Population Pharmacokinetics of Valbenazine and its Active Metabolite

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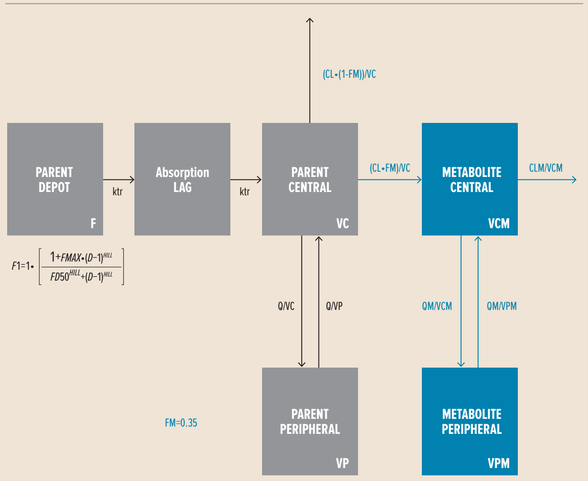
INTRODUCTION

Valbenazine (VBZ; INGREZZA®) is a vesicular monoamine transporter 2 (VMAT2) inhibitor approved in the US for the treatment of adults with tardive dyskinesia and under development for the treatment of Tourette syndrome. Following oral administration, VBZ is extensively metabolized by hydrolysis of the valine ester to form an active metabolite ([+]-α-HTBZ, NBI-98782) and by oxidative metabolism, primarily by cytochrome P450 (CYP) 3A4/5, to form mono-oxidized VBZ and other minor metabolites.[1] [+]-α-HTBZ is metabolized in part by CYP2D6. VBZ and [+]-α-HTBZ have elimination half-lives of approximately 15 to 22 hours,[2] thus supporting once-daily dosing. VBZ and [+]-α-HTBZ exposures are reduced when VBZ is administered with a strong CYP3A4 inducer (e.g., rifampin) and are increased when VBZ is administered with a strong CYP3A4 inhibitor (e.g., ketoconazole).[3] A population pharmacokinetic (pop PK) model was developed to enable determination of the effects of additional demographic and environmental variables on the PK of VBZ and [+]-α-HTBZ.

METHODS

Plasma VBZ and [+]-α-HTBZ concentration data from 14 clinical studies were used for the analysis. VBZ and [+]-α-HTBZ PK were simultaneously fit to a joint parent-metabolite model using NONMEM version 7.3 (**Figure 1**). The base structural model was a 2-compartment disposition model with transit compartment (N=2) absorption and linear elimination for VBZ and a 2-compartment disposition model with linear elimination for [+]-α-HTBZ. A first-order transit absorption rate constant (ktr) was used to characterize the absorption process and was dependent on formulation and meal status. Based on metabolism data from prior studies, the fraction of VBZ metabolized to [+]-α-HTBZ was set to 35%. The effects of demographic (age, gender, race, creatinine clearance, body weight, CYP2D6 genotype [poor or non-poor metabolizer]) and environmental (dose, formulation, food, concomitant potent CYP2D6 inhibitors [e.g., paroxetine, fluoxetine, bupropion]) variables on VBZ and [+]-α-HTBZ PK were evaluated (**Table 1**).

Figure 1. Model Structure for Combined VBZ and [+]-α-HTBZ Population Pharmacokinetic Modeling



CL, clearance (parent); CLM, clearance (metabolite); D, dose; F1, relative bioavailability; FM, fraction of valbenazine (parent) converted to [+]-α-HTBZ (metabolite); FMAX, maximum increase in F1 relative to 1 mg; FD50, dose producing half of the maximum dose effect on F1; HILL, Hill coefficient; ktr, transit absorption rate constant; Q, intercompartmental clearance (parent); QM, intercompartmental clearance (metabolite); VBZ, valbenazine; VC, central volume of distribution (parent); VCM, central volume of distribution (metabolite); VP, peripheral volume of distribution (parent); VPM, peripheral volume of distribution (metabolite).

Table 1. Summary of Characteristics (Covariates) for Subjects Included in the Population Pharmacokinetic Analysis

Covariate	Statistic/Descriptor	Total (N=799)
Age, years	Mean	42.1
	Min, max	6, 83
Body weight, kg	Mean	75.9
	Min, max	18.1, 155.4
Creatinine clearance, mL/min or mL/min/1.73 m^2	Mean	121.1
	Min, max	23.5, 386.7
Gender, n (%)	Male	517 (64.7)
	Female	282 (35.3)
Race, n (%)	Asian	50 (6.3)
	Black or African American	170 (21.3)
	Other	22 (2.8)
	Unknown	7 (0.9)
	White	550 (68.8)
CYP2D6 genotype, n (%)	Non-poor metabolizer	755 (94.5)
	Poor metabolizer	39 (4.9)
	Missing	5 (0.6)
Strong CYP2D6 inhibitor, n (%)	No	743 (93.0)
	Yes	56 (7.0)
Strong CYP3A inducer, n (%)	No	795 (99.5)
	Yes	4 (0.5)
Strong CYP3A inhibitor, n (%)	No	794 (99.4)
	Yes	5 (0.6)

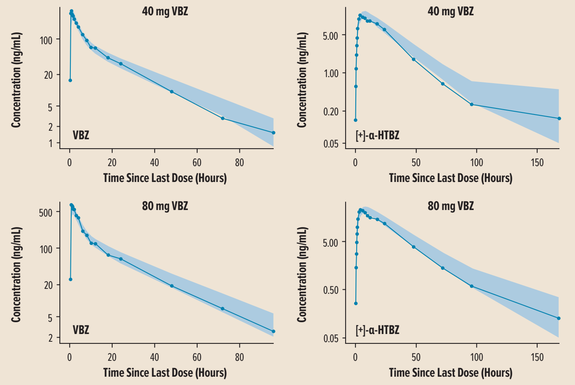
RESULTS

A joint parent-metabolite model including 2-compartment disposition, transit compartment absorption, and linear elimination for VBZ and 2-compartment disposition and linear elimination for [+]-α-HTBZ adequately described the plasma concentration-time profiles of both drug molecules. Final model parameters are described in **Table 2**. The goodness of fit of the model is presented in **Figures 2 and 3**. A sigmoid E_{max} model characterized the relationship between dose and relative bioavailability, with doses greater than 35 mg having approximately 30% higher bioavailability compared to a 1-mg dose. The relative bioavailability was similar for all doses above 35 mg. Increases in baseline body weight resulted in increases in clearance and central volume of distribution for both the parent and metabolite with subsequent decreases in steady-state C_{max} and AUC.

Table 2. Final Population Pharmacokinetic Model Parameters

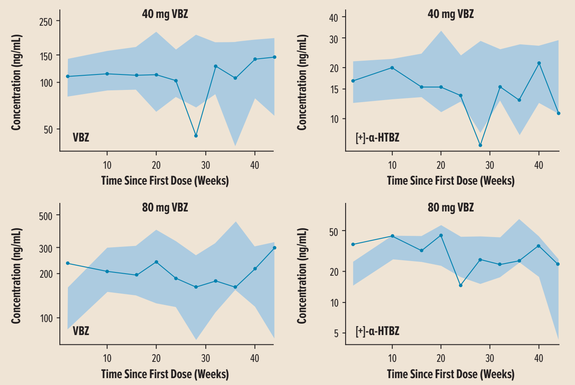
Parameter Description	Estimate	90% Confidence Interval
CL/F (L/hr)	12.5	(12.2, 12.9)
VC/F (L)	109	(102, 117)
Q/F (L/hr)	12.7	(12.3, 13.2)
VP/F (L)	123	(121, 125)
ktr (1/hr)	4.17	(3.91, 4.45)
CLM/F (L/hr)	34.2	(33.1, 35.3)
VCM/F (L)	313	(301, 325)
QM/F (L/hr)	1.34	(1.26, 1.43)
VPM/F (L)	169	(156, 182)
Change in ktr for Solution (log fraction)	2.01	(1.86, 2.17)
Change in ktr for Meal=Fed (log fraction)	0.195	(0.187, 0.205)
Change in ktr for Pediatrics (log fraction)	0.439	(0.368, 0.525)
Change in CLM for CYP2D6 Poor Metabolizer (log fraction)	0.603	(0.554, 0.657)
Change in CLM for CYP2D6 Inhibitor (log fraction)	0.8	(0.725, 0.883)
Change in F for Dose ≤35 (log fraction)	0.768	(0.751, 0.785)
Change in Log CLP per unit Change in Log WTKG	0.438	(0.349, 0.526)
Change in Log VCP per unit Change in Log WTKG	0.693	(0.465, 0.921)
Change in Log CLM per unit Change in Log WTKG	0.348	(0.249, 0.447)
Change in Log VCM per unit Change in Log WTKG	0.816	(0.687, 0.946)
Change in Log VCM per unit Change in Log AGE	0.276	(0.228, 0.325)
Change in VCP for SEX=Female (log fraction)	0.837	(0.759, 0.923)
Change in VCM for SEX=Female (log fraction)	1.11	(1.06, 1.16)
Change in F for RACE=Asian (log fraction)	1.25	(1.2, 1.29)
Change in CLM for RACE=Asian (log fraction)	1.2	(1.1, 1.31)
Change in VCM for RACE=Asian (log fraction)	1.45	(1.36, 1.55)

Figure 2. Visual Predictive Check of Plasma VBZ and [+]-α-HTBZ Concentrations Following Single Oral Dose Administration of 40 or 80 mg VBZ to Healthy Subjects



Symbols represent median observed value and blue shaded regions reflect 90% prediction intervals.
VBZ, valbenazine.

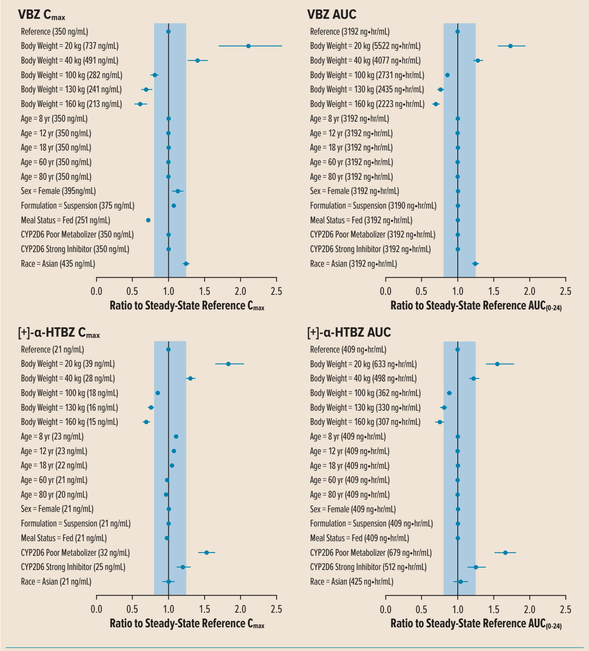
Figure 3. Visual Predictive Check of Plasma VBZ and [+]-α-HTBZ Concentrations Following Once-Daily Oral Administration of 40 or 80 mg VBZ to Patients with Tardive Dyskinesia



Symbols represent median observed value and blue shaded regions reflect 90% prediction intervals.
VBZ, valbenazine.

The effect of covariates on peak (C_{max}) and overall (AUC) VBZ and [+]-α-HTBZ exposure is presented in **Figure 4**. A 2.5-fold increase in body weight (from 40 kg to 100 kg) resulted in exposure decrease of 38% for VBZ and 34% for [+]-α-HTBZ. After accounting for body weight, age had no clinically meaningful effect on VBZ or [+]-α-HTBZ exposure. CYP2D6 poor metabolizers were predicted to have an approximate 50% reduction in [+]-α-HTBZ clearance, which resulted in approximately 2-fold increases in steady-state [+]-α-HTBZ AUC and C_{max}. Sex, solution formulation, creatinine clearance, and fed meal status were not predicted to have a clinically-meaningful impact on VBZ or [+]-α-HTBZ exposure. Predicted [+]-α-HTBZ exposure was approximately 25% higher in patients receiving a concomitant potent CYP2D6 inhibitor.

Figure 4. The Effect of Covariates on Steady-State VBZ and [+]-α-HTBZ Peak (C_{max}) and Overall (AUC) Exposure



Ratios and 90% confidence intervals are relative to a 70 kg, 40 yr old, CYP2D6 non-poor metabolizer white male with a CLcr of 125 ml/min administered VBZ 40 mg once-daily in fasting conditions. Shaded area represents a 0.8 to 1.25 ratio range.
AUC, area under the curve; C_{max}, maximum serum concentration; VBZ, valbenazine.

CONCLUSIONS

A simultaneous pop PK model of VBZ and [+]-α-HTBZ was developed. Although body weight and concomitant potent CYP2D6 inhibitors can affect predicted [+]-α-HTBZ exposure, no specific VBZ dose adjustments are required based on these variables. Dose reductions may be required in individual CYP2D6 poor metabolizers based on tolerability.

REFERENCES

1. Grigoriadis DE, Smith E, Hoare SR, et al. *J Pharmacol Exp Ther.* 2017;361:454-61.
2. Luo R, Bozigian H, Jimenez R, et al. *Psychopharmacol Bull.* 2017;47:44-52.
3. Loewen G, Luo R, Smith E, et al. Presented at the 30th Annual Psych Congress; September 16-19, 2017; New Orleans, LA.

Disclosures: This study was supported by Neurocrine Biosciences, Inc., San Diego, CA. G. Loewen, H. Bozigian, and R. Luo are full-time employees of Neurocrine Biosciences, Inc. Editorial support was provided by Prescott Medical Communications Group, Inc., Chicago, IL.

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