

Population Pharmacokinetic Analysis of Deutetrabenazine (AUSTEDO®) in Children and Adolescents with Tourette Syndrome

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Background

- Tourette syndrome (TS) is a neurodevelopmental disorder characterized by multiple motor and phonic tics frequently co-occurring with a variety of behavioral and psychiatric problems. ^[1]
- Austedo (deutetrabenazine, Teva), a deuterated modification of tetrabenazine, a VMAT2 inhibitor, has been studied as a potential treatment for TS. ^[2]
- In 2 recent placebo controlled phase 2/3 studies in children and adolescents with TS, the primary endpoint was the reduction in motor and phonic tics assessed by the Total Tic Score of the Yale Global Tic Severity Scale and was not met.

Objectives

To characterize the pharmacokinetics (PK) and to predict individual steady state PK exposure parameters of deutetrabenazine (parent) and its 2 active metabolites (α-HTBZ, and β-HTBZ) from data in children and adolescents with TS via a non-linear mixed-effects (NLME) modeling approach.

Methods

- Deutetrabenazine, deuterated α-HTBZ, and β-HTBZ PK concentrations from 2 sparsely sampled phase 2/3 (ARTIST 1) and phase 3 (ARTIST 2) studies in children and adolescents (>6 to 16 years of age) with TS were pooled with richly sampled data from 9 Phase 1/2 studies in healthy adults (HV) (**Table 1**).
- Population PK models for deutetrabenazine, deuterated active metabolite α-HTBZ, and β-HTBZ were developed and qualified based on the rich adult data.
- The predictive performances of the developed models were evaluated on the TS patient's data before and after parameter re-estimation on the pooled data.
- Qualified models were used to predict the steady state minimal ($C_{min,ss}$), maximal ($C_{max,ss}$), and average ($C_{avg,ss}$) deutetrabenazine, α-HTBZ and β-HTBZ concentrations which were subsequently used in exposure response analyses.
- The bias and precision of individual PK exposure parameters were evaluated through a simulation and re-estimation process. [3; **Poster 9813**]
- All population PK models were developed in NONMEM 7.4.3 using the stochastic approximation expectation maximization (SAEM) algorithm.

Table 1: Overview of the data included in the analysis

Population	Count	Deutetrabenazine	Deuterated α-HTBZ	Deuterated β-HTBZ
Healthy Adults	Individual profiles ^a	830	863	863
	Included samples	12,765	16,582	14,311
TS patients (ARTIST 1/2)	Individual profiles	138	139	138
	Included samples	264	265	263

^a Accounts for several crossover profiles in a single individual

Results

Healthy adults

- The developed population PK models for deutetrabenazine, α-HTBZ, and β-HTBZ in HV are represented in **Figure 1**

Deutetrabenazine

α-HTBZ and β-HTBZ

Figure 1: Schematic representation of the model structure used for deutetrabenazine (left) and the metabolites (right). ALAG_{1/2}: lag times, CL/F: apparent elimination clearance, F_{rel}: relative bioavailability, K_{A1/2}: absorption (metabolization) rate constant, Q/F: apparent distribution clearance, V_c/F: apparent central volume, V_p/F: apparent peripheral volume.

Before re-estimation

After re-estimation

α-HTBZ

β-HTBZ

deutetrabenazine

Figure 2: Dose-normalized Visual predictive check (VPC) of the concentration over time since previous dose in TS patients prior the parameter re-estimation. Generated by 500 simulations of the data and by representation of 90% prediction intervals of the observed (lines) and simulated data (areas)

Conclusion

- Deutetrabenazine, deuterated α-HTBZ, and β-HTBZ population PK models were developed using rich data from healthy adults and successfully applied to predictions in TS children and adolescents' data.
- Despite the sparseness of the TS patient data the individual $C_{max,ss}$ and $C_{avg,ss}$ (**Table 2**) were expected to be reliably predicted from the pooled model. However, the individually predicted $C_{min,ss}$ were expected to be systematically over-predicted.

Results (cont'd)

Healthy adults (cont'd)

- Clinically relevant effects of body weight were implemented on clearance and volume parameters of the metabolite models. For deutetrabenazine, due to more limited data, no statistically significant effect of body weight could be identified.
- All 3 models gave good predictive performances of the healthy adult data and were deemed qualified on that data.

TS patients

- The deuterated α-HTBZ, and β-HTBZ adult models were predictive of the TS patient data, while the deutetrabenazine model under predicted the observations over time (**Figure 2**, left column).
- The HV models were re-estimated on the pooled data (i.e., HV and TS patients) all displayed acceptable predictive performances (**Figure 2**, right column).
- The qualified models predicted the individual $C_{max,ss}$ and $C_{avg,ss}$ with acceptable bias and precision for TS patients. For $C_{min,ss}$, a systematic bias toward over-prediction (25%) and loss of precision was expected in the individually predicted values. [3; **Poster 9813**]

Table 2: Statistical summary of the predicted dose normalized exposures in the TS patients

Metric	Summary	Deutetrabenazine	Deuterated α-HTBZ	Deuterated β-HTBZ
$C_{min,ss-D}$ (ng/mL/mg)	Median [range]	0.000834 [0.000322 - 0.0193]	0.462 [0.0815 - 2.57]	0.16 [0.00124 - 3.39]
	Geo-mean (CV%)	0.00102 (85.4)	0.455 (67.5)	0.166 (206)
$C_{avg,ss-D}$ (ng/mL/mg)	Median [range]	0.00338 [0.00106-0.0214]	1.03 [0.334-3.52]	0.518 [0.0498-3.93]
	Geo-mean (CV%)	0.00366 (54.6)	1.01 (48)	0.523 (106)
$C_{max,ss-D}$ (ng/mL/mg)	Median [range]	0.00986 [0.00304 - 0.0332]	1.7 [0.492 - 4.19]	0.965 [0.175 - 4.4]
	Geo-mean (CV%)	0.0102 (48.8)	1.63 (43.7)	0.981 (83.5)

$C_{min,ss-D}$: dose-normalized steady state C_{min} ; $C_{max,ss-D}$: dose-normalized steady state C_{max} ; $C_{avg,ss-D}$: dose-normalized C_{avg} at steady state over the dosing interval; Geo mean CV%: $\sqrt{\exp(\text{variance for log transformed data})-1} \times 100$.

References

[1] Jankovic & Kurlan 2011, Tourette syndrome: evolving concepts. Mov Disord 2011;26(6):1149.

[2] Porta, 2008, Tourette's syndrome and role of tetrabenazine: review and personal experience. Clin Drug Investig. 2008;28(7):443-59

[3] Kaschek *et al.* 2021, Determination of the individual pharmacokinetic exposure parameter uncertainty to support of pediatric exposure-response trial design. www.page-meeting.org/?abstract=9813

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