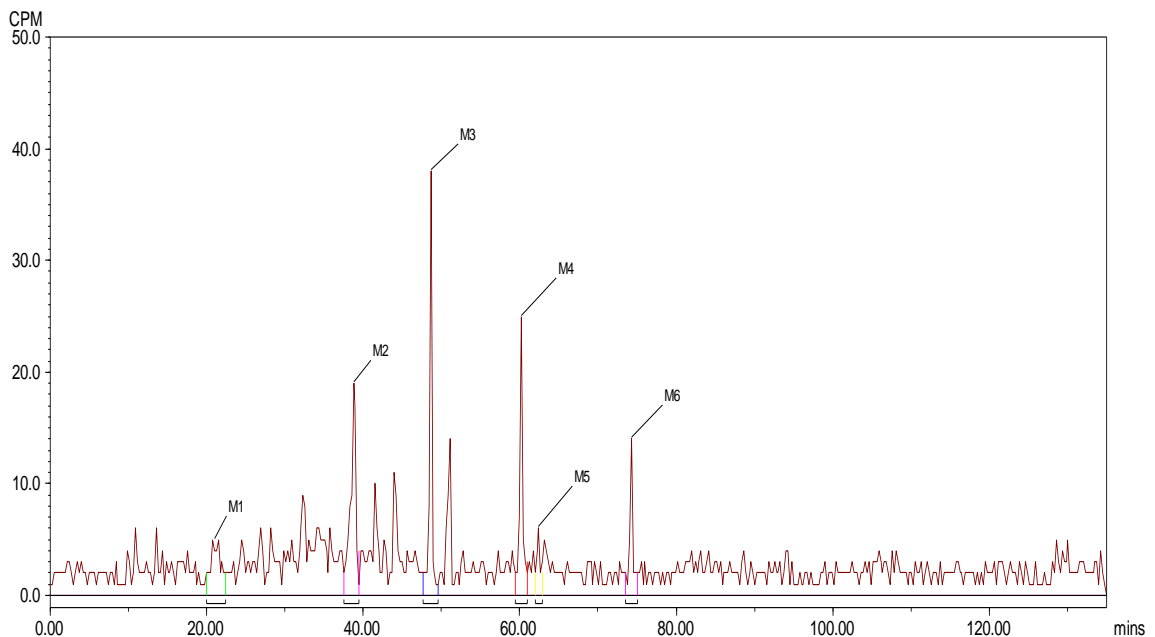


Figure S2B. Radiochromatogram of an AUC pooled plasma samples from subjects treated with [14C]-tetrabenzazine



These plasma metabolites were subsequently identified as: M1 (2-methylpropanoic acid metabolite of β -HTBZ [originally identified as a carboxylic acid]); M2 (sulphate conjugate of O-desmethyl β -HTBZ); M3 (sulphate conjugate of O-desmethyl α -HTBZ); M4 (mono-hydroxy metabolite of parent (deutetrabenzazine or tetrabenzazine)); M5 (β -HTBZ) and M6 (α -HTBZ)

Figure S3. Radioactive chromatograms of urine samples

In the urine, five metabolites were observed, each accounting for at least 10% of the sample radioactivity. These urinary metabolites were subsequently identified as:

- U1 2-methylpropanoic acid metabolite of β -HTBZ [originally identified as a carboxylic acid]
- U2 mono-hydroxy β -HTBZ
- U3 sulphate conjugate of O-desmethyl β -HTBZ
- U4 co-elution of glucuronide of α -HTBZ, sulphate conjugate of O-desmethyl HTBZ and monohydroxy α -HTBZ
- U5 sulphate conjugate of O-desmethyl α -HTBZ

Figure S3A. Radioactive chromatogram of a 0-72 hour pooled urine sample obtained from subjects treated with [14 C]-deutetrabenazine

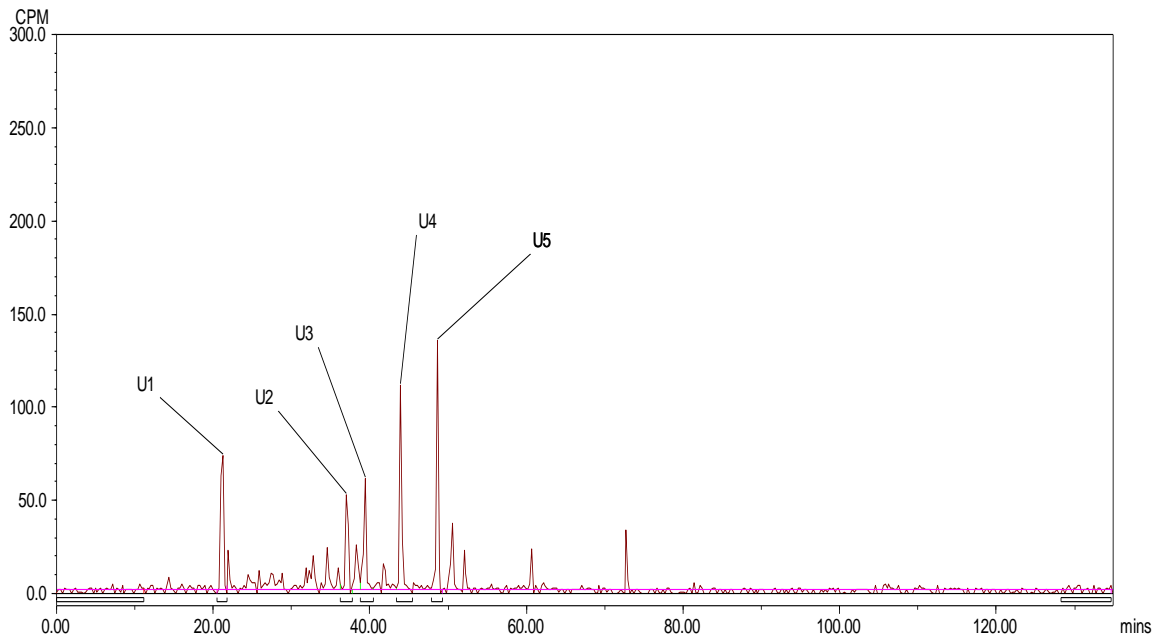


Figure S3B. Radioactive chromatogram of a 0-72 hour pooled urine sample obtained from subjects treated with [14 C]-tetrabenazine

