VMAT2 Inhibitor Pharmacology: Tetrabenazine, Valbenazine, and Deutetrabenazine

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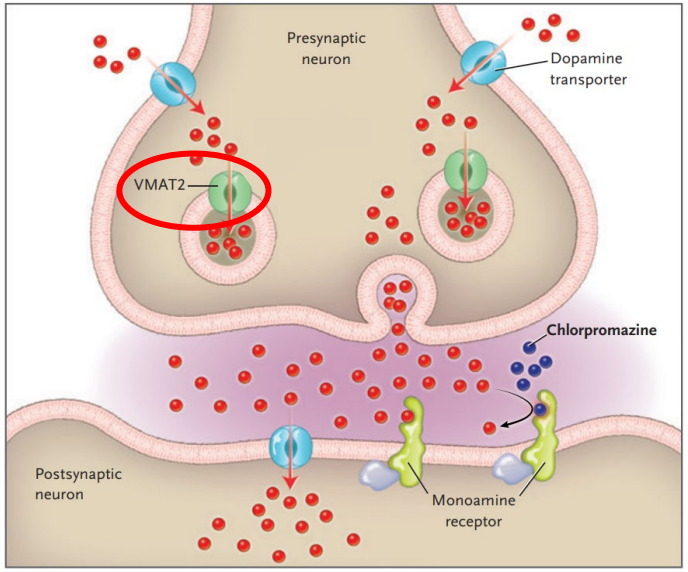
VMAT2 is Monoamine Transporter that Aids Neurotransmission

- Vesicular monoamine transporter (VMAT) shuttles monoamines, such as dopamine, into synaptic vesicles to allow for extracellular release[1]
- VMAT2 inhibitors exhibit subtype specificity and localization[1-3]

Image adapted from Davis MC, et al. *NEJM*. 2017; 376(26): p. 2504.

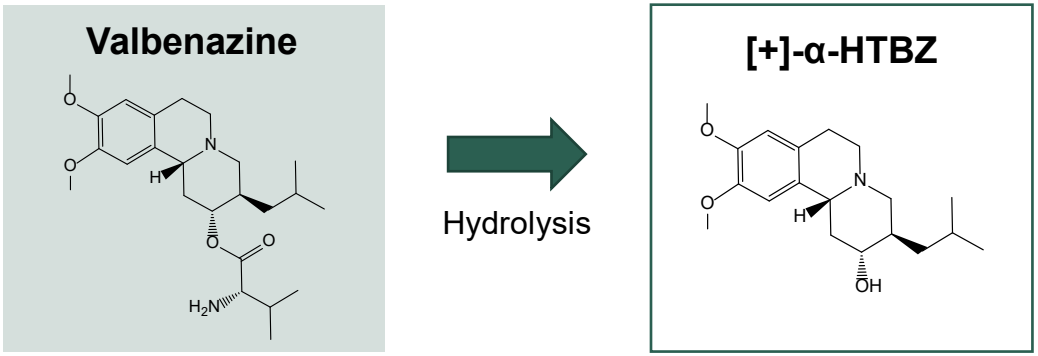


VMAT1	VMAT2
Not expressed in neurons[1]	**Highly expressed in monoamine neurons in basal ganglia[2]**
Inhibited by reserpine only, no affinity for tetrabenazine[1]	**Inhibited by BOTH reserpine and tetrabenazine[1]**

1. Adam Y, et al. *Am J Physiol Cell Physiol*. 2008;294(4):C1004-C1011. 2. Tong J, et al. *J Cereb Blood Flow Metab*. 2011;31(10):2065-2075. 3. Koeppe RA, et al. *J Cereb Blood Flow Metab*. 1999;19(12):1376-1384. 4. Davis MC, et al. *NEJM*. 2017; 376(26): 2503-2506.

Pharmacological Rationale for the Development of Valbenazine

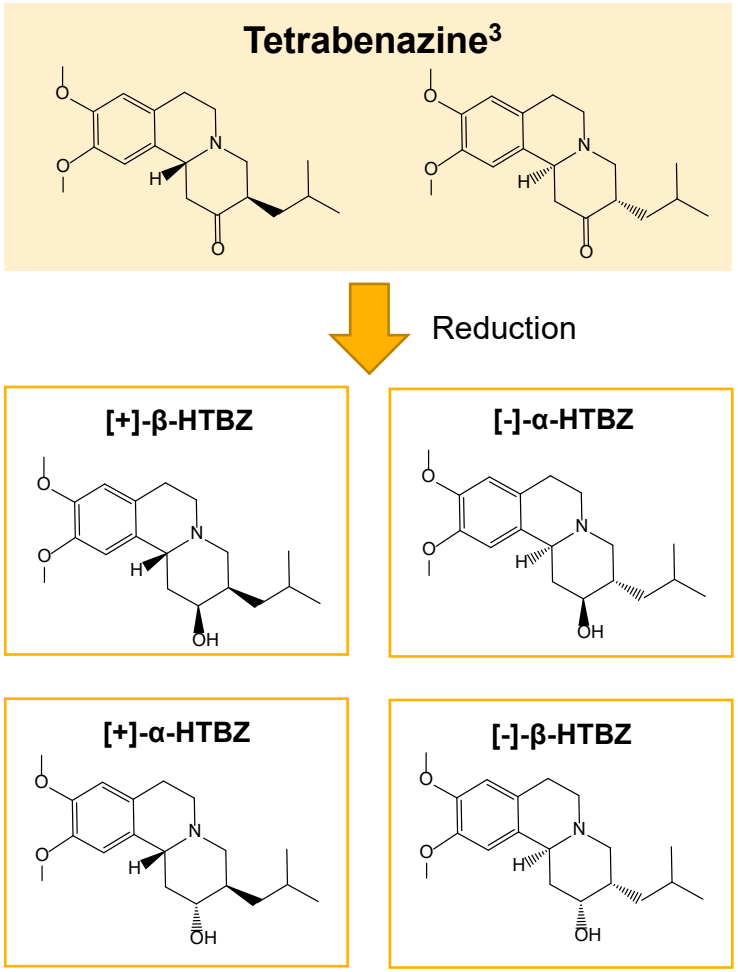
- Hypothesis: If the efficacy of tetrabenazine in movement disorders is partially mechanistically driven through VMAT2, then perhaps a selective VMAT2 inhibitor could also be effective in the treatment of movement disorders
- Tetrabenazine's 4 isomers were examined independently for their pharmacologic and pharmacokinetic isomers[2]
- By attaching a valine substituent to the (+)-α-HTBZ isomer, valbenazine's pharmacokinetic profile can be controlled and metabolized to only one active isomer[3]
  - Cleavage of the valine ester is the rate-limiting step in the clearance of valbenazine, as seen in the long half-life of the (+)-α-HTBZ isomer (22.2 hours) compared to valbenazine (18 hours)[4]



1. XENAZINE [package insert]. Deerfield, IL: Lundbeck Pharmaceuticals LLC; 2019. 2. Skor et al. *Drugs R D*. 2017; 17(3):449-459. 3. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego. 4. Vijan A, et al. ASCP 2021

Tetrabenazine: The First Reversible VMAT2 Inhibitor

- Tetrabenazine is a reversible VMAT2 inhibitor (selective for VMAT2 over VMAT1)[1]
- Tetrabenazine is administered as a racemic mixture of two enantiomers, though its pharmacological activity is thought to result from four isomeric dihydrotetrabenazine (HTBZ) metabolites[2-5]
- Although current published data for tetrabenazine only report the combined concentrations of enantiomeric pairs of metabolites (α- and β-HTBZ), each of the four isomers has a unique profile of VMAT2 inhibition and off-target binding (e.g., antagonist activity at dopamine D2 and serotonergic receptors)[3]

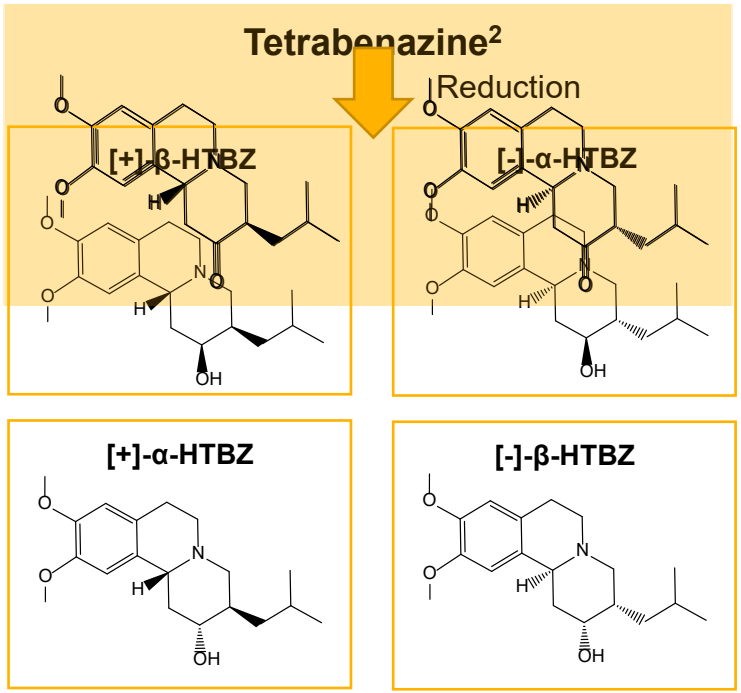


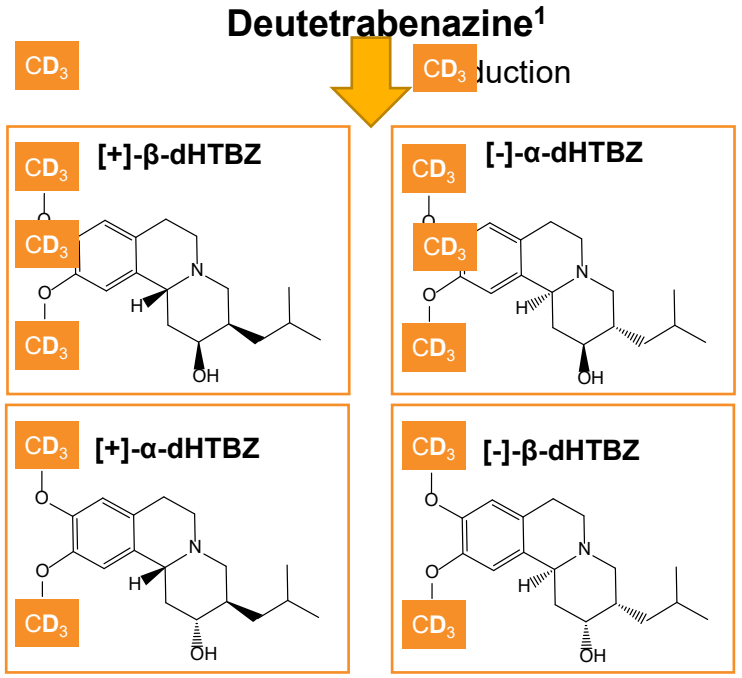
VMAT2, vesicular monoamine transporter 2.

1. XENAZINE [package insert]. Deerfield, IL: Lundbeck Pharmaceuticals LLC; 2019. 2. Kilbourn M, et al. *Eur J Pharmacol*. 1995;278(3):249–52. 3. Grigoriadis DE, et al. *J Pharmacol Exp Ther*. 2017;361:454–61. 4. Yao Z, et al. *Eur J Med Chem*. 2011;46(5):1841–8. 5. Jankovic J, et al. *Expert Rev Neurother*. 2011;11(11):1509–23.

Deutetrabenazine is a Deuterated Form of Tetrabenazine[1]

- Like tetrabenazine, deutetrabenazine is a racemic mixture of 2 enantiomers that are reduced to form 4 deuterated dihydrotetrabenazine (dHTBZ) stereoisomers[1]





1. Schneider F, et al. *Clin Transl Sci.* 2020; 13: 707-717. 2. Grigoriadis DE, et al. *J Pharmacol Exp Ther*. 2017;361:454–61.

One Tetrabenazine Metabolite ([+]-α-HTBZ) is the Most Selective but Not Most Abundant Isomer

Study 1

Tetrabenazine[1]

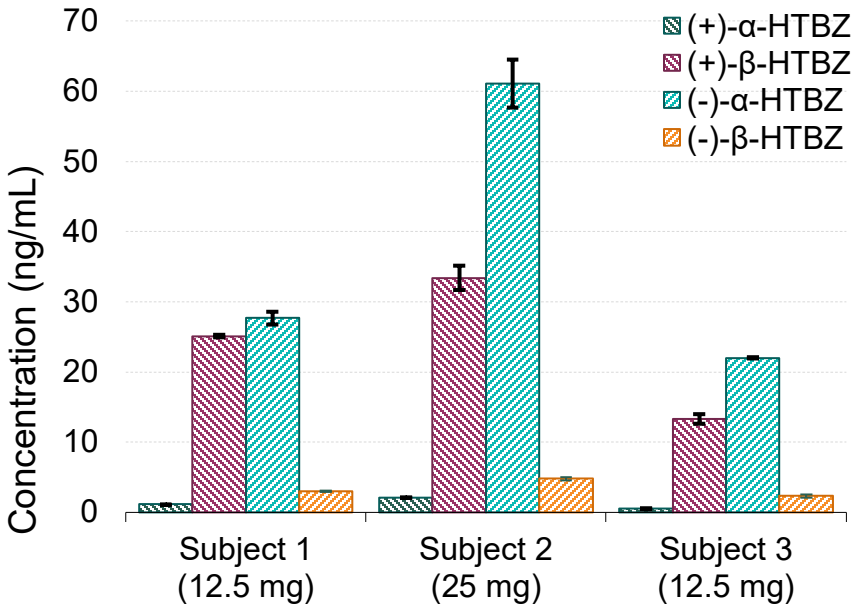
Receptor	(+)-α-HTBZ	(+)-β-HTBZ	(-)-α-HTBZ	(-)-β-HTBZ
	Isomer Binding Affinity,[1] K_i (nM)			
VMAT2	**4.2**	**9.7**	**250**	**690**
D_1	>1000	>1000	>1000	>1000
D_2	>1000	>1000	180	53
5-HT_{1A}	>1000	>1000	750	>1000
5-HT_{2A}	>1000	>1000	>1000	>1000
5-HT_{2B}	>1000	>1000	600	460
5-HT_7	>1000	970	71	5.9
α_{1A}	>1000	>1000	>1000	980
α_{2A}	>1000	>1000	>1000	220

Pharmacological profiles of isomers were assessed *in vitro* through radioligand binding assays

Smaller K_i number = Tighter Binding

Study 2

Human HTBZ Isomer Profiles[2]



Concentrations of HTBZ isomers were determined in serum samples, from patients taking tetrabenazine, that were purchased from a commercial specimen bank.

These data do not imply superiority of any compound. Head-to-head trials comparing tetrabenazine to valbenazine have not been conducted.

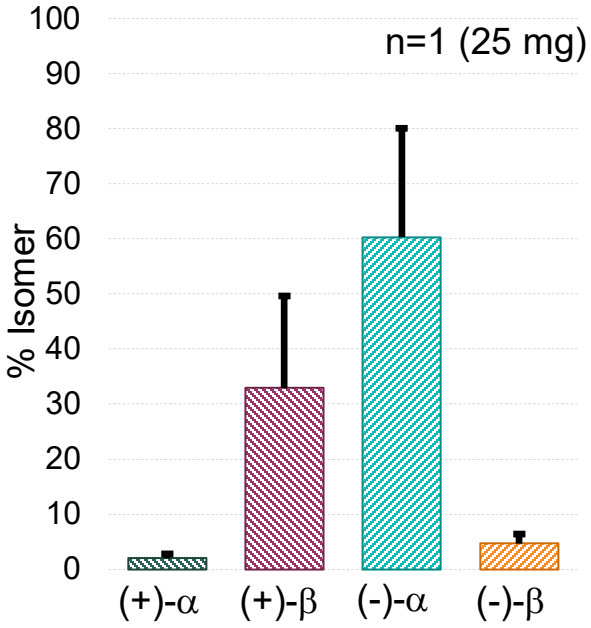
HTBZ, dihydrotetrabenazine; nM, nanomolar; mg, milligram.

1. Grigoriadis DE, et al. *J Pharmacol Exp Ther*. 2017;361(3):454-461. 2. Skor H, et al. *Drugs R D*. 2017;17(3):339-359.

Valbenazine Delivers a Unique Metabolite Profile and Pharmacology Inhibiting VMAT2

Study 2

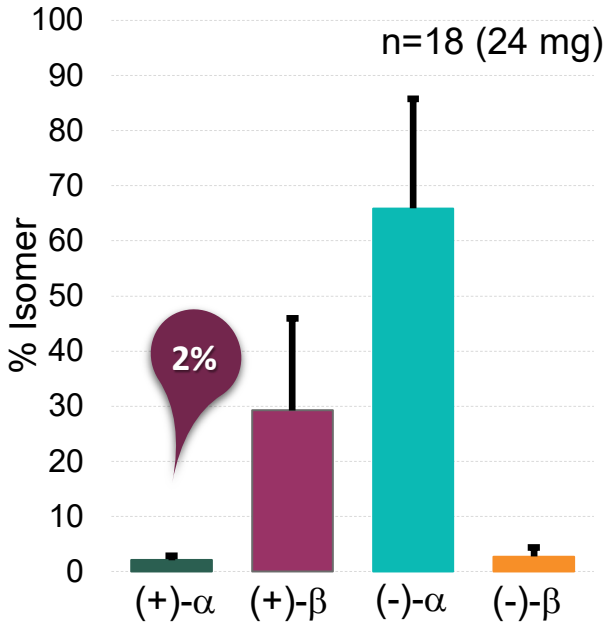
Tetrabenazine
HTBZ Isomer Profile[2]



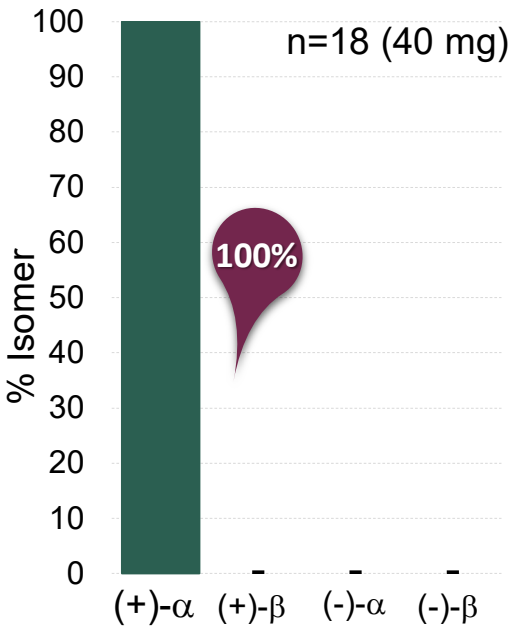
Concentrations of HTBZ isomers were determined in a serum sample, from 1 patient taking tetrabenazine 25 mg, that was purchased from a commercial specimen bank.

Study 3

Deutetrabenazine
HTBZ Isomer Profile[3]



Valbenazine
HTBZ Isomer Profile[3]



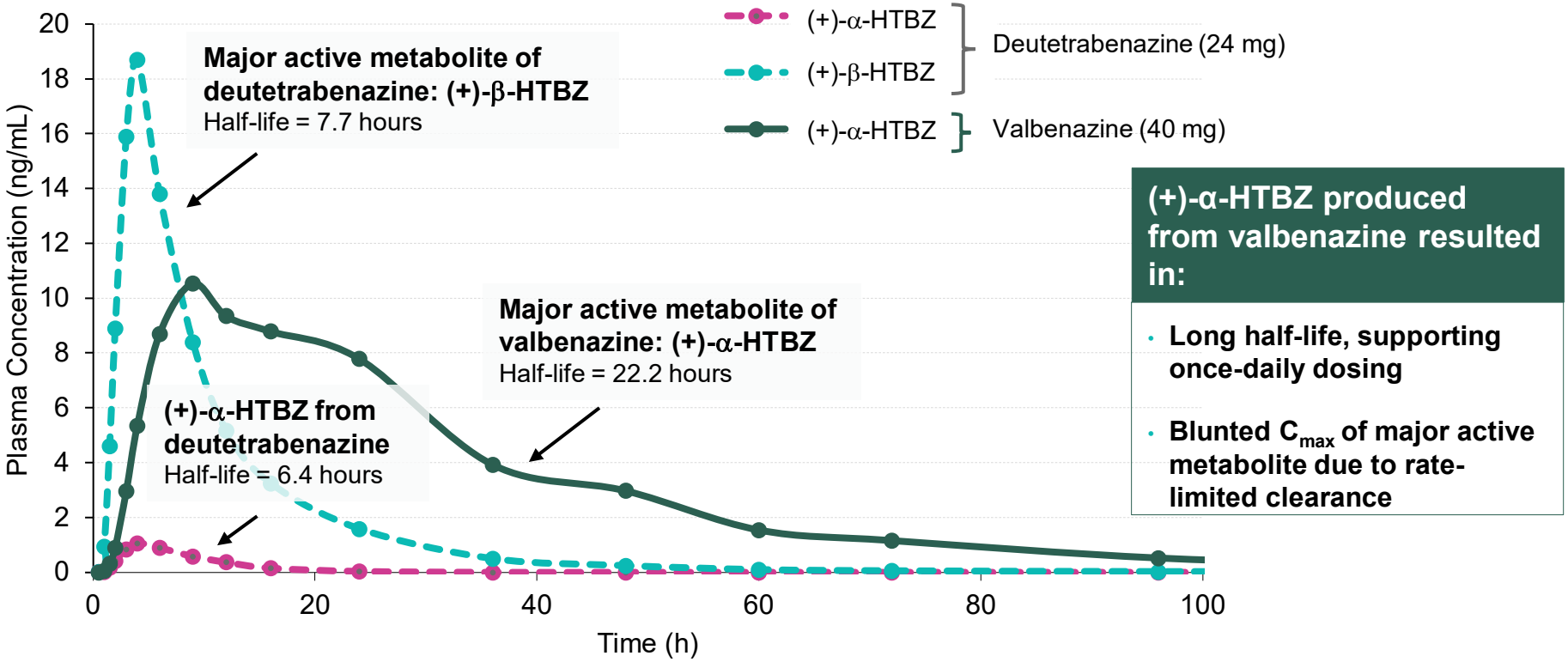
The pharmacokinetics of valbenazine and its [+]-α-HTBZ metabolite, and each of the 4 deutetrabenazine metabolites, were assessed in 18 male subjects randomized to receive single-dose valbenazine 40 mg and deutetrabenazine 24 mg (two 12 mg tablets). In this phase 1, open-label, crossover study, blood samples were obtained predose and at multiple intervals postdose. Graphs represent % isomer of area under the curve from time 0 to infinity.

These data do not imply superiority of any compound. Head-to-head trials comparing tetrabenazine, deutetrabenazine, or valbenazine have not been conducted.

1. INGREZZA. Package insert. Neurocrine Biosciences, Inc. 2. Skor H, et al. *Drugs* R D. 2017;17(3):339-359 3. Vijan A, et al. ASCP 2021. 4. Grigoriadis DE, et al. *J Pharmacol Exp Ther*. 2017;361(3):454-461.

Valbenazine Administration Resulted in Slow and Stable Production of the Active (+)-α-HTBZ Isomer

Concentrations of Active Metabolites After a Single Dose of Deutetrabenazine or Valbenazine (N=18)[a]



(+)-α-HTBZ produced from valbenazine resulted in:

- **Long half-life, supporting once-daily dosing**
- **Blunted C_{max} of major active metabolite due to rate-limited clearance**

The pharmacokinetics of valbenazine and its [+]-α-HTBZ metabolite, and each of the 4 deutetrabenazine metabolites, were assessed in 18 male subjects randomized to receive single-dose valbenazine 40 mg and deutetrabenazine 24 mg (two 12 mg tablets). In this phase 1, open-label, crossover study, blood samples were obtained predose and at multiple intervals postdose.

[a]These data do not imply superiority of any compound. Head-to-head trials comparing deutetrabenazine to valbenazine have not been conducted.

Vijan A, et al. ASCP 2021.

VMAT2 Inhibitor Pharmacology: Summary

- There are important differences in the pharmacologic, pharmacokinetic, and pharmacodynamic profiles of valbenazine compared to other available VMAT2 inhibitors (i.e., tetrabenazine and deutetrabenazine)
- Valbenazine is metabolized to a single active HTBZ metabolite, [+]-α-HTBZ, which is a potent and selective inhibitor of VMAT2 that has no discernible off-target activity at therapeutic exposures
- Both tetrabenazine and deutetrabenazine are metabolized to four stereoisomers, two of which interact with VMAT2 ([+]-α-HTBZ/[+]-α-dHTBZ and [+]-β-HTBZ/[+]-β-dHTBZ)
- The most abundant metabolites for tetrabenazine and deutetrabenazine are [-]-α-HTBZ and [-]-α-dHTBZ, respectively
  - [-]-α-HTBZ exhibits much lower VMAT2 inhibition compared to the other metabolites, but have increased affinity for other CNS targets
  - The most abundant metabolite that is active at VMAT2 is [+]-β-HTBZ/[+]-β-dHTBZ
- The PK profile of valbenazine (i.e., active metabolite with a half-life of 22.2 hours) supports once-daily dosing for valbenazine
- The active metabolites of deutetrabenazine have half-lives ranging from 5.2 to 12.3 hours, supporting twice-daily dosing

VMAT2, vesicular monoamine transporter 2; HTBZ, dihydrotetrabenazine; dHTBZ, deuterated dihydrotetrabenazine; PK, pharmacokinetics.
Vijan A, et al. ASCP 2021.

Valbenazine VMAT2 Target Occupancy Study

Valbenazine VMAT2 Target Occupancy Study

- Valbenazine is extensively metabolized to a clinically active metabolite, [+]-α-dihydrotetrabenazine ([+]-α-HTBZ), through hydrolysis of its valine ester[1]
- Positron emission tomography (PET) studies in nonhuman primates (NHPs) provide valuable information on the binding of pharmacologic compounds to desired targets in the brain[1]
- Using valbenazine doses with clinical efficacy in TD (40 and 80 mg), along with known pharmacokinetics of valbenazine, PET methods were applied to determine what percent of target occupancy (%TO) for VMAT2 is needed to treat TD[2]

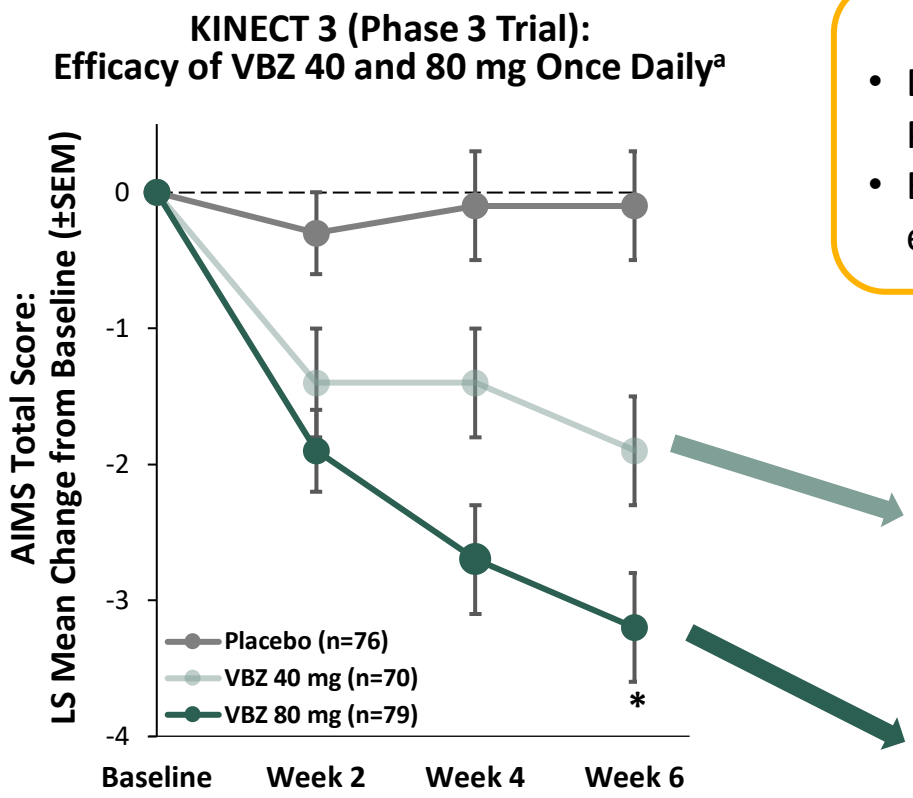
Study Method Details

NHP Procedures

TD, tardive dyskinesia; VMAT2, vesicular monoamine transporter 2.

1. Grigoriadis DE, et al. J Pharmacol Exp Ther 2017;361:454-61. 2. Terry-Lorenzo R, et al. ACCP 2021; September 13-17, 2021.

Valbenazine VMAT2 Target Occupancy Study Objectives



Objectives

- Determine %TO of [+]-α-HTBZ using NHP PET methods
- Estimate VMAT2 %TO at valbenazine efficacious doses in humans

Valbenazine Treatment Effects and Plasma Concentrations

Valbenazine 40 mg
- d = 0.5 (moderate effect size)
- C_{ave} = 16.1 ng/mL
- %TO at C_{ave} = **??%**

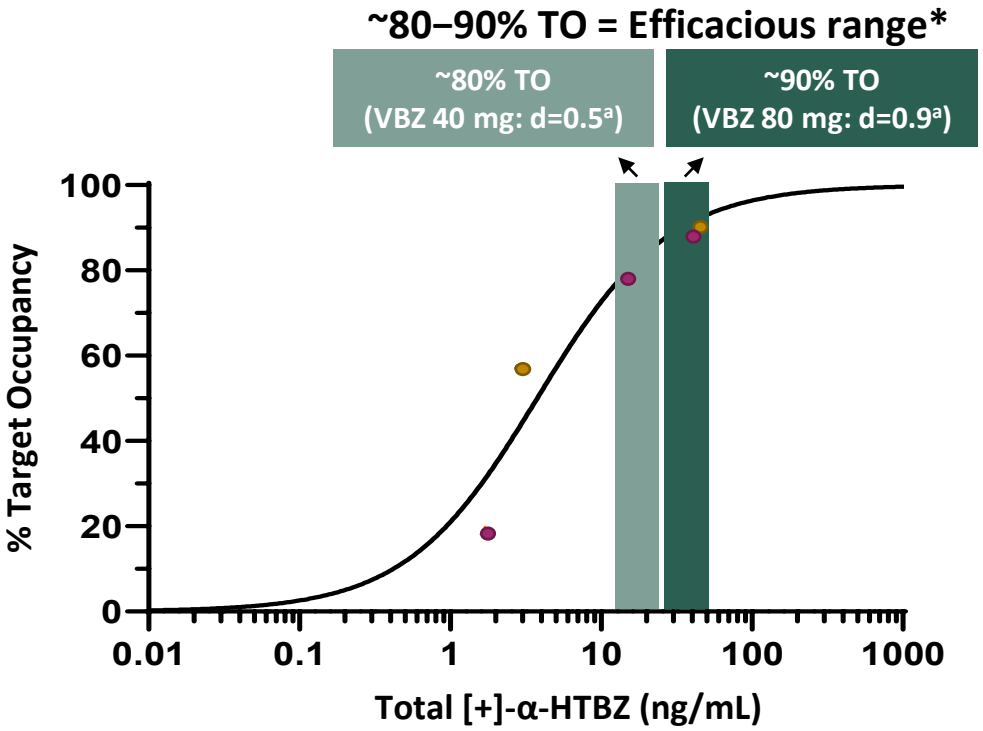
Valbenazine 80 mg
- d = 0.9 (large effect size)
- C_{ave} = 32.3 ng/mL
- %TO at C_{ave} = **??%**

*P<0.001 for valbenazine 80 mg, dose that was statistically significantly different from placebo after adjusting for multiplicity.
[a]From Hauser RA et al., *Am J Psychiatry* 2017.
[+]-α-HTBZ, [+]-α-dihydrotetrabenazine; %TO, target occupancy; AIMS, Abnormal Involuntary Movement Scale; C_{ave}, average plasma concentration of [+]-α-HTBZ at steady state; d, Cohen's effect size; LS, least squares; NHP, nonhuman primate; PET, positron emission tomography; SEM, standard error of the mean; VBZ, valbenazine; VMAT2, vesicular monoamine transporter 2.
Terry-Lorenzo R, et al. ACCP 2021; September 13-17, 2021.

Valbenazine VMAT2 Target Occupancy Study: Results

- At doses approved for the treatment of TD, valbenazine is estimated to maintain a high VMAT2 occupancy (≥73%) throughout each 24-hour period
- Relevant target occupancy (~80% for C_{ave}) was achieved for valbenazine 40 mg indicating a potential biological effect from the beginning of treatment

VMAT2 %TO			
VBZ Dose	**C_{trough}**	**C_{ave}**	**C_{max}**
40 mg	73%	79%	82%
60 mg	82%	86%	88%
80 mg	85%	89%	91%



*Benchmarks are consistent with rat pharmacology (not shown)
[a]Cohen's effect size (d) from Hauser RA et al., *Am J Psychiatry* 2017.
Colored circles represent results for 2 female cynomolgus macaques as follows: A7701 (orange), A702 (purple). Boxes represent minimum-to-maximum plasma concentrations for valbenazine 40 mg (light green) and 80 mg (dark green).
[+]-α-HTBZ, [+]-α-dihydrotetrabenazine; %TO, target occupancy; VBZ, valbenazine.
Terry-Lorenzo R, et al. ACCP 2021; September 13-17, 2021.

Valbenazine VMAT2 Target Occupancy Study: Summary

- Using the two valbenazine doses that demonstrated efficacy in the Phase 3 trial of valbenazine in adults with TD (40 and 80 mg), along with the known pharmacokinetic properties of valbenazine and [+]-α-HTBZ, PET methods in nonhuman primates were applied to estimate VMAT2 target occupancy at therapeutic levels of valbenazine approved for TD treatment.

- Valbenazine is estimated to maintain a high VMAT2 occupancy throughout each 24-hour period as follows: 40 mg (73% to 82%), 60 mg (82% to 88%), and 80 mg (85% to 91%).

    - These data are supportive of valbenazine as a once-daily medication for TD at the approved doses

- Relevant target occupancy (~80% for C_{ave}) was achieved for valbenazine 40 mg once daily, which is the recommended initiation dose for all patients with TD indicating a potential biological effect from the beginning of treatment

- Based on the larger effect size for valbenazine 80 mg observed in the Phase 3 clinical trial, results from this study suggest that a high sustained occupancy (≥85%) and inhibition of VMAT2 underpins maximal efficacy for TD

Terry-Lorenzo R, et al. ACCP 2021; September 13-17, 2021.