Key Words: anxiety, double-blind method, psychopharmacology, single-blind method, sleep initiation and maintenance disorders, tardive dyskinesia, tetrabenazine, triglycerides, valbenazine, valine, vesicular monoamine transport proteins

Single Dose and Repeat Once-Daily Dose Safety, Tolerability and Pharmacokinetics of Valbenazine in Healthy Male Subjects

By Rosa Luo, Haig Bozigian, Roland Jimenez, Gordon Loewen, Christopher F. O'Brien

ABSTRACT *~ Valbenazine (VBZ) is a vesicular monoamine transporter 2 (VMAT2) inhibitor approved for the treatment of tardive dyskinesia. The safety, tolerability and pharmacokinetics of VBZ following single and repeat once-daily (QD) dosing were evaluated in 2 randomized, single-center, double-blind studies in healthy male subjects. In the first study, 2 cohorts of 8 subjects were administered single doses (SD) of placebo (PBO; N = 2/period) or VBZ (N = 6/period; 1, 2, 5, or 12.5 mg for Cohort 1 and 12.5, 25, 50, or 75 mg for Cohort 2) using a sequential escalation scheme. The second study consisted of 2 phases. In the initial phase, subjects were administered SD PBO (N = 2/period) or VBZ (N = 6/period; 75, 100, 125 or 150 mg) with sequential escalation. In the second phase, subjects received PBO, or 50 or 100 mg VBZ (N = 4:8:8) QD for 8 days (Cohort 1) or PBO or 50 mg VBZ (N = 6:6) QD for 8 days (Cohort 2). For both studies, plasma concentrations of VBZ and its active metabolite, NBI-98782, were determined. Safety was assessed throughout the studies. PK parameters were determined using noncompartmental methods. In both studies, VBZ was rapidly absorbed with peak concentrations typically observed within 1.5 hours. Peak NBI-98782 concentrations were typically observed at 4.0 to 9.0 hours. Terminal elimination half-life for both VBZ and NBI-98782 was ~20 hours. Across the 1 to 150 mg SD range evaluated across the studies, VBZ and NBI-98782 C_{max} and AUC increased dose-proportionally from 50 to 150 mg and more than dose-proportionally from 1 to 50 mg. QD VBZ and NBI-98782 C_{max} and AUC parameters were also dose-proportional between the 50 and 100 mg doses. Steady-state for both analytes appeared to be achieved by Day 8. The accumulation index was ~1.5 for VBZ and ~2.5 for NBI-98782. Peak to trough fluctuation was approximately 250% for VBZ and 70% for NBI-98782. Across both studies, NBI-98782 exposure was approximately*

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20%–30% that of VBZ based on molar ratios. In the first study, the maximum-tolerated dose was not achieved; headache (2 events) was the only treatment-emergent adverse event (TEAE) reported by more than one subject. In the second study, fatigue (4 events) was the only TEAE reported by more than one subject following SD VBZ. Following QD VBZ, the TEAEs of fatigue, insomnia, disturbance in attention, and nervousness were dose-dependent; the latter three TEAEs were considered dose-limiting. Subject withdrawals due to TEAEs were 1 each for PBO and 50 mg VBZ QD, and 3 for 100 mg VBZ QD. Clinically relevant effects on laboratory parameters, vital signs or ECGs were limited to increased CPK (SD: 1 each for 5 mg VBZ and PBO), ALT (QD: 1 each for 50 and 100 mg VBZ and PBO), and triglycerides (QD: 1 each for 50 mg VBZ and PBO). VBZ has an acceptable safety profile and predictable pharmacokinetics that result in stable concentrations of active compounds with low peak-to-trough fluctuation following once-daily dosing. Psychopharmacol Bull. *2017;47(3):44–52.*

Introduction

- Valbenazine (INGREZZA) is a novel, highly selective vesicular monoamine transporter 2 (VMAT2) inhibitor[1] that is approved for the treatment of tardive dyskinesia and is in development for Tourette syndrome
- The clearance of valbenazine is in part mediated by hydrolysis to [+]-α-dihydrotetrabenazine ([+]-α-HTBZ, NBI-98782) and by oxidation to other metabolites; [+]-α-HTBZ is metabolized in part by cytochrome P450 (CYP) 2D6
- The *in vivo* activity of valbenazine is believed to be largely mediated by [+]-α-HTBZ, with possible minor contribution from valbenazine, based on potency and plasma concentrations[2]

Objective

- To assess the safety, tolerability, and pharmacokinetics (PK) of valbenazine following single and repeat once-daily (QD) dosing in healthy male subjects

Methods

Study Design

Study 1: single-center, double-blind, placebo-controlled, single-dose, sequential dose-escalation, four-period, fixed-sequence study

- Included 16 healthy male subjects (2 cohorts with 8 subjects each), 18 to 45 years of age (inclusive), who met eligibility criteria and had not used any medication within 7 days of Day-1

- Each cohort consisted of 4 treatment periods with a ⩾7-day washout between each dose
- Within each treatment period, 6 subjects received valbenazine and 2 received placebo; each subject received placebo and 3 escalating doses of valbenazine as 1 mg/mL oral solution under fasting conditions over the course of the study: 1, 2, 5, or 12.5 mg for Cohort 1; and 12.5, 25, 50, or 75 mg for Cohort 2
- Safety and PK were reviewed before initiation of the next higher dose

Study 2: single-center, double-blind, placebo-controlled, single- and multiple-dose study

- Included 40 healthy male subjects, 18–45 years of age (inclusive), who met eligibility criteria and had not used any medication within 7 days of Day-1
- Single-dose cohort: 8 subjects and 3 treatment periods with a ⩾7-day washout between each dose
  - Within each treatment period, 6 subjects received valbenazine and 2 received placebo
  - Each subject received placebo and 2 or 3 escalating doses of valbenazine over the 3 treatment periods: 75 or 100 mg for period 1; 100 or 125 mg for period 2; 150 mg (all subjects) for period 3
  - Safety and PK results were reviewed after each treatment period
- Multiple-dose cohort: 2 groups
  - **Group 1**: 20 healthy subjects randomized (1:2:2) to receive QD placebo (n = 4), valbenazine 50 mg (n = 8), or valbenazine 100 mg (n = 8) for 8 consecutive days
  - **Group 2**: 12 subjects characterized as extensive CYP2D6 metabolizers randomized (1:1) to QD placebo (n = 6) or 50 mg valbenazine (n = 6) for 8 days
- Valbenazine was administered as 2 mg/mL oral solution under fasting conditions
- Safety and PK of Group 1 were reviewed before initiation of dosing

Pharmacokinetic and Safety Analyses

- Plasma concentrations of valbenazine and [+]-α-HTBZ were determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method
- PK parameters were determined using standard noncompartmental methods and calculated using WinNonlin® Professional v5.2
- Safety was assessed throughout the studies using typical Phase 1 study endpoints

TABLE 1

Valbenazine and [+]-α-HTBZ PK Parameters after Single Valbenazine Doses

	VALBENAZINE MEAN (SD)					[+]-α-HTBZ MEAN (SD)			
ANALYTE DOSE	t_{max}[a] (HR)	C_{max} (NG/ML)	AUC_{0-INF} (NG × HR/ML)	$t_{1/2}$ (HR)	CL/F (L/HR)	t_{max}[a] (HR)	C_{max} (NG/ML)	AUC_{0-INF} (NG × HR/ML)	$t_{1/2}$ (HR)
1 mg (N = 8)	1.3 (0.8, 3.0)	2.94 (1.33)	40.7 (15.9)	16 (2.4)	26.9 (7.06)	7.0 (4.0,12)	0.19 (0.04)	9.22 (4.30)	32 (17)
2 mg (N = 4)	1.5 (0.5, 3.0)	6.42 (3.09)	102 (35.2)	15 (2.7)	21.4 (7.22)	9.0 (6.0, 10)	0.46 (0.11)	21.9 (5.92)	31 (22)
5 mg (N = 6)	0.5 (0.3, 1.3)	17.4 (7.21)	207 (82.2)	17 (3.0)	26.6 (7.63)	7.0 (4.0, 12)	0.98 (0.16)	29.9 (7.35)	16 (3.0)
12.5 mg (N = 11)	0.5 (0.5, 4.0)	56.9 (18.9)	614 (148)	16 (2.3)	21.6 (5.67)	6.0 (4.0, 10)	2.55 (0.67)	93.0 (36.2)	19 (4.0)
25 mg (N = 6)	0.6 (0.3, 0.8)	156 (68.2)	1,610 (304)	20 (3.7)	16.0 (3.42)	7.0 (3.0, 24)	6.39 (1.57)	255 (118)	23 (4.2)
50 mg (N = 5)	0.5 (0.3, 4.0)	412 (236)	4,120 (1680)	19 (2.4)	14.1 (6.22)	4.0 (4.0, 6.0)	20.4 (7.51)	575 (350)	20 (2.8)
75 mg[b] (N = 8)	1.0 (0.3, 2)	788 (220)	7,170 (1540)	20 (2.4)	11.0 (2.81)	6.0 (4.0, 12)	31.7 (11.4)	1,150 (706)	21 (2.2)
100 mg (N = 6)	0.5 (0.3, 0.8)	779 (293)	6,590 (1560)	19 (3.9)	15.9 (3.70)	5.0 (4.0, 8.0)	31.9 (11.0)	872 (284)	20 (2.4)
125 mg (N = 4)	0.7 (0.5, 1.3)	1,030 (293)	9,130 (1660)	17 (3.3)	14.1 (2.81)	6.0 (4.0, 8.0)	45.2 (13.9)	1,310 (260)	18 (2.1)
150 mg (N = 6)	0.6 (0.5, 2.0)	1,230 (281)	12,200 (2940)	20 (3.6)	13.0 (3.17)	7.0 (4.0, 12)	56.2 (25.4)	1,840 (1290)	19 (1.5)

Notes: AUC_{0-inf} = area under the plasma concentration versus time curve from time 0 to Infinity; C_{max} = maximum plasma concentration; $t_{1/2}$ = apparent terminal half-life; t_{max} = time to maximum plasma concentration; CL/F = apparent systemic clearance after oral administration.
[a]Median (min, max) is reported for t_{max}. [b]2 out of 8 subjects are CYP2D6 poor metabolizers.

Results

Pharmacokinetics

- Valbenazine was rapidly absorbed $t_{max} \leqslant \sim 1.0$ hours; valbenazine plasma concentrations declined with an apparent $t_{1/2}$ of approximately 15 to 20 hours (Table 1, Figure 1A)
- The metabolite [+]-α-HTBZ was formed slowly, reaching C_{max} after 4.0 to 9.0 hours; [+]-α-HTBZ plasma concentrations declined with an apparent $t_{1/2}$ of approximately 16 to 23 hours (Table 1, Figure 1B)
- Valbenazine and [+]-α-HTBZ $t_{1/2}$ after repeat doses were comparable to single dose values
- C_{max} and AUC of valbenazine and [+]-α-HTBZ increased proportionally between 25 and 150 mg, which range brackets the therapeutic dose range of 40 mg to 80 mg
- Systemic accumulation of valbenazine was low after repeat dosing (1.5-fold), whereas [+]-α-HTBZ accumulated 2.3- to 2.6-fold (Table 2); accumulation was consistent with half-life values
- Valbenazine and [+]-α-HTBZ steady-state was achieved by Day 8

FIGURE 1

Valbenazine and [+]-α-HTBZ Plasma Concentrations after Single Valbenazine Doses (Log Scales)

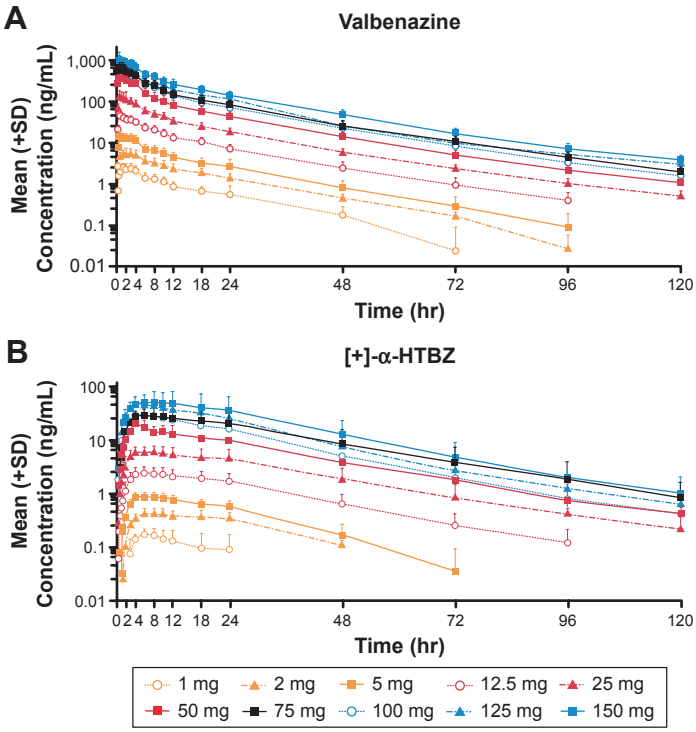

TABLE 2

Valbenazine and [+]-α-HTBZ PK Parameters Following Repeat Once-Daily Valbenazine Doses

		VALBENAZINE 50 MG MEAN (SD)		VALBENAZINE 100 MG MEAN (SD)	
		DAY 1	DAY 8	DAY 1	DAY 8
ANALYTE	PK PARAMETER	(N = 14)	(N = 13)	(N = 8)	(N = 4)
Valbenazine	t_{max}[a] (hr)	0.5 (0.2, 3.0)	0.8 (0.5, 1.5)	0.5 (0.3, 1.3)	0.5 (0.5, 1.3)
	AUC_{0-24} (ng × hr/mL)	2580 (709)	3590 (1050)	5390 (1710)	6730 (3100)
	C_{max} (ng/mL)	393 (157)	400 (132)	813 (392)	878 (638)
	$t_{1/2}$ (hr)	NA[b]	21 (3.7)	NA[b]	20 (1.7)
	Accumulation Index	1.4 (0.2)		1.5 (0.2)	
	% Fluctuation	225 (27.5)		253 (65.8)	
[+]-α-HTBZ	t_{max}[a] (hr)	8.0 (4.0, 10)	4.1 (3.0, 6.0)	6.0 (4.0, 10)	4.0 (4.0, 4.0)
	AUC_{0-24} (ng × hr/mL)	314 (151)	630 (218)	557 (159)	1110 (243)
	C_{max} (ng/mL)	18.1 (7.58)	35.1 (11.1)	31.8 (6.75)	64.0 (13.2)
	$t_{1/2}$ (hr)	NA[b]	21 (2.1)	NA[b]	19 (1.6)
	Accumulation Index	2.3 (0.52)		2.6 (0.55)	
	% Fluctuation	68.3 (14.6)		69.8 (5.68)	

Notes: AUC_{0-24} = area under the plasma concentration versus time curve from time 0 to 24 hours, C_{max} = maximum plasma concentration; $t_{1/2}$ = apparent terminal half-life. t_{max} = time to maximum plasma concentration. Accumulation Index = Day 8 AUC_{0-24} divided by Day 1 AUC_{0-24}; %Fluctuation = Day 8 C_{max} minus C_{max} on Day 8 divided by C_{avg}.
[a]Median (min. max) is reported for t_{max}.
[b]NA = Not applicable – not determined following single dose.

- CYP2D6 poor metabolizers had higher [+]-α-HTBZ exposures compared to non-poor metabolizers (~2-fold); valbenazine exposure was unaffected by CYP2D6 genotype status
- Peak-to-trough fluctuation was approximately 250% for valbenazine after repeat QD dosing; however, the gradual formation and slow elimination of [+]-α-HTBZ results in low fluctuation (approximately 68%)
- Stable concentrations of [+]-α-HTBZ were obtained after repeat QD administration of valbenazine (Figure 2)

Safety & Tolerability

Study 1

- The maximum tolerated dose was not achieved; headache (2 events) was the only treatment-emergent adverse event (TEAE) reported by >1 subject
- There was no clinically relevant effect on lab parameters
- No subject had a cardiovascular-related TEAE or clinically significant ECG result using triplicate 12-lead ECG recordings

FIGURE 2

Valbenazine and [+]-α-HTBZ Plasma Concentrations After Repeat QD Administration of Valbenazine (Log Scales)

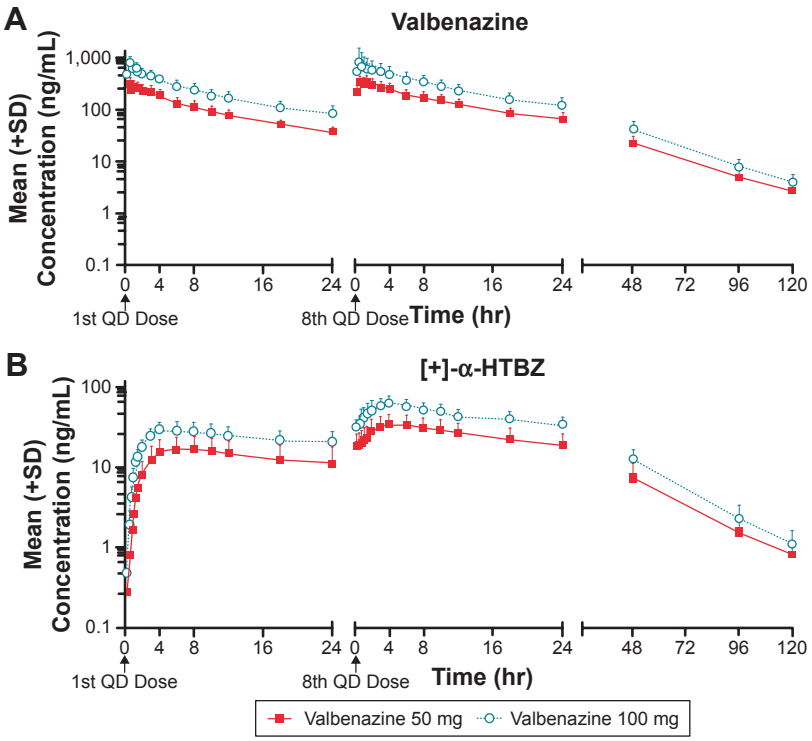

TABLE 3

Treatment-Emergent Adverse Events that Occurred in ⩾Two Subjects in Study 2, Multiple Dose Cohort

MedDRA System Organ Class/Preferred Term	Placebo (N = 10) n (%)	Valbenazine 50 mg (N = 14) n (%)	Valbenazine 100 mg (N = 8) n (%)
Overall	6 (60.0)	8 (57.1)	6 (75.0)
Nervous System Disorders	3 (30.0)	3 (21.4)	3 (37.5)
Dizziness postural	1 (10.0)	1 (7.1)	1 (12.5)
Disturbance in attention	0	0	2 (25.0)
Investigations	3 (30.0)	2 (14.3)	1 (12.5)
Alanine aminotransferase increased	1 (10.0)	1 (7.1)	1 (12.5)
Blood triglycerides increased	1 (10.0)	1 (7.1)	0
General Disorder and Administration Site Condition	1 (10.0)	2 (14.3)	3 (37.5)
Fatigue	0	1 (7.1)	2 (25.0)
Musculoskeletal & Connective Tissue Disorders	1 (10.0)	3 (21.4)	1 (12.5)
Musculoskeletal stiffness	0	1 (7.1)	1 (12.5)
Pain in extremity	1 (10.0)	1 (7.1)	0
Psychiatric Disorders	0	0	4 (50.0)
Insomnia	0	0	3 (37.5)
Nervousness	0	0	2 (25.0)
Skin & Subcutaneous Tissue Disorders	0	1 (7.1)	1 (12.5)
Hyperhidrosis	0	1 (7.1)	1 (12.5)

Notes: TEAEs are classified by system organ class and preferred term using MedDRA version 12.0. Subjects who experienced the same coded event more than once were counted only once per preferred term and once per SOC.

Study 2

- Fatigue (4 events) was the only TEAE reported by >1 subject following single-dose administration of valbenazine
- Following repeat QD doses of valbenazine, TEAEs of fatigue, insomnia, disturbance in attention and nervousness were dose-dependent (Table 3); the latter three TEAEs were considered dose-limiting
- Subject withdrawals due to TEAEs were 1 each in placebo and 50 mg QD dose groups, and 3 in 100 mg QD dose group
- Clinically-relevant effects on laboratory parameters or vital signs were limited to increased CPK (single-dose cohort: 1 each in placebo and 5 mg dose groups), triglycerides (repeat-dose cohort: 1 each in placebo and 50 mg dose groups), and ALT (repeat-dose cohort: 1 each in placebo, 50, and 100 mg dose groups)
- No indication of prolongation of the QT interval for the valbenazine groups compared with placebo was observed using triplicate 12-lead ECG recordings and 24-hour Holter monitoring (Day 8 compared to baseline)

Conclusion

- Valbenazine has an acceptable safety profile and predictable PK that result in stable concentrations of active compounds with low peak-to-trough fluctuation following once-daily dosing ✤

Disclosure

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