CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209241Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Mitchell V. Mathis, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	209241 O-1 (priority review/NME)
Applicant	Neurocrine Biosciences, Inc.
Date of Submission	11 August 2016
PDUFA Goal Date	11 April 2017
Proprietary Name / **Non-Proprietary Name**	Ingrezza/valbenazine
Dosage Form(s) / Strength(s)	40 mg capsule
Applicant Proposed Indication(s)/Population(s)	Treatment of Tardive Dyskinesia in Adults
Action/Recommended Action for NME:	*Recommend Approval*
Approved/Recommended Indication/Population(s) (if applicable)	*Tardive Dyskinesia in Adults*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Michael C. Davis, MD, PhD** **Brian J. Miller, MD, MBA, MPH** **Marc Stone, MD, Deputy Director for Safety**
Statistical Review	**Thomas Birkner, PhD** **Peiling Yang, PhD** **H.M. James Hung, PhD**
Pharmacology Toxicology Review	**Darren Fegley, PhD, DABT**

Reference ID: 4082860

	Aisar Atrakchi, PhD
OPQ Review	**Sharon Kelly** **Rao Kambhampati** **Chunshen Cai** **Steven Hertz** **Ta-Chen Wu** **Grafton Adams** **Jim Laurenson** **David Claffey**
Microbiology Review	**N/A**
Clinical Pharmacology Review	**Di Zhou, PhD** **Huixia Zhang, PhD** **Gopichand Gottipati, PhD** **Jeffrey Kraft, PhD** **Hao Zhu, PhD** **Kevin Krudys, PhD** **Christian Grimstein, PhD** **Mehul Mehta, PhD**
OPDP	**Chirsite Bradshaw, PharmD**
OSI	**Cara Alfaro, PharmD** **Susan Thompson, MD** **Kassa Ayalew, MD, MPH**
CDTL Review	**Javier Muniz, MD**
OSE/DMEPA	**Ebony Whaley, PharmD, BCPPS** **Lolita White, PharmD**
OSE/DRISK	**Leah Hart, PharmD** **Jamie Wilkins Parker, PharmD**
QT IRT	**Nan Zheng** **Lars Johannesen** **Moh Jee Ng** **Qianyu Dang** **Michael Y Li**

	Christine E Garnett

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
QTIRT=QT Interdisciplinary Review Team

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Valbenazine is a new molecular entity not approved for marketing in any country. It is a vesicular monoamine transporter type 2 (VMAT2) inhibitor that has been developed for the treatment of tardive dyskinesia (TD). TD is an iatrogenic hyperkinetic movement disorder encountered in patients chronically treated with dopamine receptor blocking drugs. There are no drugs approved to treat TD. The involuntary movements of TD are socially and functionally disabling to the patient. The primary purpose of treating TD is to reduce involuntary movements and therefore decrease disability fromTD. Patients who develop TD often have a debilitating psychotic illness or mood disorder that requires continuation of treatment with antipsychotics.

The Applicant has submitted two studies that demonstrate a statistically and clinically significant reduction in abnormal involuntary movements in adult patients with TD treated with valbenazine. Several adverse reactions were identified, but all are manageable with labeling and a patient package insert. The review team has recommended approval of this application and I agree with them.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• TD is a socially (hyperkinetic movements/unintelligible speech) and functionally (some difficulty swallowing or ambulating) disabling iatrogenic disorder. • Prevalence estimates vary, but have been cited as high as 8.5% of those chronically treated with conventional antipsychotics. • Current treatment is to discontinue or change the drug needed to control the psychiatric disorder, or reduce the dose, but this is not always clinically feasible.	TD is a socially and functionally disabling iatrogenic disorder occurring in a significant proportion of patients treated with antipsychotic drugs. Discontinuing the offending drug can exacerbate the underlying psychiatric condition.
Current Treatment Options	None approved. Second generation antipsychotics ("atypical antipsychotics") are thought to be pharmacologically less likely to cause TD, but many patients with TD have a chronic exposure history to conventional antipsychotics, making this difficult to accurately	Current treatment options are insufficient and discontinuing the offending drug is likely to exacerbate the underlying psychiatric illness.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	assess.	
Benefit	Evidence of effectiveness was presented in two studies submitted by the Applicant. The Abnormal Involuntary Movement Scale (AIMS) was developed to assess and track symptoms of TD and is considered an appropriate measure to use in clinical drug trials of patients with TD. The AIMS was significantly improved in patients randomized to valbenazine 80 mg/day and in a second flexible-dose study. These data were considered to be substantial evidence of efficacy by the review team.	Efficacy has been established. The majority of patients on 80 mg/day of valbenazine experienced a decrease in the symptoms of TD.
Risk	• The safety database was of adequate size and was primarily composed of US patients. Adverse reactions include somnolence (11%), balance problems/falls (4%), and akathisia (3%). • A dose-related QT prolongation was identified by the review team which could be clinically significant in patients with CYP2D6 or CYP 3A4 inhibition/poor metabolizer status. • Suicidal ideation and behavior were actively assessed during the trials and no signal of increased risk/harm was identified.	These adverse reactions can be managed with appropriate labeling/patient information. No increased risk of self-harm was identified.
Risk Management	Adverse reactions do not outweigh the clinical benefit of the drug and are manageable with labeling and a patient package insert (PPI).	Product labeling and PPI are adequate for management of risk.

2. Background

Tardive Dyskinesia is a movement disorder caused by dopamine receptor blocking drugs. Most dopamine receptor blocking drugs are antipsychotics, although some are approved for gastrointestinal motility disorders (e.g., metoclopramide). TD is a socially and functionally disabling iatrogenic disorder that is chronic and not always reversible by discontinuing the offending dopamine blocking drug.

There is no clear way to predict who will be affected by TD. There is some evidence from the literature that patients with acute dystonic syndromes (extrapyramidal syndrome, EPS) may be more susceptible to late (tardive) dyskinesias, but regardless of susceptibility, patients with major psychiatric disorders often, as standard of care, receive treatment with antipsychotics, and are therefore at risk of TD.

There is some evidence that the newer, second-generation antipsychotics are less likely to cause TD, but these analyses are complicated by the fact that many patients living with TD were at one time also treated with conventional antipsychotics and therefore were exposed to the drug class with increased risk.

Iatrogenic involuntary movements from a drug used to treat severe psychiatric illness can have a significant negative impact on already very sick patients who require dopamine blocking medications to function normally. Review of this drug was designated priority by the Division because there are no approved treatments for TD, and Breakthrough Status was granted.

The Division agreed with the sponsor during development that a statistically significant change in the AIMS would provide evidence of drug efficacy and that decreased involuntary movements were, on face, clinically significant and the core feature of TD. The sponsor has presented substantial evidence of effectiveness of valbenazine for the treatment of adults with TD and they have adequately characterized the safety of the drug. The review team has recommended that the drug be approved and I agree with them. While 80 mg/day was identified as the target dose, doses higher than 80 mg were not evaluated and should be studied post-marketing.

Valbenazine's active metabolite (+-alpha-dihydrotetrabenazine) is an enantiomer of the approved drug tetrabenazine's active metabolite. Tetrabenazine is approved for the treatment of chorea associated with Huntington's disease. Tetrabenazine is labeled with a boxed warning for suicidality and depression, but these were not seen in the valbenazine trial with active monitoring for suicidal ideation and behavior, and the populations are much different, with a higher risk of suicidal ideation and behavior in Huntington's disease patients.

3. Product Quality

The Integrated Quality Assessment team has recommended approval from a product quality perspective. The drug product is available in a single strength 40 mg capsule of valbenazine tosylate.

4. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology reviews for details; important nonclinical findings are presented here.

Metabolism was demonstrated by radiolabeled mass balance studies to be qualitatively similar in rats, dogs, and humans. Valbenazine-related radioactivity was found in the pigmented cells of the retina, but there were no valbenazine treatment-related eye findings in dog or pigmented mouse and phototoxicity was not observed; therefore, the clinical significance of distribution of drug in the eye is unclear.

The safety pharmacology evaluation determined that valbenazine moderately inhibits hERG channels and produces moderate QTc prolongation in dogs at doses 6 times the maximum recommended equivalent dose in humans.

Primary organ toxicity was the central nervous system (CNS) in dogs and mouse. Clinical signs consistent with CNS monoamine depletion (decreased activity, ataxia, ptosis) were observed in rat, mouse, and dog. There was an increased activity prior to dosing (drug trough) suggesting a possible withdrawal phenomenon, which the applicant plans to investigate in the postmarketing period. There were no CNS findings on histology.

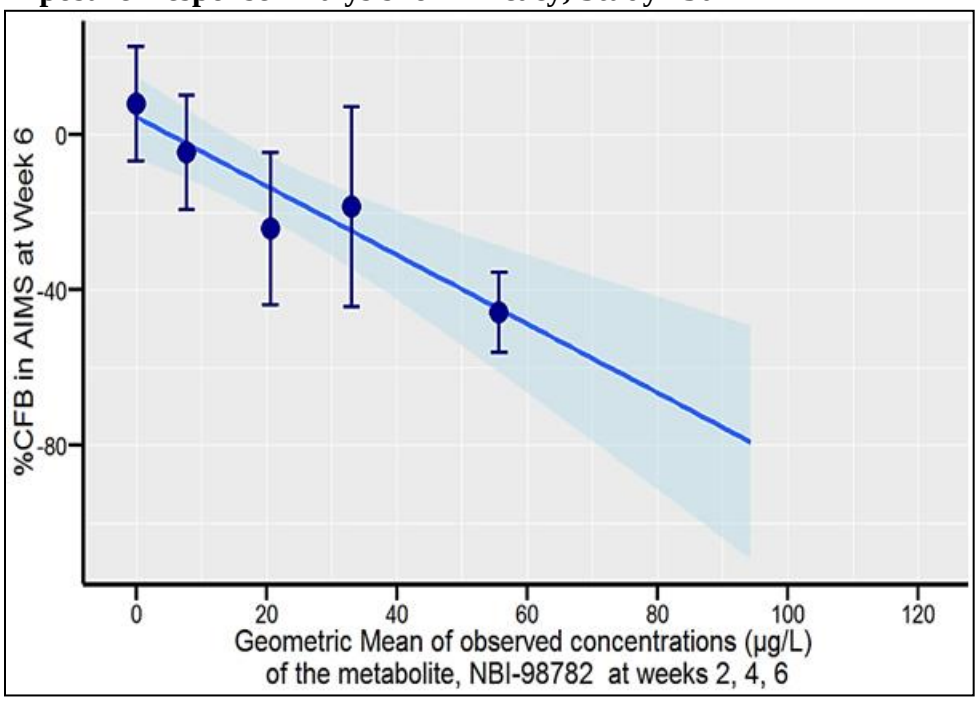
Valbenazine was found to be nongenotoxic in several tests of genotoxicity and did not produce tumors in rats or mice. Fertility was disrupted in rats, but the dysfunction was thought to be mediated by hyperprolactinemia rather than direct toxicity.

5. Clinical Pharmacology

Key recommendations from the Clinical Pharmacology reviews include dosing recommendations for patients with CYP2D6 and CYP3A4 inhibition/poor metabolism and dosing in patients with renal impairment. Several post-marketing studies have been suggested and are included under section 13 of this document.

PK sampling was included in Study 1304 and an exposure-response analysis for efficacy was conducted using % change from baseline in Week 6 AIMS total dyskinesia score as a function of concentration of +-alpha-dihydrotetrabenazine. This analysis demonstrated an exposure-response relationship that did not plateau in the tested dose range up to 80 mg/day (see below). This finding led to a post-marketing request to study a higher dose; the sponsor has agreed to conduct this study in Phase 4.

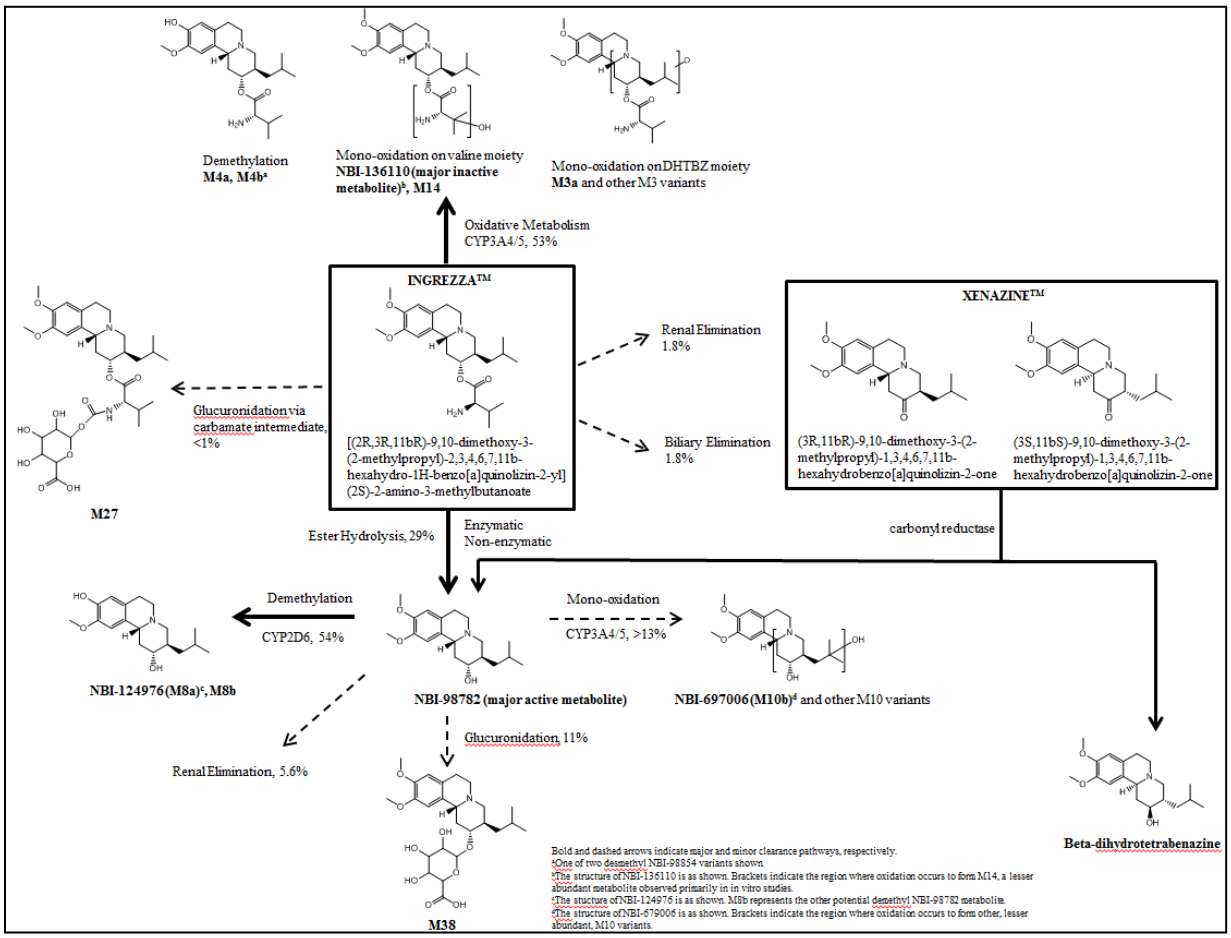
Exposure-Response Analysis for Efficacy, Study 1304



Pharmacokinetics

Oral bioavailability is estimated to be 49% of dose. The Tmax following oral administration is 30-60 minutes for the parent drug and 4-8 hours for +-alpha-dihydrotetrabenazine metabolite. AUC and Cmax are proportional to dose in the range of 40 mg/day to 300 mg/day. The metabolic pathways for valbenazine are diagramed below. Note that a major active metabolite from tetrabenazine (Xenazine in the figure) is in common with valbenazine's major active metabolite (+-alpha-dihydrotetrabenazine, labeled NBI-98782 in the figure).

Valbenazine Metabolic Pathways



Clinical Pharmacology Dose Adjustment Recommendations:

- The daily dose should be reduced by half, based on therapeutic response and tolerability, when co-administered with a strong CYP3A4 inhibitor.

- Dose reduction should be considered, based on clinical response, when co-administered with a strong CYP2D6 inhibitor or in a known CYP2D6 poor metabolizer.
- Concomitant use with CYP3A4 inducers should be avoided.
- The daily dose should be reduced to 40 mg/day for patients with moderate or severe hepatic impairment (Child-Pugh score 7 to 15).
- No dose adjustment is necessary for patients with mild to moderate renal impairment.
- Dosing instructions for patients with severe renal impairment and patients receiving concomitant CYP2D6 substrates are pending further investigation postmarketing.
- Digoxin concentrations should be monitored when co-administering. Dose adjustment of digoxin may be necessary based on digoxin concentration.

- Valbenazine can be taken with or without food.

6. Microbiology

Not applicable for this application.

7. Clinical/Statistical-Efficacy

The clinical development program for valbenazine consisted of 20 studies. There were 14 Phase 1, 4 Phase 2, and 2 Phase 3 studies. The Applicant considers studies 1304 and 1202 pivotal and studies 1201 and 1402 supportive for the evaluation of valbenazine for the treatment of TD. Phase 2 and 3 studies are listed in the table below.

Phase 2 and Phase 3 Trials: Valbenazine for Tardive Dyskinesia

Trial Identity[1]	Trial Design	Regimen/schedule/ route[2]	Study Endpoints[3]	Treatment Duration / Follow Up	No. of patients enrolled	Study Population	No. of Centers and Regions
Controlled Studies to Support Efficacy and Safety							
1101	Phase 2, randomized, double-blind, placebo-controlled, two-period crossover study	VBZ 12.5 or 50 mg PO daily or PBO PO daily	Primary: AIMS dyskinesia total (change from baseline)	14 days VBZ and 14 days PBO for each treatment period	37	Adults (age 18-65) with neuroleptic-induced tardive dyskinesia and schizophrenia or schizoaffective disorder	12 sites in the USA
1201	Phase 2, randomized, double-blind, placebo-controlled, parallel-group study followed by open-label extension	VBZ 100 mg PO daily x 2 weeks, then 50 mg PO daily x 4 weeks, or 50 mg PO daily or PBO x 6 weeks (1:1:2); followed by open-label VBZ 50 mg PO daily	Primary: AIMS dyskinesia total (change from baseline) Key Secondary: CGI-TD	6 weeks, followed by 6 week open-label extension	109	Adults (age 18-65) with neuroleptic-induced tardive dyskinesia and schizophrenia or schizoaffective disorder	35 sites in the USA and Puerto Rico

Trial Identity[1]	Trial Design	Regimen/schedule/ route[2]	Study Endpoints[3]	Treatment Duration / Follow Up	No. of patients enrolled	Study Population	No. of Centers and Regions
1202	Phase 2, randomized, double-blind, placebo-controlled, dose-titration study	VBZ 25, 50, or 75 mg PO daily (flexible) or PBO PO daily (1:1)	Primary: AIMS dyskinesia total (change from baseline)	6 weeks	102	Adults (age 18-85) with neuroleptic-induced tardive dyskinesia and schizophrenia, schizoaffective disorder, mood disorder, or a gastrointestinal disorder (the latter treated with metoclopramide)	29 sites in the USA and Puerto Rico
1304	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study followed by subject- and investigator-blinded extension	VBZ 40 mg, 80 mg, or PBO PO daily (1:1:1); PBO subjects re-randomized to VBZ 40 mg or 80 mg (1:1) for extension	Primary: AIMS dyskinesia total (change from baseline) Key Secondary: CGI-TD	6 weeks, followed by 42 week extension	234	Adults (age 18-85) with neuroleptic-induced tardive dyskinesia and schizophrenia, schizoaffective disorder, or mood disorder	63 sites in the USA, Canada, and Puerto Rico
Additional Phase 2/3 Studies to Support Safety							
1001	Phase 2, open-label, dose titration study	VBZ 12.5 mg → 25 mg → 50 mg PO daily	Safety: AEs, laboratory tests, physical examinations, 12-lead ECGs, BPRS Efficacy (uncontrolled): AIMS, CGI-TD	12 days (4 days of each dose)	6	Adults (age 18-65) with neuroleptic induced tardive dyskinesia and schizophrenia or schizoaffective disorder	1 (Canada)

Reference ID: 4082860

Trial Identity[1]	Trial Design	Regimen/schedule/ route[2]	Study Endpoints[3]	Treatment Duration / Follow Up	No. of patients enrolled	Study Population	No. of Centers and Regions
1402	Phase 3, open-label, fixed-dose escalation study	VBZ 40 mg → 80 mg PO daily	Safety: AEs, laboratory tests, physical examinations, 12-lead ECGs, C-SSRS, BARS, SAS, CDSS, MADRS, PANSS, YMRS Efficacy (uncontrolled): AIMS, CGI-TD, PGIC, TDIS, AMBMTD	48 weeks	168	Adults (age 18-85) with neuroleptic-induced tardive dyskinesia and schizophrenia, schizoaffective disorder, or mood disorder	45 sites in the USA, Canada, and Puerto Rico

[1]All 4-digit identity numbers are prefaced by NBI-98854- for the full trial identifier; [2]VBZ = valbenazine; PO = by mouth; PBO = placebo; [3]AIMS dyskinesia = Abnormal Involuntary Movement Scale Items 1-7; CGI-TD = Clinical Global Impression of Change-Tardive Dyskinesia; ECG = electrocardiogram; BPRS = Brief Psychiatric Rating Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; BARS = Barnes Akathisia Rating Scale; SAS = Simpson-Angus Scale; CDSS = Calgary Depression Scale for Schizophrenia; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; YMRS = Young-Mania Rating Scale; PGIC = Patient Global Impression of Change; TDIS = Tardive Dyskinesia Impact Scale; AMBMTD = Assessment of Most Bothersome

The efficacy review was conducted by Dr. Michael Davis (Medical Officer) and supplemented with analyses by Dr. Douglas Warfield (Associate Director of Biomedical Informatics). The statistical review was conducted by Dr. Thomas Birkner (Biometrics Reviewer). The review of safety was conducted by Dr. Brian Miller (Medical Officer, Safety Team).

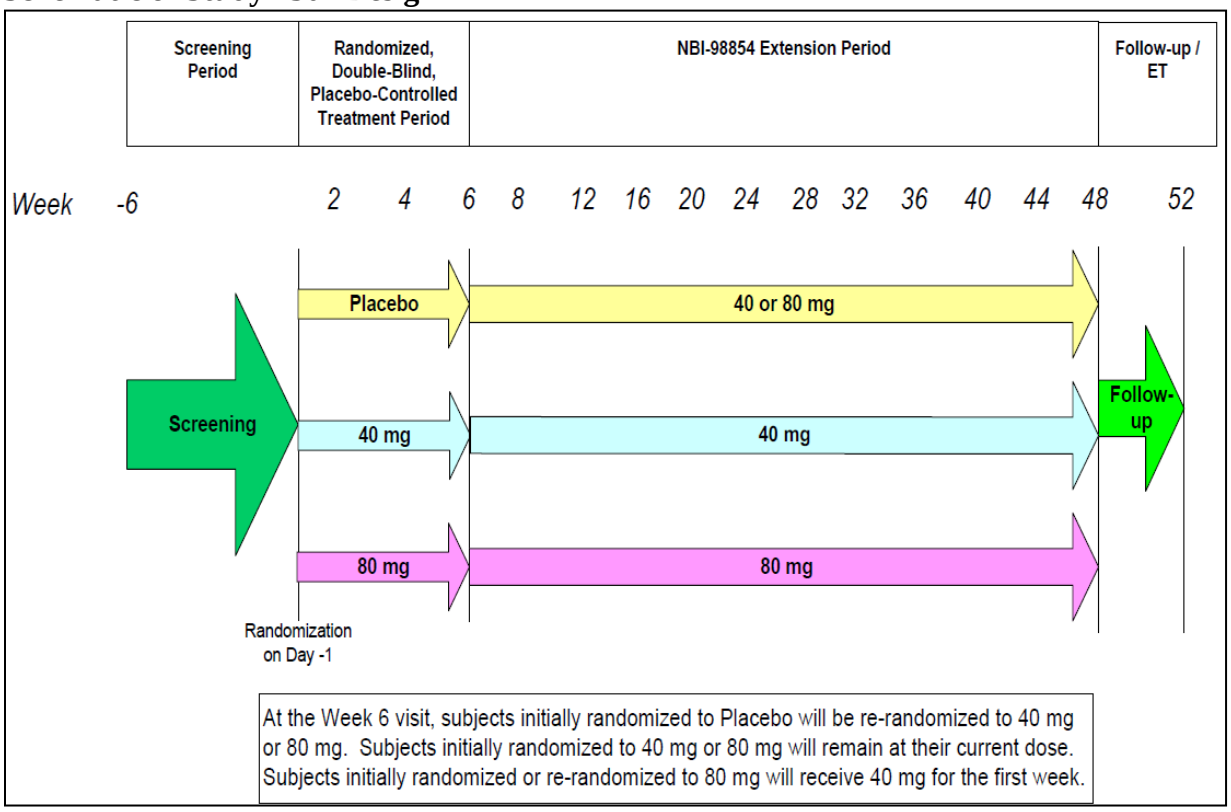
The two positive efficacy studies (Studies 1304 and 1202) submitted support the claim that the 80 mg/day dose of valbenazine reduces the symptoms of TD as measured by the modified AIMS. From Study 1304, the 40 mg/day dose did not meet the strict statistical standard for efficacy due to a proximal testing sequence failure for the secondary endpoint at 80 mg/day, but it was, indeed, numerically significant (see below).

The Phase 2 study submitted in support of this application, Study 1202, examined flexible-dose valbenazine in the range of 25-75 mg/day, and was statistically positive with the mean dose at Week 6 of 64 mg/day. These findings served as substantiation of the finding in Study 1304 and suggest that a dose closer to 80 mg/day is required for efficacy (see Dr. Birkner's Review).

Study 1304

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel, Fixed-dose Study to Assess the Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Tardive Dyskinesia. A schematic representation of Trial 1304 is presented below.

Schematic of Study 1304 Design



Design: Eligible patients with TD were randomized (1:1:1). Two doses of valbenazine (40 mg/day and 80 mg/day) were compared to placebo in patients with TD meeting appropriate eligibility criteria. The primary endpoint was the modified AIMS score. The AIMS was modified from the original scale which was designed to assess the severity of TD by examining 12 items of which 7 of these items related to involuntary movements in the orofacial region, trunk, and extremities, and 5 items related to global severity, patient awareness and distress, and problems with teeth or dentures. The modified version included only items 1-7, and the Division agreed to this approach prior to initialization of the trials.

The AIMS were collected on-site by investigators and the assessments were video-recorded. Video recordings were sent to two central raters who were required to reach agreement on the scores for Items 1-7 of the AIMS from the video. The raters were blinded to treatment and to sequence of measurement (which visit in the trial the patient video was taken from). The AIMS, as modified for this study, is an appropriate endpoint for measuring change in TD

Reference ID: 4082860

symptoms, and the use of central raters was an intelligent design feature to reduce variability and sequence/expectation bias.

Primary Efficacy Assessment—Abnormal Involuntary Movement Scale (AIMS, modified)

Score	Descriptors (For items 1-7)
0	No dyskinesia
1	Minimal or slight dyskinesia: Low amplitude, present during some but not most of the exam
2	Mild dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam)
3	Moderate dyskinesia: Moderate amplitude and present during most of exam
4	Severe dyskinesia: Maximal amplitude and present during most of exam

Facial and Oral Movements	None	Minimal	Mild	Moderate	Severe
1. Muscles of Facial Expression e.g., movements of forehead, eyebrows, periorbital area, cheeks, include frowning, blinking, smiling, grimacing	0	1	2	3	4
2. Lips and perioral area e.g., puckering, pouting, smacking	0	1	2	3	4
3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement	0	1	2	3	4
4. Tongue Rate only increase in movement both in and out of mouth, NOT inability to sustain movement	0	1	2	3	4
Extremity Movements					
5. Upper *(arms, wrists, hands, fingers)* Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic)	0	1	2	3	4
6. Lower *(legs, knees, ankles, toes)* e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0	1	2	3	4
Trunk Movements					
7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic gyrations	0	1	2	3	4

The Clinical Global Impression of Change—Tardive Dyskinesia (CGI-TD) was the second outcome measure. This is a modified version of the CGI relative only to TD symptoms (see below). The Division prospectively agreed to the CGI-TD as a meaningful secondary endpoint.

Reference ID: 4082860

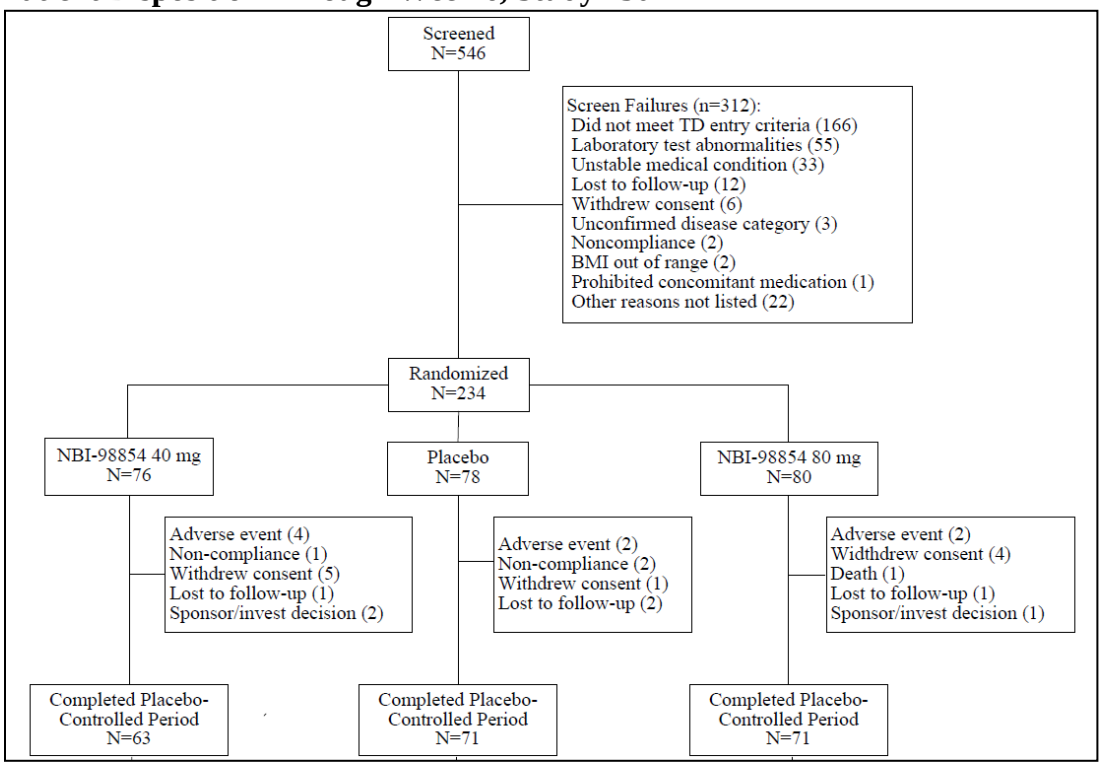
Clinical Global Impression—Tardive Dyskinesia

The investigator (or designee) will evaluate the change in the subject's Tardive Dyskinesia (TD) symptoms since initiation of study drug by choosing one of the 7 responses. Since the subject started taking the study medication, his/her TD symptoms are:
☐ Very Much Improved
☐ Much Improved
☐ Minimally Improved
☐ Not Changed
☐ Minimally Worse
☐ Much Worse
☐ Very Much Worse

There were several distal secondary endpoints measured; see Dr. Davis' review for details.

Disposition: The majority of patients finished the first 6 weeks of the trial (see below).

Patient Disposition Through Week 6, Study 1304



Source: Study 1304 Clinical Study Report, Figure 2, p. 69

Demographics: The majority of patients were under 65 years old with mean treatment age in the mid-50s, representing the age of patients seen clinically with TD (who must be on the dopamine receptor-blocking drug long enough to cause symptoms of TD). Demographics are presented below.

Baseline Characteristics, Study 1304

Parameter	Placebo (N=76) n (%)	Valbenazine (N=149)		Total (N=225) n (%)
		Valbenazine 40 mg daily (N=70) n (%)	Valbenazine 80 mg daily (N=79) n (%)	
Sex				
Male	42 (55.3%)	40 (57.1%)	39 (49.4%)	121 (53.8%)
Female	34 (44.7%)	30 (42.9%)	40 (50.6%)	104 (46.2%)
Age				
Mean years (SD)	57.0 (10.5)	55.3 (8.6)	56.0 (10.0)	56.1 (9.8)
Median (years)	58	56	57	57
Min, max (years)	30, 84	26, 74	32, 83	26, 84
Age Group				
≥ 17 - < 65 years	60 (78.9%)	62 (88.6%)	67 (84.8%)	189 (84.0%)
≥ 65 years	16 (21.1%)	8 (11.4%)	12 (15.2%)	36 (16.0%)
Race				
Caucasian	43 (56.6%)	41 (58.6%)	44 (55.7%)	128 (56.9%)
Black or African American	29 (38.2%)	25 (35.7%)	32 (40.5%)	86 (38.2%)
Asian	0	0	0	0
American Indian or Alaska Native	0	1 (1.4%)	1 (1.3%)	2 (0.9%)
Native Hawaiian or Other Pacific Islander	1 (1.3%)	0	0	1 (0.4%)
Other[1]	3 (3.9%)	3 (4.3%)	2 (2.5%)	8 (3.6%)
Ethnicity				
Hispanic or Latino	23 (30.3%)	22 (31.4%)	14 (17.7%)	59 (26.2%)
Not Hispanic or Latino	53 (69.7%)	48 (68.6%)	65 (82.3%)	166 (73.8%)

[1] *Includes identified races "Arabic," "Hispanic," "Mexican," and Mixed*
Source: Data derived from 1304 Clinical Study Report (Tables 14.1.6 and 14.1.8) and analysis dataset DM.XPT

Efficacy Results, Study 1304

Valbenazine 80 mg/day was statistically superior to placebo on the primary endpoint, and 40 mg/day was nominally significant—nominally significant but not statistically significant

secondary to a testing sequence failure proximal to examining the primary endpoint in the 40 mg/day group. The results presented below were confirmed by Biostatistics.

Results: Primary Efficacy Endpoint, Change from Baseline AIMS, Study 1304

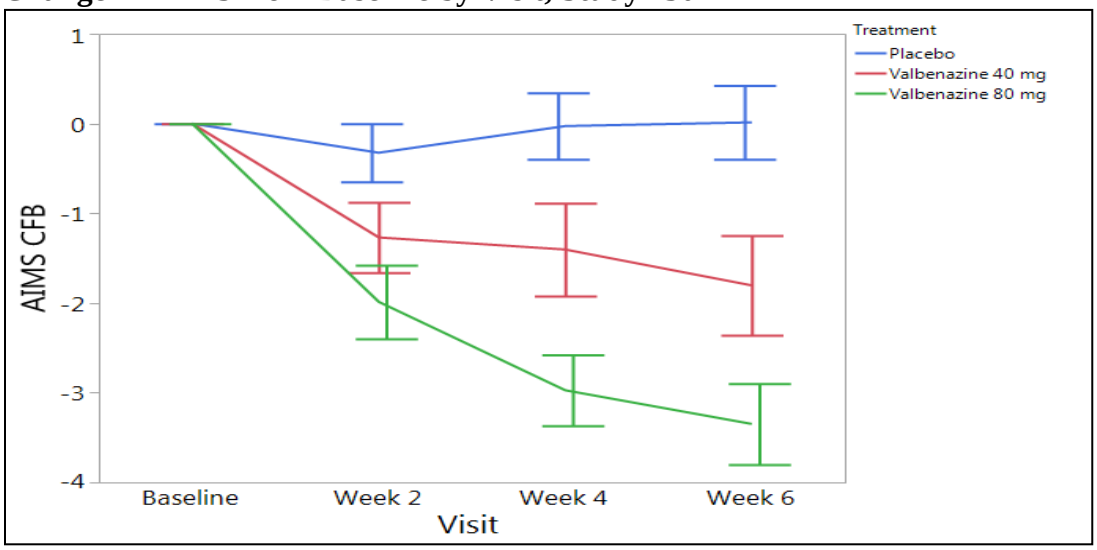
	Placebo (N=76)	Valbenazine 40 mg (N=70)	Valbenazine 80 mg (N=79)
6-week AIMS CFB: LS mean (SEM)[1]	-0.1 (0.4)	-1.9 (0.4)	-3.2 (0.4)
LS mean difference vs. placebo (SEM)		-1.8 (0.6)	-3.1 (0.6)
95% confidence interval		-3.0, -0.7	-4.2, -2.0
p value[2]		0.0021	<0.0001

Source: Study 1304 Clinical Study Report, Table 22, p. 86

[1]Least-squares (LS) mean was based on the MMRM model, which included baseline AIMS dyskinesia total score as a covariate and treatment group, primary psychiatric diagnosis, visit, baseline by visit interaction, and treatment group by visit interaction as fixed effects, and subject as a random effect.

[2]p value for test of null hypothesis that difference between the treatment group LS mean is equal to zero

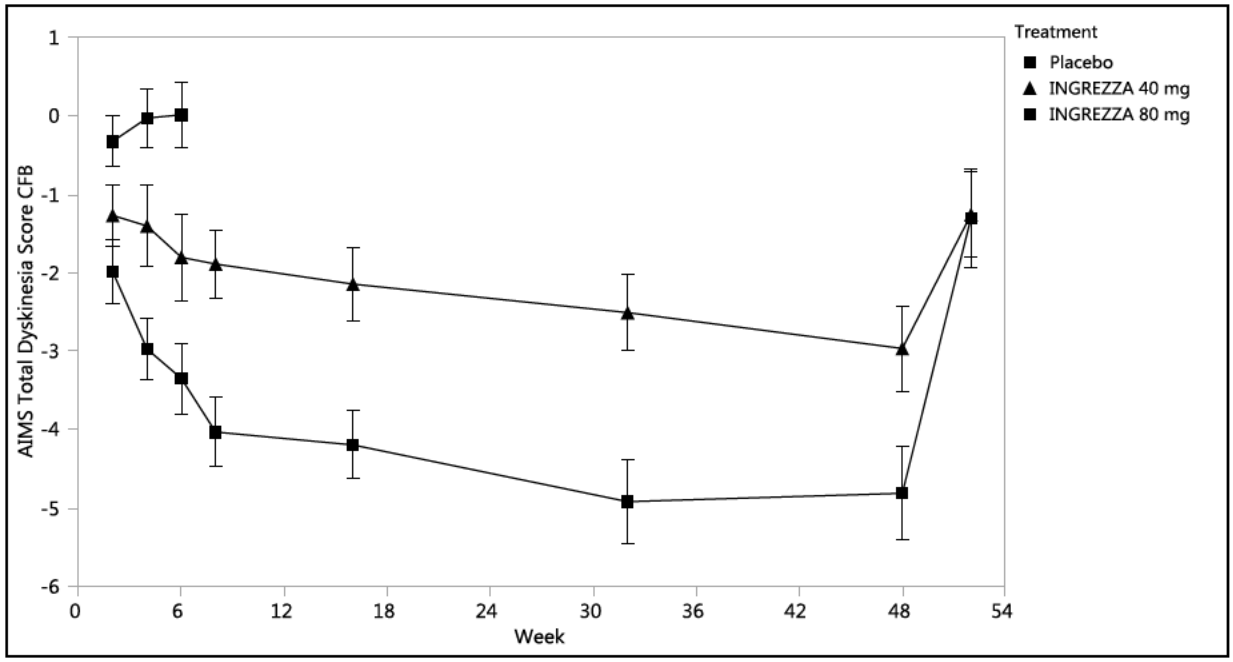
Change in AIMS from Baseline by Visit, Study 1304



Source: Reviewer-created, using Study 1304 analysis dataset A_AIMS.XPT. Error bars represent standard error of the mean. CFB = change from baseline.

The primary endpoint for Study 1304 was at Week 6, but data on both doses were collected through week 48. Although there is no placebo control after Week 6 (placebo patients were randomly assigned to either 40 mg/day or 80 mg/day for the rest of the study), there was internal dose control because both 40 mg/day and 80 mg/day were continued through week 48. The data are plotted below (Ingrezza is the requested tradename for valbenazine). From the graph, AIMS scores continued to decrease after 6 weeks for both doses and returned towards baseline after discontinuation (Week 48).

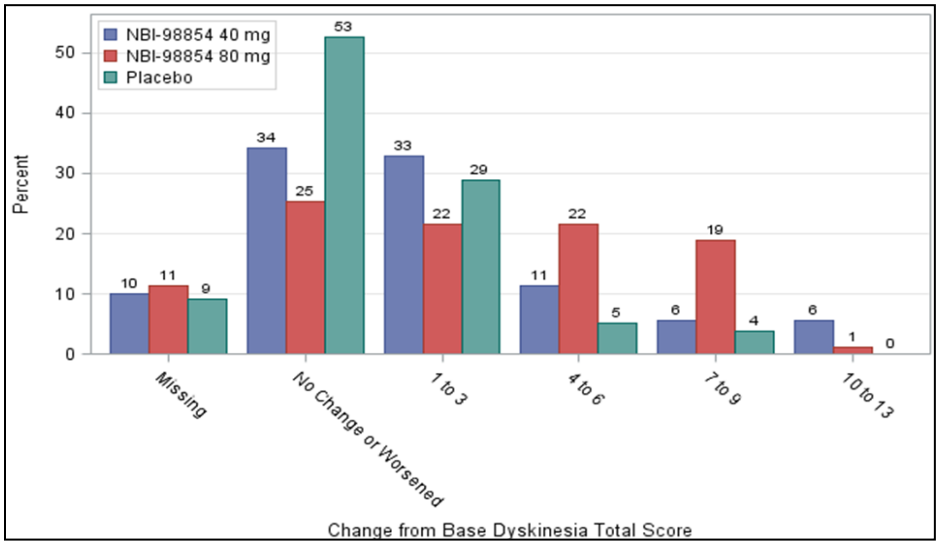
Change in AIMS from Baseline by Visit, Full Study Duration by Central Video Raters, Study 1304



Source: Primary reviewer-created, using Study 1304 analysis dataset A_AIMS.XPT. Subjects who received placebo and were re-randomized to valbenazine after 6 weeks are grouped with the 40 mg and 80 mg treatment groups from Weeks 8-52. Data from early termination visits were excluded. Each error bar is constructed using 1 standard error from the mean.

The review team examined efficacy data for Study 1304 by magnitude of response and found the data to be consistent with the conclusions from their examination of the primary endpoint. The data are presented visually in this figure:

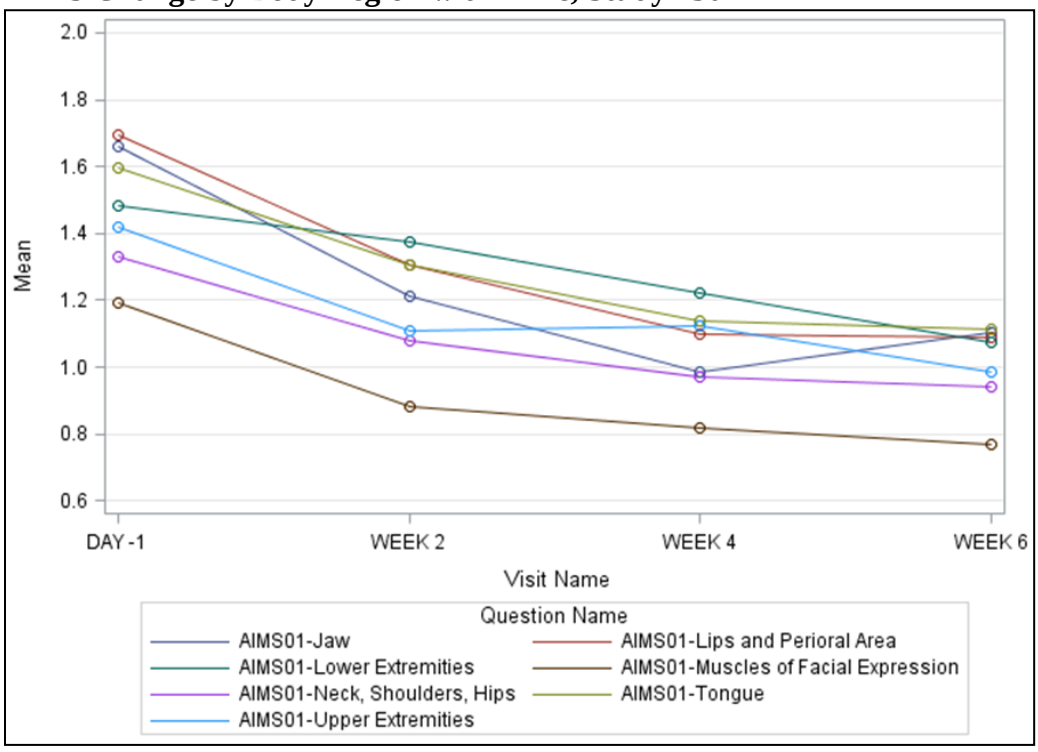
Percent of Patients with AIMS Improvement at Week 6 by Magnitude of Response, Study 1304



Source: Generated by Biometrics reviewer Dr. Thomas Birkner. NBI-98854=valbenazine.

Examination of change in AIMS by body region over time were also examined and a visual depiction is presented here:

AIMS Change by Body Region with Time, Study 1304



Source: created by Biometrics reviewer Dr. Thomas Birkner; Day -1=Baseline.

Efficacy, Secondary Endpoint CGI-TD
The mean CGI-TD score at Week 6 was not statistically significant for either dose, although the change directionally favored valbenazine.

Change in CGI-TD, Study 1304

	Placebo (N=76)	Valbenazine 40 mg (N=70)	Valbenazine 80 mg (N=79)
Week 2			
N	76	70	77
LS Mean (SEM)	3.6 (0.1)	3.5 (0.1)	3.5 (0.1)
LS Mean Difference (95% CI)		-0.1 (-0.3, 0.1)	-0.1 (-0.4, 0.1)
p value		0.2872	0.1782
Week 4			
N	74	65	73
LS Mean (SEM)	3.5 (0.1)	3.2 (0.1)	3.1 (0.1)
LS Mean Difference (95% CI)		-0.3 (-0.5, -0.1)	-0.4 (-0.6, -0.1)
p value		0.0180	0.0022
Week 6 (Key Secondary Endpoint)			
N	69	63	70
LS Mean (SEM)	3.2 (0.1)	2.9 (0.1)	2.9 (0.1)
LS Mean Difference (95% CI)		-0.3 (-0.5, 0)	-0.3 (-0.5, 0)
p value		0.0742	0.0560

Source: Primary reviewer-created, using information from 1304 Clinical Study Report

Note: it is because the statistical analysis plan dictated sequenced testing of CGI-TD at 80 mg/day prior to AIMS at 40 mg/day, that the primary endpoint at 40 mg/day was not considered to be statistically significant.

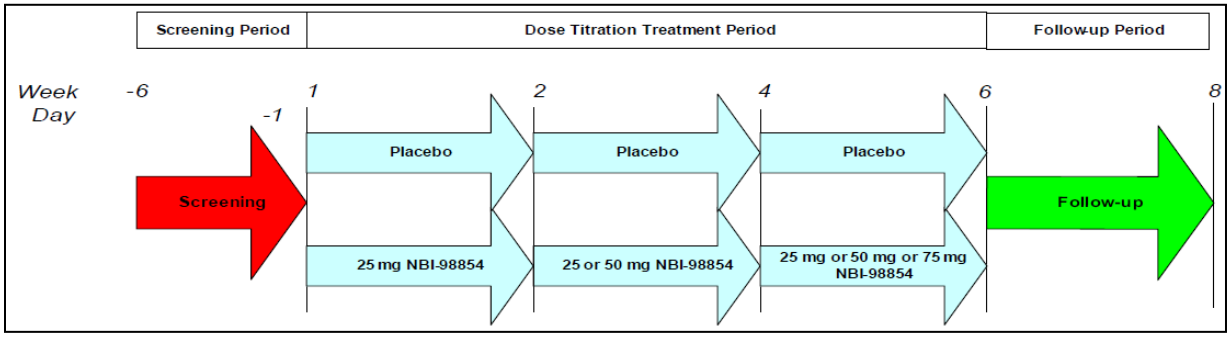
Efficacy Summary of Study 1304

Efficacy was established. The 80 mg/day dose is statistically superior to placebo and more effective than the 40 mg/day dose at reducing the symptoms of TD as measured by the modified AIMS.

Study 1202

Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Dose Titration Study to Assess the Safety, Tolerability, and Efficacy of Valbenazine for the Treatment of Tardive Dyskinesia

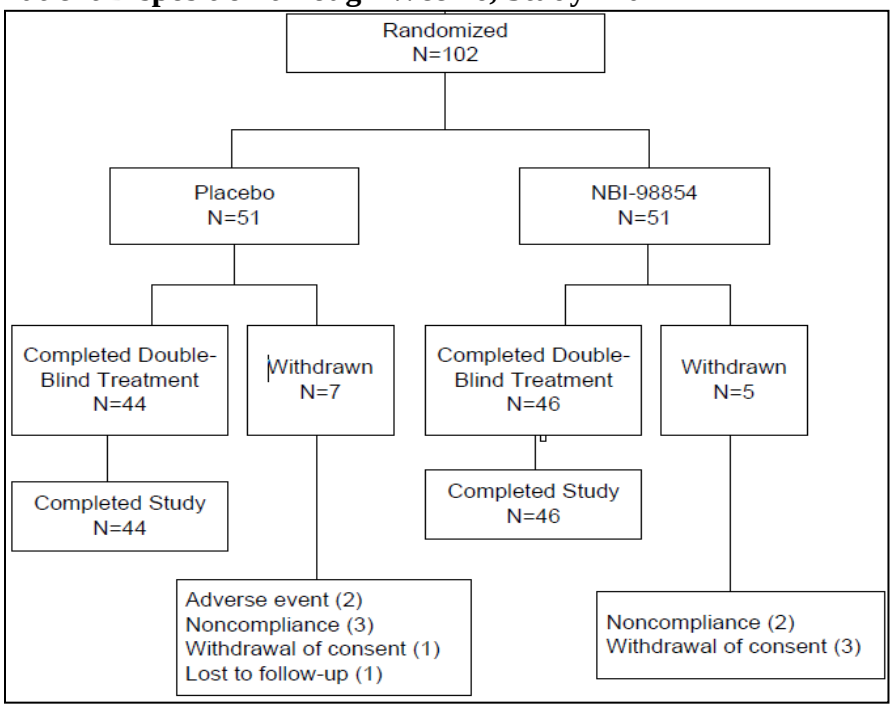
Schematic of Study 1202 Design



Eligible patients with TD were randomized 1:1 to receive dose-escalated valbenazine or placebo treatment with the dose increases based upon persistence of symptoms (eligible to increase dose if any individual AIMS item 1-7 score $\geq$ 2), and safety/tolerability of the lower dose. The primary endpoint was the modified AIMS (described above, same as Study 1304) and the ratings were performed by blinded central raters at Week 6. At the End-of-Phase-2 Meeting the Agency agreed with the use of central video raters and that the change from baseline in AIMS items 1-7 total score would be acceptable as the primary endpoint. The CGI-TD was the secondary outcome measure of interest. The primary and secondary endpoints are the same for Studies 1304 and 1202, and are described in detail above.

Reference ID: 4082860

Patient Disposition through Week 6, Study 1202



Source: Study 1202 Clinical Study Report, Figure 3, p. 68

Demographics: There was a minimal imbalance in sex. Most patients were aged to mid-50s, which is a reasonable age for the target population with TD. Multiple races were well-represented (with the exception of Asian and Native American), and the majority of study participants were US patients.

Demographics, Study 1202

Parameter	Placebo (N=44) n (%)	Valbenazine (N=45) n (%)	Total (N=89) n (%)
Sex			
Male	25 (56.8)	28 (62.2)	53 (59.6)
Female	19 (43.2)	17 (37.8)	36 (40.4)
Age			
Mean years (SD)	55.3 (1.3)	57.0 (1.5)	55.6 (1.0)
Median (years)	57.0	56.0	56.0
Min, max (years)	34, 70	32, 78	32, 78
Race			
Caucasian	25 (56.8)	29 (64.4)	54 (60.7)
Black or African American	16 (36.4)	16 (35.6)	32 (36.0)
Asian	0	0	0
American Indian or Alaska Native	1 (2.3)	0	1 (1.1)
Mixed	2 (4.5)	0	2 (2.2)
Ethnicity			
Hispanic or Latino	14 (31.8)	18 (40.0)	25 (32.9)
Not Hispanic or Latino	30 (68.2)	27 (60.0)	51 (67.1)

Source: Data from 1202 Clinical Study Report (Table 14.4.2), p. 149

Efficacy Results, Study 1202

The primary efficacy endpoint was the change from baseline in the modified AIMS total dyskinesia score at Week 6, based upon central rater assessment. Efficacy results are presented below—there is significantly greater improvement (decrease) in the AIMS score in the drug vs. the placebo group.

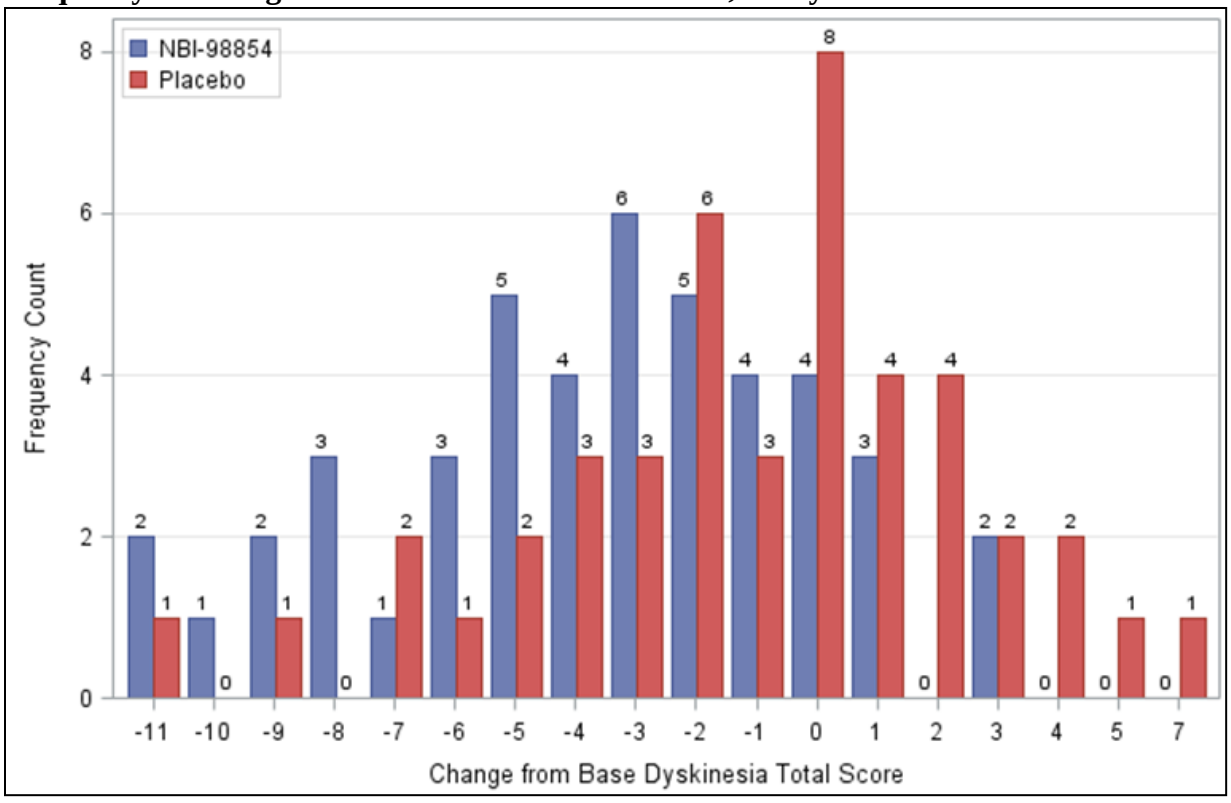
Forty-five patients were present at Week 6 in the valbenazine group and 31 of them were receiving 75 mg/day, 9 were receiving 50 mg/day, and 5 were receiving 25 mg/day (mean dose overall was 64 mg/day). Per protocol and ITT analyses were both significant.

Primary Efficacy Endpoint Analysis, Change from Baseline AIMS, Study 1202

Statistic	PP Analysis Set		ITT Analysis Set	
	Placebo N=44	NBI-98854 N=32	Placebo N=44	NBI-98854 N=45
Mean (SEM)	-1.1 (0.6)	-4.3 (0.6)	-1.1 (0.6)	-3.6 (0.5)
SD	3.7	3.2	3.7	3.5
Median	-0.5	-4.0	-0.5	-3.0
Min, max	-11, 7	-11, 1	-11, 7	-11, 3
LS mean (SEM)[a]	-0.3 (1.1)	-3.4 (1.2)	-0.2 (1.1)	-2.6 (1.2)
95% confidence interval	(-2.5, 1.8)	(-5.7, -1.0)	(-2.4, 2.0)	(-4.9, -0.3)
LS mean difference NBI-98854 vs. placebo (SEM)	-3.0 (0.7)		-2.4 (0.7)	
95% confidence interval	(-4.5, -1.6)		(-3.7, -1.1)	
p-value[b]	**<0.0001**		**0.0005**	

AIMS=Abnormal Involuntary Movement Scale; ITT=intent-to-Treat; LS=least squares; PP=per protocol.
[a] Least-squares mean based on the analysis of covariance (ANCOVA) model, which includes baseline AIMS dyskinesia total score value as a covariate and treatment group and disease category as fixed effects.
[b] p-value for test of null hypothesis that difference between treatment group LS means is equal to zero.

Frequency of Change from Baseline AIMS at Week 6, Study 1202



Source: Created by Biometrics reviewer Dr. Thomas Birkner. Negative change values indicate clinical improvement. NBI-98854=valbenazine. Sample is the ITT analysis set (N=45 valbenazine, N=45 placebo).

Secondary Efficacy Measure, CGI-TD, Study 1202

See the description of the CGI-TD above. CGI-TD score at Week 6 was a secondary efficacy measure for this study the results are presented below.

Change from Baseline in CGI-TD Summary at Week 6, Study 1202

	Placebo (N=44)	Valbenazine (N=45)
CGI-TD		
Mean (SEM)	3.1 (0.1)	2.3 (0.1)
LS mean (SEM)[1]	3.1 (0.3)	2.2 (0.3)
Difference Valbenazine – Placebo (SEM)	-0.8 (0.2)	
Difference 95% Confidence Interval	(-1.2, -0.5)	
p-value[2]	<0.0001	
CGI-TD Response		
Very much improved n= (%)	2 (4.5)	6 (13.3)
Much improved n= (%)	5 (11.4)	24 (53.3)
Minimally improved n= (%)	24 (54.5)	12 (26.7)
No change n= (%)	13 (29.5)	3 (6.7)

Source: Adapted from Study 1202 Clinical Study Report, Table 17 (p. 92).
CGI-TD scores: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change. No subjects had scores >4 at the end of Week 6 in either group.
[1]Least-squares mean based on the ANOVA model which included treatment group and disease category as fixed effects.
[2]p-value for test of null hypothesis that difference between treatment group LS means = 0.

Note: The applicant had several secondary endpoints in this study and no pre-specified plan for controlling for multiple statistical tests. This information was not replicated in study 1304 (b) (4) however, it does add to the efficacy consideration for valbenazine.

Efficacy Summary of Study 1202
This study serves as confirmatory evidence of efficacy for valbenazine. Dose-response cannot be assessed secondary to the flexible-dose design, but the majority of patients were on the 75 mg/day dose at the Week 6 efficacy assessment. No secondary endpoint information is statistically available for consideration.

Conclusions: Efficacy
In my view, substantial evidence of efficacy has been presented by the Applicant; Studies 1304 and 1202 provide substantial evidence of efficacy of valbenazine for the treatment of TD in adults. Although40 mg/day and 80 mg/day have evidence of efficacy, 80 mg/day had a greater efficacy signal than 40 mg/day and should be the target dose for most patients.

Reference ID: 4082860

The primary outcome measure, the AIMS Total Dyskinesia Score, Items 1-7 was agreed to prior to the study start dates and the AIMS was developed and designed to measure symptoms of TD. There was a fair amount of discussion among the Division Clinical Staff about what would represent a meaningful change in the AIMS, but all agreed that any statistically supported decrease in abnormal involuntary movements maybe meaningful for patients, and some patients had substantial dose-related improvement (see analyses above and the detailed response analyses by Dr. Davis in his review).

The secondary outcome measure, the Clinical Global Improvement, Tardive Dyskinesia (CGI-TD), was not statistically significantly decreased in the only study (1304) that had pre-specified multiplicity adjustment in the Statistical Analysis Plan. In fact, it was this miss on CGI-TD in the 80 mg/day group that prevented the statistical endorsement of the 40 mg/day dose, in addition to the clear better result from the 80 mg/day dose compared to 40 mg/day.

Recommendations for Labeling from the Efficacy Review

Dosing: The review team has recommended an initial dose of 40 mg/day and an increase after one week to 80 mg/day, and I agree with this recommendation.

Time to Onset: Separation of drug from placebo can be seen as early as 2 weeks in Study 1304 and although no multiplicity adjustments were made, this information should be provided to treating clinicians in labeling.

Durability of effect: From the 42-week extension period of Study 1304, there is no evidence of a loss of effect with time through 48 weeks of treatment. This information is clinically relevant may be included in labeling graphically for the treating clinician. While not placebo-controlled beyond 6 weeks, it is internally controlled by dose and considered clinically useful information to convey.

8. Safety

The safety review was conducted by Brian Miller, MD. He comprehensively reviewed the safety data submitted by the applicant and conducted independent analyses of the submitted data. In addition, he examined the pre- and post-marketing safety data related to tetrabenazine, an approved product (Huntington's disease) that is metabolically related to valbenazine (metabolism discussed above).

Exposure

The safety database was composed of 14 Phase 1 studies, 4 Phase 2 studies, and 2 Phase 3 studies. Two hundred forty-one patients were exposed to relevant doses for at least 6 months, and 185 patients were exposed for at least 40 weeks. Dr. Miller concludes that exposure was adequate to assess safety for a population believed to number close to the orphan drug population range, and I agree with him.

Demographic Features of Safety Database

	Safety Population Characteristic (N = 613)	
Age	Mean (years)	56.4
	Min (years)	26.0
	Max (years)	84.0
	Standard deviation (years)	10.0
	Over 65 years of age (%)	16.2%
	Over 75 years of age (%)	2.4%
Sex	Men	57.1%
	Women	42.9%
Race	Caucasian (%)	59.9%
	Black or African-American (%)	36.7%
	Native American/Alaskan (%)	1.0%
	Asian (%)	0.3%
	Native Hawaiian/Pacific Islander (%)	0.5%
	Other (%)	1.6%
Ethnicity	Hispanic or Latino (%)	29.5%
	Not Hispanic or Latino (%)	70.5%
Weight (lbs)	Mean	179.5
	Min	92.0
	Max	344.0
	S.D.	38.6
BMI	Mean (mg/m^2)	28.3
Diagnosis	Schizophrenia or schizoaffective disorder with neuroleptic-induced TD	72.4%
	Mood disorder with neuroleptic-induced TD	26.9%
	Gastrointestinal disorder with metoclopramide-induced TD	0.7%
Georgaphy	USA	97.1%
	Canada	1.3%
	Puerto Rico	1.4%
	N	613

Source: Reviewer-created table from demographics datasets (DM.xpt) for Studies 1201, 1202, 1304, and 1402

Reference ID: 4082860

Concomitant Medications for Safety Population

Concomitant Medication Properties	*N*	*%*
Anticholinergic agent	348	56.8%
Antihistaminergic agent	137	22.3%
Antipsychotic - Atypical	456	74.4%
Antipsychotic - Typical	119	19.4%
Benzodiazepine	218	35.6%
Centrally Acting Muscle Relaxant	37	6.0%
Dopamine agonist	1	0.2%
Opioid	78	12.7%
Psychostimulant	4	0.7%

Source: Reviewer-created table from concomitant medications datasets (CM.xpt) for Studies 1201, 1202, 1304, and 1402 (medication properties as classified by the reviewer)

From the table above, the majority of patients were taking an antipsychotic medication, the prerequisite for developing medication-induced TD.

Safety Results

Deaths
There were four deaths determined not to be related to study drug, and I agree.

Serious Adverse Events (SAEs)
Dr. Miller reviewed each Case Report Form for adverse events resulting in hospitalization, permanent disability, congenital malformations and/or overdoses. He concluded that there was no discernible pattern of SAEs related to valbenazine treatment and the SAEs that did occur during the trials were likely related to pre-existing medical conditions.

Discontinuations Due to Adverse Events (AEs)
Discontinuation due to AEs were similar in frequency in drug and placebo groups

Significant Adverse Events
Dr. Miller confirmed a clear signal for balance disorders/falls and somnolence in the controlled safety population. The somnolence rate was significant enough (11% on drug vs. 4% on placebo) to necessitate a Warning in the product label.

Close examination of assessments of depression and suicidality were negative for worsening caused by drug and there was no relationship to dose. Suicidal ideation occurred in drug patients at a rate comparable to the background rate for the patient population. There was no worsening of mania, depression, or schizophrenia associated with valbenazine treatment.

Dr. Miller specifically examined the Columbia Suicide Severity Rating Scale (C-SSRS) data collected prospectively in each of three controlled studies: 1201, 1202, and 1304 in the target

population with TD. The C-SSRS is a validated instrument to assess suicidal ideation and behavior. The C-SSRS summary data from these three studies are presented below.
Study 1201 was a Phase 2 study of 100 mg per day for two weeks, followed by 50 mg/day for four more weeks. Note that the rate of suicidal ideation or behavior during the controlled period was lower in drug group.

C-SSRS Data for Study 1201

		Placebo		VBZ (50 - 100 mg)	
	Item	*N*	*%*	*N*	*%*
Suicidal Ideation	Wish to be Dead	2	3.7%	1	1.8%
	Non-Specific Active Suicidal Thoughts	2	3.7%	0	0.0%
	Active Suicidal Ideation without Intent	0	0.0%	0	0.0%
	Active Suicidal Ideation with Some Intent	0	0.0%	0	0.0%
	Active Suicidal Ideation with Specific Plan and Intent	0	0.0%	0	0.0%
Suicidal Behavior	Preparatory Acts or Behavior	0	0.0%	0	0.0%
	Aborted attempt	0	0.0%	0	0.0%
	Interrupted attempt	0	0.0%	0	0.0%
	Non-fatal suicide attempt	0	0.0%	0	0.0%
	Completed suicide	0	0.0%	0	0.0%
	Ideation or Behavior	2	3.7%	1	1.8%
	N	54		55	

Source: Dr. Miller's review.

Study 1202 was a dose-titration study. Patients with TD were titrated from 25 mg per day to 75 mg per day during the 6-week controlled period. No suicidal ideation or behavior was detected by C-SSRS in the placebo group. In the drug group, 5.9% of patients experienced suicidal ideation, and none had suicidal behavior detected by C-SSRS. The trend was found by Dr. Miller to not be statistically significant (Fisher's exact test, P>0.05, two-tailed).

C-SSRS Data for Study 1202

		Placebo		VBZ (25 - 75 mg)	
	Item	*N*	*%*	*N*	*%*
Suicidal Ideation	Wish to be Dead	0	0.0%	3	5.9%
	Non-Specific Active Suicidal Thoughts	0	0.0%	1	2.0%
	Active Suicidal Ideation without Intent	0	0.0%	1	2.0%
	Active Suicidal Ideation with Some Intent	0	0.0%	1	2.0%
	Active Suicidal Ideation with Specific Plan and Intent	0	0.0%	0	0.0%
Suicidal Behavior	Preparatory Acts or Behavior	0	0.0%	0	0.0%
	Aborted attempt	0	0.0%	0	0.0%
	Interrupted attempt	0	0.0%	0	0.0%
	Non-fatal suicide attempt	0	0.0%	0	0.0%
	Completed suicide	0	0.0%	0	0.0%
	Ideation or Behavior	0	0.0%	3	5.9%
	N	49		51	

Source: Dr. Miller's review.

Study 1304 was a fixed-dose placebo-controlled trial that did not show clear drug effect or dose response for suicidal ideation/behavior as measured by C-SSRS.

Reference ID: 4082860

C-SSRS Data for Study 1304

		Placebo		VBZ 40 mg		VBZ 80 mg	
	Item	*N*	*%*	*N*	*%*	*N*	*%*
Suicidal Ideation	Wish to be Dead	3	3.9%	4	5.6%	2	2.8%
	Non-Specific Active Suicidal Thoughts	3	3.9%	0	0.0%	2	2.8%
	Active Suicidal Ideation without Intent	1	1.3%	0	0.0%	1	1.4%
	Active Suicidal Ideation with Some Intent	0	0.0%	0	0.0%	1	1.4%
	Active Suicidal Ideation with Specific Plan and Intent	0	0.0%	0	0.0%	1	1.4%
Suicidal Behavior	Preparatory Acts or Behavior	0	0.0%	0	0.0%	1	1.4%
	Aborted attempt	0	0.0%	0	0.0%	0	0.0%
	Interrupted attempt	0	0.0%	0	0.0%	0	0.0%
	Non-fatal suicide attempt	0	0.0%	0	0.0%	1	1.4%
	Completed suicide	0	0.0%	0	0.0%	0	0.0%
	Ideation or Behavior	4	5.3%	4	5.6%	2	2.8%
	N	76		71		79	

Source: Dr. Miller's review.

Dr. Miller concluded, that when prospectively measured in controlled trials, there is no increased risk from valbenazine for suicidal ideation and behavior, and I agree with him. These data are consistent with the baseline rate of suicide in the schizophrenic/schizoaffective disorder population (estimated lifetime risk of suicide is 5% in patients with schizophrenia).

Laboratory findings include a consistent increase in prolactin, but no treatment-related adverse reactions occurred due to prolactin increase. There was an also an increase in blood glucose, but a decrease in hemoglobin A1C noted (see Dr. Miller's review).

The QT team examined a Thorough QT Study (TQT) conducted by the sponsor and detected prolongation. The largest upper bound of the 2-sided 90% CI for the mean difference between valbenazine 160 mg and placebo (double delta QTcF) was 11.7 ms. They had some concern that the metabolite accumulation could add to QT prolongation, especially in CYP2D6 poor metabolizers. They have made recommendations for labeling to include editing the Warning for QT Prolongation.

Conclusions: Safety
The risk associated with QT prolongation, somnolence, and balance disorders/falls can be mitigated with proper labeling. Somnolence will be labeled as a Warning as will QT prolongation. There is no clear drug effect on instruments that specifically measure suicidal ideation and behavior or depression. Minor laboratory abnormalities from the clinical trial database include increased blood glucose and prolactin, and these risks can be mitigated with labeling.

9. Advisory Committee Meeting

The review team determined that this NDA did not require a public discussion. The rationale for this decision was that while it is a New Molecular Entity, valbenazine has a similar mechanism of action of a previously approved drug, the VMAT2 inhibitor tetrabenazine. In

addition, the primary endpoint is well accepted, the effect size was clear, and there were no major safety issues identified that would preclude approval.

10. Pediatrics

TD, while not unheard of in children, is very rare secondary to the fact that prolonged treatment with antipsychotics is required in most cases to produce the disease. In the very rare cases that do happen in people under 18 years old, the treatment is to discontinue the offending medication and anticipate resolution of symptoms. Therefore, a study of TD in children would be highly impracticable. The labeling will be clear that valbenazine is approved for adult patients with TD.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) audited 5 sites based upon enrollment numbers and date of most recent inspection. The results were 4 sites with No Action Indicated (NAI) designations and one site with Voluntary Action Indicated (VAI). The overall recommendation from OSI was to consider the data to be acceptable and the studies to have been conducted adequately.

The Division of Risk Management assessed the need for a Risk Evaluation and Mitigation Strategy (REMS) and determined that a REMS was not needed and that the risks of QT prolongation and somnolence could be adequately managed with labeling.

12. Labeling

Revisions were proposed by the review team for the Dosing and Administration section of labeling to specify the titration schedule used in the clinical trials (40 mg/day for the first week and then 80 mg/day). A sentence was also proposed to inform the prescriber that 40 mg/day was effective in some patients.

Revisions to labeling for dosing with concomitant strong CYP3A4 and CYP2D6 inhibitors and CYP3A4 induces were made based upon recommendations from the OCP review team. These revisions are to avoid use of valbenazine with CYP3A4 inducers and to reduce the dose of valbenazine with strong inhibitors.

The Contraindications section was revised from the Applicant-proposed labeling to remove [redacted] (b) (4) It was reasoned by the review team that [redacted] (b) (4) [redacted]

The relationship between valbenazine and prolonged QT interval is being better described in current labeling negotiations to specifically caution about the use with strong CYP2D6 and

CYP3A4 inhibitors and in patients known to be relevant poor metabolizers. These conditions of use and poor metabolism of valbenazine are expected to result in higher valbenazine concentrations and could increase the QT interval.

The Adverse Reactions (AR) section of labeling is currently being negotiated to reflect appropriately pooled safety data. A table of the important ARs was generated by the review team (see below).

Adverse Reaction	*Placebo* *(n = (b) (4) (%)*	*INGREZZA* *(n = (b) (4) (%)*
Nervous System Disorders		
Anticholinergic effects	4.9%	5.5%
Balance disorders/fall	2.2%	3.8%
Akathisia	0.5%	2.7%
Headache	2.1%	3.4%
General Disorders		
Somnolence	4.2%	11.0%
Gastrointestinal Disorders		
Nausea	2.1%	2.3%
Vomiting	0.5%	2.7%
Musculoskeletal Disorders		
Arthralgia	0.5%	2.3%

Source: Reviewer-created table (adapted from analysis by Dr. Marc Stone)

The Clinical Studies section of labeling was revised by the review team to include several graphical depictions of the efficacy data that should be useful to prescribers. These presentations graphically depict response based on different amounts of change on AIMS as well as Change in AIMS plotted over time, to include the 42-week Extension Period for Study 1304. See Dr. Davis' review for details on these and several other edits made to Section 14.

The Applicant proposed a Medication Guide (MG) initially, but the review team determined that a MG is not necessary for safe use of valbenazine. The proposed MG was converted to a Patient Package Insert (PPI) to describe common adverse reactions and when and under what circumstances the patient should contact the prescriber.

The Applicant has received two rounds of labeling negotiation from the Division, and negotiations are underway at the time of this writing.

13. Postmarketing

The team has recommended the following Post-marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs), which are currently being negotiated with the Applicant:

PMR

- Effect of CYP2D6 Inhibition: A pharmacokinetic trial to quantify the impact of CYP2D6 inhibition on the exposures of the parent compound and major metabolites,

either in the presence of a strong CYP2D6 inhibitor or in subjects who are CYP2D6 poor metabolizers

- Effect of Severe Renal Impairment on PK: A pharmacokinetic trial should be conducted to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose.
- CYP2B6 Effects of Metabolite: Conduct an in vitro study to assess the induction potential of NBI-136110 on the CYP2B6 enzyme.
- Withdrawal Effects: Evaluate clinical dependence and withdrawal as part of ongoing studies; administer withdrawal scales and assess withdrawal-related adverse events.

PMC

- Potential for Improved Therapeutic Benefit at Doses Higher Than the Recommended Dose of 80 mg/day: A (b) (4) randomized, (b) (4), efficacy and safety trial should be conducted to test doses of 80 mg and a higher dose (b) (4) in patients not demonstrating adequate response at the dose of 80 mg. Depending on the findings from the clinical pharmacology trial to assess the effect of CYP2D6 inhibition, CYP2D6 PMs may be excluded from this trial to avoid exposure related adverse events (e.g., QT prolongation).

- Assess Persistence of Drug Effect: Conduct a study in patients who have had an adequate response to valbenazine by randomizing these stable patients to continue their current dose of valbenazine, or switch to placebo. Stratify the randomization based upon concomitant (continued) antipsychotic use.
- Directly Assess Clinical Meaningfulness: Conduct a study to define whether and what magnitude of change in AIMS total dyskinesia scores translate into long-term functional improvements.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
04/11/2017