CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memorandum

Date	April 11, 2017
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	209241
Applicant Name	Neurocrine Biosciences, Inc.
Date of Submission	August 11, 2016
PDUFA Goal Date	April 11, 2017
Proprietary Name/ Established (USAN) Name	Ingrezza™ Valbenazine capsules
Dosage Forms/ Strengths	40-mg capsules
Indication	INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.
Action:	*Approval*

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OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Valbenazine is a new molecular entity, a vesicular monoamine transporter type 2 (VMAT2) inhibitor, developed for the treatment of tardive dyskinesia (TD). Valbenazine is not yet marketed in any country. TD is an iatrogenic hyperkinetic movement disorder that occurs in patients who have been treated chronically with dopamine receptor blocking drugs. The involuntary movements of TD are functionally disabling and cause social stigma and isolation. The primary goal of treatment is to reduce involuntary movements and decrease disability. Most patients who develop TD have a debilitating psychotic illness or mood disorder that requires lifetime treatment with antipsychotic drugs. No treatments are approved for TD.

The efficacy of valbenazine was established in 2 placebo-controlled studies that used the Abnormal Involuntary Movement Scale (AIMS), a well-accepted measure of dyskinesia, as the 1° outcome measure. The AIMS was used to quantify involuntary movements of 7 body regions, each assessed on a 0 to 4 scale (none, minimum, mild, moderate, severe), with an overall score ranging from 0 (no involuntary movements) to 28. Both studies showed a statistically significant treatment effect of valbenazine relative to placebo. The results of these predominantly US studies were statistically persuasive, robust to sensitivity analyses, and consistent across important subgroups. One of the studies evaluated two valbenazine doses and provided good evidence of a dose-response, further supporting efficacy.

In Study 1304, the more persuasive of the two studies, the mean baseline AIMS score was ~10 points, and the mean treatment effect at Week 6 (valbenazine vs. placebo) was -3.1 points (95% confidence interval -4.2, -2.0). A number of responder analyses were undertaken to determine the number needed to treat (NNT). Defining a "responder" as a patient with at least a 4-point improvement on the AIMS, response rates were 33% and 7% in the valbenazine and placebo groups, respectively, for a NNT of ~4. If *any* improvement on the AIMS were considered a "response," then the NNT would be ~5.

Tetrabenazine is a related VMAT2 inhibitor, approved in 2008 for the treatment of chorea associated with Huntington's disease. Because active metabolites of the two drugs are enantiomers, the valbenazine safety database was closely examined with consideration of tetrabenazine's known adverse effects, including sedation and somnolence, akathisia, depression, and suicidality. Several adverse reactions were identified, notably somnolence, potential QT prolongation, balance disorders, falls, akathisia, and anxiety. The main potential for *irreversible* harm is QT prolongation, which can cause potentially serious, sometimes fatal, arrhythmias; and falls, which can cause injury. Some of these injuries will be serious, and *rarely*, they could be fatal. Harms that were looked for and not found include depression/suicidality and visual changes (because valbenazine's metabolites selectively bind to pigments in the eye).

The benefit-risk calculus seems straightforward here: the potential benefit for patients is a reduction in debilitating symptoms; the potential harms are mostly manifested as symptoms. Thus, individual patients can make their own decisions with respect to initiating and, if desired, discontinuing the drug. Patients should be careful about somnolence and falls. The drug's benefits outweigh its risks, and with adequate instructions for use, it will be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	TD is a socially and functionally disabling, typically irreversible, iatrogenic disorder. Prevalence may be as high as 8.5% for patients treated chronically with conventional antipsychotics. Second generation antipsychotics ("atypical antipsychotics") are thought to be less likely to cause TD than first-generation antipsychotics, but many patients with TD have a history of chronic exposure to conventional antipsychotics, making this assessment difficult.	TD is a socially and functionally disabling iatrogenic disorder occurring in a significant proportion of patients treated with antipsychotic drugs.
Current Treatment Options	None approved. Current treatment is to discontinue or change the drug needed to control the psychiatric disorder, or reduce the dose. This is not always feasible, however, and discontinuing the causative drug(s) is not always effective in reducing TD symptoms.	Current treatment options are insufficient. Discontinuing the offending drug is likely to exacerbate the underlying psychiatric illness and typically does not relieve the movement disorder.
Benefit	Substantial evidence of effectiveness was provided by two studies, both showing an effect on the Abnormal Involuntary Movement Scale (AIMS), a scale developed to assess and track symptoms of TD. The AIMS is considered an appropriate measure to use in clinical drug trials of TD. The AIMS was significantly improved in patients randomized to valbenazine 80 mg/day in Study 1304 and in patients randomized to a flexible-dose of valbenazine (up to 75 mg/day) in Study 1202.	Efficacy has been established. Some 50% of patients experienced a decrease in the symptoms of TD on valbenazine 80 mg/day, compared to 29% on placebo (Figure 3).
Risk	The safety database was adequate in size and length of exposure, considering the low prevalence of the disease. Adverse reactions included somnolence (11%), balance problems/falls (4%), and akathisia (3%). Dose- and blood concentration-related QT prolongation was found, which could be clinically significant in patients taking CYP2D6 or CYP3A4 inhibiting drugs, or in CYP2D6 poor metabolizers. Suicidal ideation and behavior were actively assessed during the trials and no signal was identified.	These adverse reactions can be managed with appropriate labeling/patient information.
Risk Management	Adverse reactions do not outweigh the clinical benefit of the drug and are manageable with labeling and a patient package insert.	Product labeling and the patient package insert are adequate for management of the risk.

2. Background

Tardive Dyskinesia (TD) is a serious iatrogenic, often irreversible movement disorder characterized by involuntary athetoid or choreiform movements that develop as a result of long-term use of D2 dopamine receptor antagonists. The abnormal movements of TD are debilitating, causing functional impairment, shame, social stigma, and consequential social isolation.

TD is typically caused by antipsychotic drugs (both typical and atypical), as well as related drugs used for gastrointestinal motility disorders (e.g., metoclopramide).

The clinical course is variable. If identified early and the causative drug withdrawn, TD may abate over several months. TD is frequently chronic, however, and does not necessarily remit when the offending drug is discontinued.

Valbenazine was granted designation as a Breakthrough Therapy in October, 2014, based on the Division's view that the drug is intended to treat a serious condition, and that preliminary evidence indicated it may provide substantial improvement over currently available therapies (there were none). Priority review was also granted.

Valbenazine is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor. Upon oral administration, the drug is extensively metabolized. One of the metabolites, [+]-α-dihydrotetrabenazine, is a potent VMAT2 inhibitor. By selectively inhibiting presynaptic VMAT2, both valbenazine and [+]-α-dihydrotetrabenazine are believed to cause reversible reduction of dopamine release at the presynaptic nerve terminal.

Tetrabenazine is another VMAT2 inhibitor, approved in 2008 for the treatment of chorea associated with Huntington's disease, another movement disorder. Valbenazine's active metabolite is an enantiomer of tetrabenazine's active metabolite; therefore, the pre- and post-marketing experience with tetrabenazine is relevant to valbenazine.

During development, the Division and sponsor agreed that a statistically significant change in the Abnormal Involuntary Movement Scale (AIMS) could provide evidence of efficacy, and that involuntary movements were, on face, clinically significant and the core feature of TD. As outlined in the clinical and statistical reviews, the applicant submitted substantial evidence of effectiveness of valbenazine for the treatment of adults with TD, and the clinical review team believes that the safety has been characterized, permitting adequate instructions for use. The entire review team believes that the data submitted in the NDA support valbenazine's approval, and I agree.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team and their technical lead, David Claffey, recommend approval.

There was one notable quality issue: there were significant differences between (b) (4) the drug product used in the Phase 3 studies and the proposed commercial product – (b) (4) (b) (4) A bioequivalence

study, however, successfully bridged these formulations, and *in vitro* studies (including dissolution data) supported bridging.

The review team also determined that the stability data supported an 18-month expiry period, rather than the (b)(4)-month period the applicant had requested.

These two points will be included in the action letter, as requested by OPQ:

1. We remind you of your December 23, 2016 and February 8, 2017 commitments to add bulk density, tapped density and optical rotation tests and acceptance criteria to the drug substance specification.

2. We determined that your stability data support an 18-month drug product expiry period.

4. Nonclinical Pharmacology/Toxicology

Important nonclinical findings of the Pharmacology/Toxicology reviews:

Metabolism was demonstrated by radiolabeled mass balance studies to be qualitatively similar in rats, dogs, and humans. Valbenazine-related material was highly distributed to the pigmented cells of the retina. No valbenazine treatment-related histopathologic eye findings were observed in dog or pigmented mouse, however, and no phototoxicity was observed *in vitro*. The clinical significance of distribution to pigmented structures of the eye is unknown.

Valbenazine moderately inhibits hERG channels (IC_{50} ~2 µM) and produces moderate QTc prolongation in dogs at doses 6 times the maximum recommended human dose.

The central nervous system (CNS) was the primary target organ for toxicity in dog and mouse. Signs consistent with CNS monoamine depletion (decreased activity, ataxia, trembling, and ptosis) were observed in rat, mouse, and dog. Rodents exhibited increased activity at valbenazine trough levels and following drug cessation, suggesting withdrawal. Valbenazine caused tremors and convulsions in both rats and dogs after 2 months of dosing. Seizures were not observed once dosing was discontinued, however, and there were no concerning findings on extensive neuropathology examinations.

Valbenazine was found to be non-genotoxic. There were no drug-related neoplasms in the 6-month mouse study or in the rat carcinogenicity study. Valbenazine delayed mating and increased stillbirths in rats. Moreover, valbenazine and the metabolites were detected in fetuses, as well as in milk and in pups following administration to pregnant or lactating rats. These data indicate that the benefits of the drug should be considered when administering valbenazine to pregnant or breastfeeding women, because fetal and infant exposure is likely to occur. Fertility was affected in rats, but this was thought to be mediated by hyperprolactinemia rather than direct toxicity.

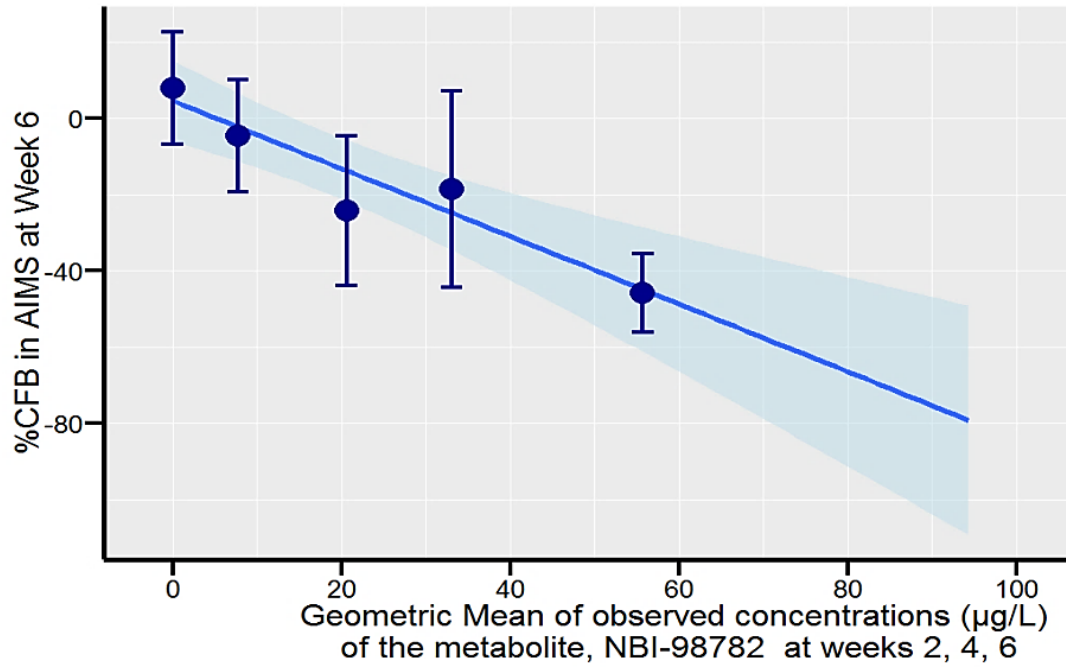
5. Clinical Pharmacology

Principal findings and recommendations from the Clinical Pharmacology reviews:

Oral bioavailability is ~49%. T_{max} is 0.5 to 1 hour for valbenazine and 4 to 8 hours for [+]-α-dihydrotetrabenazine, the major active metabolite. AUC and C_{max} are dose-proportional in the range from 40 to 300 mg. Valbenazine and [+]-α-dihydrotetrabenazine have half-lives of 15 to 22 hours. By mass balance, ~ 60% and 30% of radioactivity was recovered in urine and feces, respectively, with <2% excreted as unchanged valbenazine or the major metabolite in either urine or feces. Metabolism is extensive, with CYP3A4/5 and CYP2D6 involved.

Study 1304 included PK sampling, and an exposure-response analysis was conducted using % change from baseline in Week 6 AIMS total dyskinesia score as a function of the concentration of the major active metabolite. This analysis demonstrated what appeared to be a fairly linear exposure-response relationship (Figure 1). The critical observation is that there is no obvious plateau in efficacy. It is possible, therefore, that higher exposures to the major active metabolite would achieve greater efficacy (from Office of Clinical Pharmacology Integrated Review, page 50, figure 28).

Figure 1: Study 1304 – Exposure vs. Response



This finding led to a post-marketing commitment for the applicant to study a higher dose than studied previously (b) (4) with the goal of achieving greater efficacy.

Clinical Pharmacology Dose Adjustment Recommendations:

- The daily dose should be halved when co-administered with a strong CYP3A4 inhibitor.
- Dose reduction should be considered, based on tolerability, for CYP2D6 poor metabolizers or when co-administered with a strong CYP2D6 inhibitor.
- 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. The drug is not recommended for severe renal impairment (creatinine clearance <30 mL/min) because there are no data.
- Valbenazine increases digoxin concentrations because of inhibition of intestinal P-glycoprotein (P-gp). Digoxin levels should be monitored when co-administering the two drugs.
- Ingestion of a high-fat meal had little effect on AUC; valbenazine can be taken without regard to food.

Several post-marketing studies have been suggested and are included in Section 13 of this memorandum.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The efficacy review was conducted by Michael Davis with supplementary analyses provided by Douglas Warfield. Thomas Birkner, Peiling Yang, and H.M. (Jim) Hung conducted the statistical review. These reviews were well summarized by Javier Muñiz (Cross-Discipline Team Leader) and Mitchell Mathis (Division Director).

Valbenazine's clinical development program included 20 studies: 14 phase 1, 4 phase 2, and 2 phase 3 studies. Studies 1304 and 1202 provide the principal evidence of efficacy for valbenazine for the treatment of TD, and Studies 1201 and 1402 are supportive. The important phase 2 and 3 studies are shown in Table 1.

The two positive efficacy studies (Studies 1304 and 1202) support the claim that valbenazine, at 80 mg/day, reduces the symptoms of TD as measured by the modified AIMS. In Study 1304, the 40 mg/day dose did not meet the formal statistical standard for efficacy because of failure to reject the null hypothesis at a higher level in the testing sequence (the secondary endpoint at 80 mg/day). Nevertheless, the 40-mg dose was numerically superior to placebo (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 of 64 mg/day. These findings served as substantiation of the finding in Study 1304 and suggest that a dose of ~80 mg/day is required for efficacy (See Dr. Birkner's review).

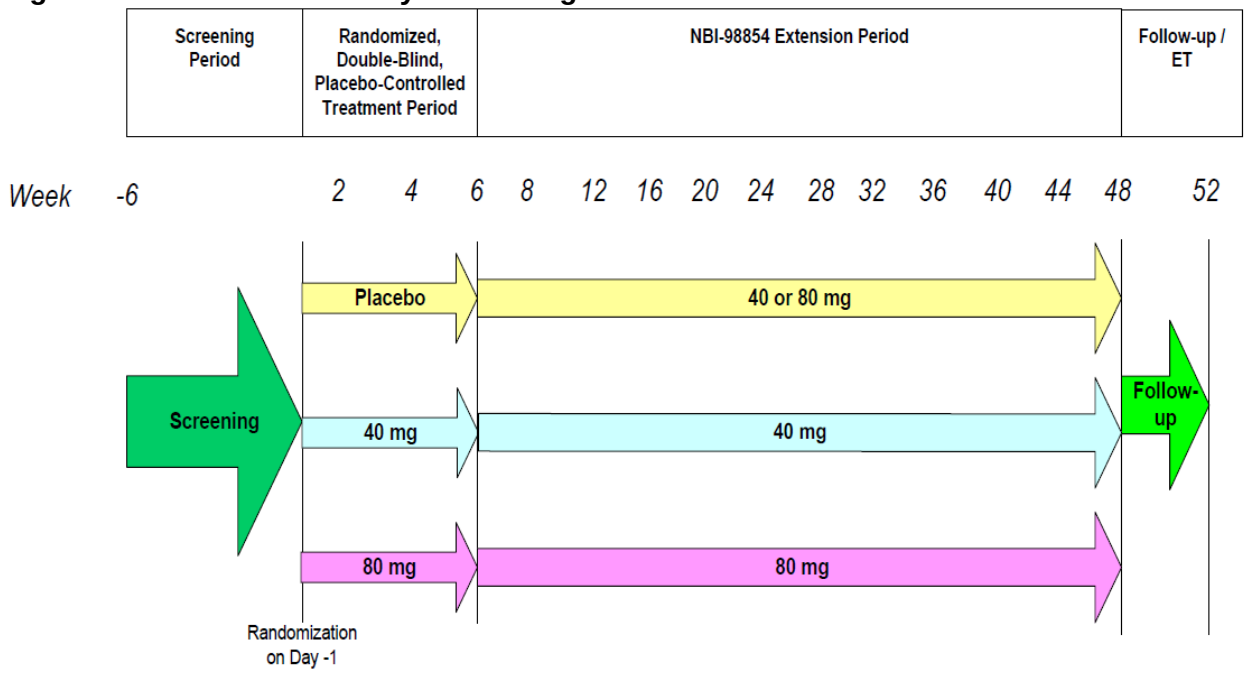
Table 1: Principal Studies in the Development Program

Study	Design	Regimen and schedude	Primary Endpoint	Duration	# Enrolled	Population (adults)	Sites
Controlled Studies to Support Efficacy and Safety							
1101	Phase 2, randomized, double-blind, placebo-controlled, 2-period crossover study	valbenazine 12.5 or 50 mg or placebo PO daily	AIMS dyskinesia total	14 days valbenzine and 14 days placebo for each treatment period	37	neuroleptic-induced TD and schizophrenia or schizoaffective disorder	12 US sites
1201	Phase 2, randomized, double-blind, placebo-controlled study followed by open-label extension	valbenazine 100 mg daily x 2 weeks, then 50 mg daily x 4 weeks, or 50 mg daily or placebo x 6 weeks (1:1:2); followed by open-label valbenazine	AIMS dyskinesia total Key Secondary: CGI-TD	6 weeks, followed by 6-week open-label extension	109	neuroleptic-induced TD and schizophrenia or schizoaffective disorder	35 sites: US and Puerto Rico
1202	Phase 2, randomized, double-blind, placebo-controlled, dose-titration study	valbenazine 25, 50, or 75 (flexible) or placebo PO daily (1:1)	AIMS dyskinesia total	6 weeks	102	neuroleptic-induced TD and schizophrenia, schizoaffective disorder, mood disorder, or metoclopramide-treated GI disorder	29 sites: US and Puerto Rico
1304	Phase 3, randomized, double-blind, placebo-controlled, fixed-dose study with subject- and investigator-blinded extension	valbenazine 40 mg, 80 mg, or placebo PO daily (1:1:1); placebo subjects re-randomized to valbenazine 40 mg or 80 mg (1:1) for extension	AIMS dyskinesia total Key Secondary: CGI-TD	6 weeks, followed by 42-week extension	234	neuroleptic-induced TD and schizophrenia, schizoaffective disorder, or mood disorder	63 sites in the USA, Canada, and Puerto Rico
Additional Phase 2/3 Study to Support Safety							
1402	Phase 3, open- label, fixed-dose escalation study	valbenazine 40 mg --> 80 mg PO daily	Safety	48 weeks	168	neuroleptic-induced TD and schizophrenia, schizoaffective disorder, or mood disorder	45 sites: US, Canada, and Puerto Rico

Study 1304

Study 1304 was a phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study to evaluate the efficacy and safety of two doses of valbenazine for the treatment of TD. The study included a 6-week double-blind, placebo-controlled treatment period followed by a 42-week extension period. Adult subjects with moderate or severe TD and an underlying diagnosis of schizophrenia, schizoaffective disorder, or mood disorder were initially randomized (1:1:1) to receive daily doses of valbenazine 40 mg, 80 mg, or placebo. Subjects randomized to 80 mg were dose-escalated in a blinded manner (40 mg for one week, then 80 mg). The dose could be decreased for tolerability reasons at a single point during the study; subjects who could not tolerate the adjusted dose were discontinued. After 6 weeks of double-blind treatment, subjects could be re-consented to enter the 42-week extension period, where subjects initially randomized to valbenazine continued at their current dose, and those initially randomized to placebo were re-randomized (1:1) to valbenazine 40 or 80 mg daily.

Figure 2: Schematic of Study 1304 Design



The 1° endpoint was the change from Baseline to Week 6 on the AIMS dyskinesia score. The original AIMS scale was designed to assess the severity of TD by examining 12 items: 7 items related to involuntary movements in the orofacial region, trunk, and extremities, and 5 items to assess global severity, patient awareness, distress, and problems with teeth or dentures. The modified version of the AIMS used in this study included only the 7 items that assess involuntary movements. Each of these 7 items was assessed on a 0 to 4 scale (none, minimum, mild, moderate, severe), for an overall score ranging from 0 (no involuntary movements) to 28. The Division agreed to this approach prospectively.

The AIMS was assessed by investigators on-site and video-recorded for central reading. Recordings were sent to two central raters, blinded to treatment and sequence.

The Clinical Global Improvement, Tardive Dyskinesia (CGI-TD) was the 2° endpoint. This was a modified version of the CGI, designed to assess the *change* in TD symptoms. The investigator was to ask each subject to assess the change in their TD symptoms since starting the study medication, and to report their status as very much improved, much improved, minimally improved, not changed, minimally worse, much worse, or very much worse. The Division prospectively agreed to the CGI-TD as a 2° endpoint. There were multiple additional exploratory 2° endpoints.

Statistical testing procedures: The 1° endpoint, the AIMS dyskinesia total score mean change from Baseline to Week 6, was assessed using a Mixed Model Repeated Measures (MMRM) analysis. The model included baseline AIMS dyskinesia total score as a covariate, with treatment group, disease category (schizophrenia/schizoaffective disorder or mood disorder), and visit (Week 2, 4, or 6) as fixed effects, and subject as a random effect. The model also included [treatment group X visit] and [baseline X visit] interaction terms. Analysis of the 2° endpoint, CGI-TD mean score at Week 6, was similar to the analysis of the 1° endpoint, but without the covariate (baseline AIMS total score) or the [baseline X visit] interaction term. Importantly, the Type-I error rate was controlled through the use of a sequential testing hierarchy: 80 mg AIMS, 80 mg CGI-TD, 40 mg AIMS, and finally 40 mg CGI-TD.

Results: A total of 234 subjects were randomized at 63 sites in North America and Puerto Rico, with 97% of patients enrolled at US sites. The safety set included 227 of these subjects (2 withdrew and returned all study drug and 5 had no post-baseline safety data). The ITT analysis set included 225 subjects; 2 subjects were excluded because they lacked post-baseline AIMS total scores.

Study retention was excellent, with 88% of subjects completing the 6-week placebo-controlled period, and the majority of the completers (~97%) entering the 42-week extension period. The completion rate was much lower during the extension period, however, which is not unexpected given the comparative lengths of the placebo-controlled period and the extension period (6 weeks vs. 42 weeks, respectively). Only 121 out of the initial 234 randomized patients (61%) completed the entire study. There was no clear relationship between valbenazine dose and study retention.

Demographics (Table 2): The majority of patients were under 65 years old, with mean age of 56, mirroring the age of patients typically seen with TD (who must be on a dopamine receptor-blocking drug long enough to cause symptoms of TD). Baseline characteristics were well balanced across treatment groups. The study included slightly more males (54%) than females. Across all 3 treatment groups, 56% of subjects were Caucasian; 38% were African American.

Table 2: Study 1304 – Demographic Characteristics

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

1° Endpoint: At baseline, the mean AIMS scores were ~10 (on a scale from 0 to 28) in all 3 treatment groups. Valbenazine 80 mg/day was statistically significantly superior to placebo on the 1° endpoint, with an effect size (difference in change from baseline) of 3.1 points (95% confidence interval -4.2, -2.0; $p<0.0001$).

The effect on the CGI-TD in the 80-mg/day group, the second endpoint in the planned testing sequence, was not statistically significant. Thus, technically the treatment effect on the AIMS could not be tested for the 40 mg/day group. In fact, the difference between the 40 mg/day group and the placebo group was nominally statistically significant. The applicant's results, presented in Table 3, were confirmed by Biostatistics.

Table 3: Study 1304, 1° Efficacy Endpoint, AIMS Dyskinesia Total Score

Treatment Group	n	Primary Efficacy Measure: AIMS Dyskinesia Total Score (ITT)		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Valbenazine (40mg/day)	70	9.8 (4.1)	-1.9 (0.4)	-1.8 (-3.0, -0.7)
Valbenazine (80mg/day)*	80	10.4 (3.6)	-3.2 (0.4)	-3.1 (-4.2, -2.0)
Placebo	76	9.9 (4.3)	-0.1 (0.4)	

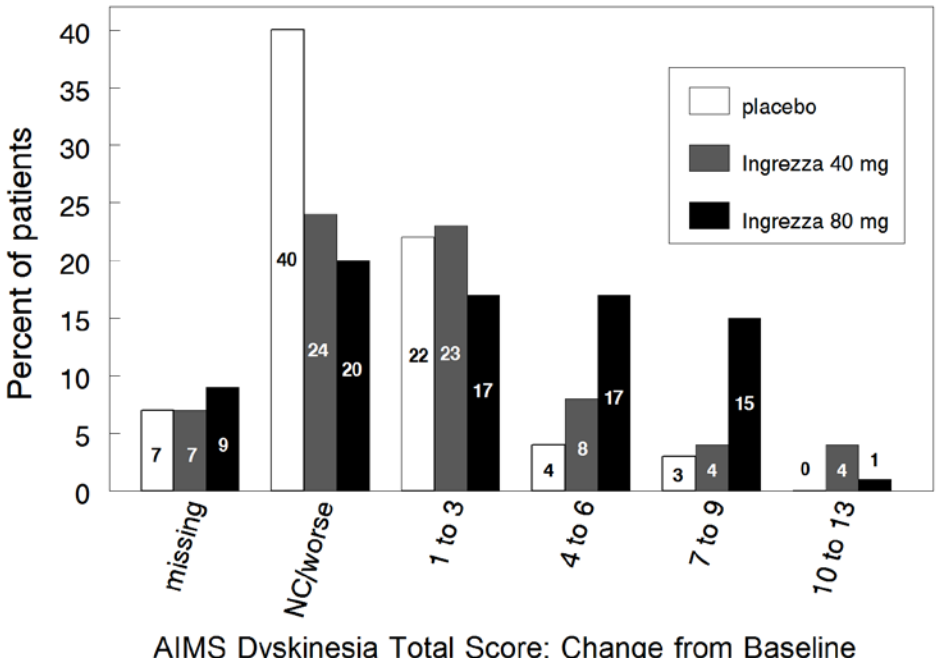
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval

[a] Difference (drug minus placebo) in least-squares mean change from baseline

* Doses statistically significantly superior to placebo

Figure 3 shows the distribution of responses. Regardless of how one might wish to define a "responder," valbenazine showed superiority to placebo at the 80-mg dose. Response to the lower dose appeared less robust. Defining a responder as a patient who had *any* improvement in AIMS from baseline, the responder rates are 50% and 29% in the valbenazine and placebo groups, respectively. Defining a responder as a patient who had at least a 4-point improvement in AIMS, the corresponding responder rates are 33% and 7%.

Figure 3: Study 1304, Percent of Patients with AIMS Improvement at Week 6 by Magnitude of Response



Drs. Davis and Birkner performed comprehensive subgroup analyses on the 1° endpoint (Table 14, page 77 of clinical review), including age, sex, race, ethnicity, BMI, TD duration, underlying

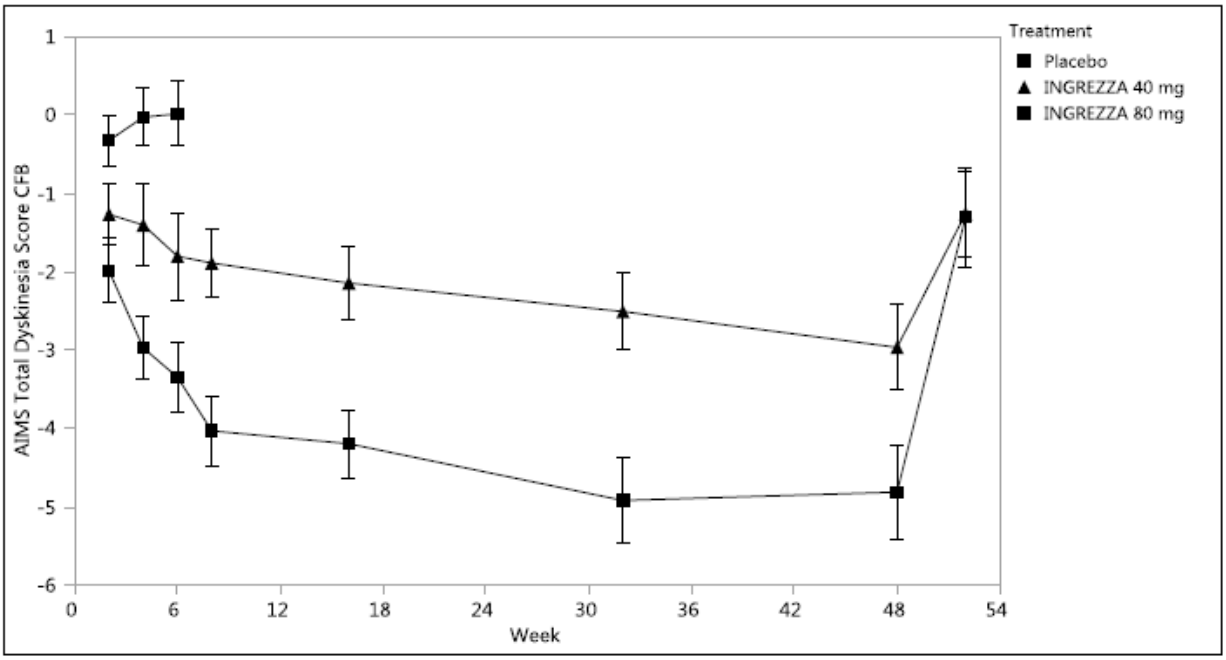
diagnosis, antipsychotic use, and CYP2D6 genotype. Although the sample sizes of these subgroups were limited, all showed a numeric reduction in AIMS total dyskinesia score for the 80-mg treatment group relative to placebo.

The review team examined the data integrity and inspectional results and found no significant issues. Dr. Birkner evaluated the study results by site, and found no information that would call the results into question. There were no large sites responsible for "driving" the treatment effect. No financial conflicts of interest were reported for investigators.

The 1° endpoint for Study 1304 was assessed at Week 6, but data were collected through Week 48. Although there is no placebo control after Week 6, assignment to higher or lower dose was blinded to subjects and investigators through Week 48 (Figure 4).

No formal hypothesis testing was performed here; nevertheless, 3 findings merit attention: 1) AIMS scores continued to improve after 6 weeks for both doses; 2) separation between the lower and higher doses was maintained between Weeks 6 and 48, and this is relevant because patients and investigators were blinded to dose during this interval; 3) AIMS scores returned towards baseline after discontinuation at Week 48. (At this point, however, all were aware that the active drug had been discontinued, and expectation bias could have played a role in worsening AIMS scores.)

Figure 4: Study 1304 – Change in AIMS from Baseline by Visit, Full Study Duration by Central Video Raters



In exploring the changes in AIMS over time by body region, the treatment effect appeared to be generalized, i.e., evident in all body regions (illustrated in Figures 5, 6, and 7 of Biostatistical review [pages 34-35], not shown).

The 2° endpoint, mean CGI-TD score at Week 6, was not statistically significant for either dose, although there were trends favoring valbenazine for both doses.

Table 4: Study 1304 – 2° Endpoint, Change in CGI-TD

	Placebo	Valbenazine	
		40 mg	80 mg
	(N=76)	(N=70)	(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		0.29	0.18
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		0.02	0.002
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		0.07	0.06

Efficacy Summary of Study 1304

Study 1304 tested two different doses of valbenazine versus placebo. Patients in the 80-mg group had a greater reduction on the 1° efficacy endpoint, the AIMS total score, change from baseline to Week 6, compared to placebo. From a baseline of ~10 points (on a 0- to 28-point scale), the mean treatment effect was 3.1 points; 95% confidence interval: -4.2, -2.0; $p<0.0001$. The 40-mg valbenazine group trended favorably, with a mean improvement on the AIMS of -1.8 points over placebo; however, the results were only nominally statistically significant because of failure to reject the null hypothesis at a more proximal point in the testing sequence. Of note, however, the two doses show a dose-response, which supports the strength of the findings.

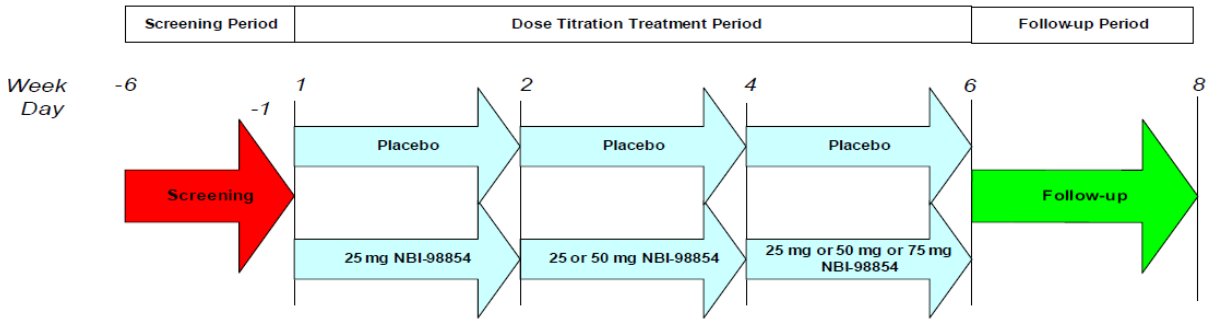
For the 80-mg group, the treatment effect was reasonable in magnitude, statistically persuasive, robust to sensitivity analyses (discussed in reviews of Drs. Birkner and Davis), and consistent and generalizable across subgroups of interest. None of the reviewers identified any issues that could importantly affect the results or interpretation of the study, other than the ordering of endpoints in the fixed testing sequence. (The Division had recommended revising the order during the IND stage, but the sponsor declined to take the Division's advice.)

Study 1202

Study 1202 was a phase 2, randomized, double-blind, placebo-controlled, dose titration study to assess the efficacy and safety of valbenazine for the treatment of TD. This study was conducted before Study 1304, but is presented second because of its dose-titration design, and because some aspects of the analysis plan were unusual and were not prospectively agreed to by the Division.

Eligible patients with TD were randomized 1:1 to receive dose-escalated valbenazine or placebo treatment with dose increases based upon persistence of symptoms (eligible to increase dose with any AIMS item score >2) and tolerability of the lower dose. Inclusion criteria were similar to those of Study 1304, except that patients with TD 2° to use of metoclopramide for a GI illness could be enrolled.

Figure 5: Schematic of Study 1202



The 1° and 2° endpoints were the same as for Study 1304, as described in detail above. The applicant instituted the use of blinded central video AIMS raters and revised the AIMS scoring descriptors during the conduct of this study in an effort to improve scoring consistency. These changes were submitted with protocol amendment 2, before study completion and database lock. The Division agreed with these changes, with input from the Clinical Outcomes Assessment group. In addition to being blinded to treatment group, the central raters were blinded to sequence.

Statistical testing procedures: The protocol and protocol amendments for Study 1202 were not reviewed by a statistical reviewer because this was a Phase 2 study that was not prospectively deemed to be used to support regulatory decision-making.

The AIMS data were analyzed using an analysis of covariance (ANCOVA) of the blinded, central video rater total score change from baseline (CFB) data at Week 6 using the per-protocol analysis set.

Importantly, it is highly unusual to base the analysis of a 1° endpoint on a per-protocol population, in part because compliance can be related to efficacy and/or side effects. In this study, only patients with detectable drug levels were deemed to be adherent to the protocol; however, there was no way to make this type of determination for patients in the placebo group. Thus, 22% of patients in the valbenazine group (but none in the placebo group) were excluded

from the analysis of the 1° endpoint on the basis of having had drug levels of zero. By design, this led to an imbalance in missing data, and missing data – not at random – undermine interpretation of the endpoint.

Dr. Davis notes in his review that "…the per protocol (PP) analysis set had substantially more subjects excluded from the valbenazine than the placebo treatment group. This was generally due to 21.6% of subjects having no quantifiable plasma concentration at Week 6. It is possible that a similar number of placebo-treated patients were noncompliant with study treatment, but this was not able to be assessed by plasma measurements. We cannot rule out that there was greater treatment noncompliance in the valbenazine treatment group for reasons of tolerability. Overall, for the purposes of evaluating this Applicant-designated pivotal efficacy study, *it is most appropriate to use the intent-to-treat (ITT) analysis set for efficacy analyses*." (Italics added for emphasis.)

The ANCOVA model included the baseline AIMS total score as a covariate and treatment group and disease category as fixed effects. The 2° endpoint, CGI-TD, was also analyzed using ANCOVA; however, the CGI-TD was not clearly pre-specified as key 2° efficacy endpoint. The protocol and statistical analysis plan listed *both* the CGI-TD and the AIMS (assessed by *site* raters) as 2° efficacy endpoints. If one assumed a fixed sequence testing procedure, it is not clear whether the CGI-TD would be tested before or after the AIMS (by site raters). This is important because the result for the AIMS (as assessed by the site raters) was not statistically significant.

Results**:**

A total of 205 subjects were screened for the study and 102 were randomized; 51 were assigned each to placebo and valbenazine. The percentage of subjects completing the study was high (88% overall) and similar between treatment groups.

Table 5: Study 1202 – Demographic Characteristics, ITT Population

Parameters	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)

Demographics: Essentially all of the study participants were from the US (97%). Baseline characteristics were well balanced for a study of this size, and fairly well matched to the US target population with TD.

At Week 6, 45 patients remained in the valbenazine group: 31 (69%) of them were receiving 75 mg/day, 9 (20%) were receiving 50 mg/day, and 5 (11%) were receiving 25 mg/day. The mean dose was 64 mg/day.

1° Endpoint (FDA ITT Analysis): At baseline, the mean AIMS scores were ~8 (on a scale from 0 to 28) in both treatment groups. Valbenazine, 25 to 75 mg/day, was statistically significantly superior to placebo, with an effect size of -2.4 points (95% confidence interval -3.7, -1.1; p=0.0005). The results, presented in Table 6, were confirmed by Biostatistics. Results for the applicant's per-protocol analysis were consistent with these.

Although the results of the FDA-preferred ITT analysis were positive, Dr. Birkner notes that analysis of the ITT population has its own inherent limitations, because the ANCOVA method essentially turns it into a completer analysis. Dr. Birkner explored the efficacy trajectories of the 12 patients who discontinued the study during the double-blind phase (and who were excluded from the ITT set). The available AIMS data (prior to drop-out) and an exploratory "tipping point" analysis suggest that omitting those patients did not materially affect the efficacy conclusion of the study.

Table 6: Study 1202, 1° Endpoint Results (FDA's ITT Analysis)

Treatment Group	n	Primary Efficacy Measure: AIMS Dyskinesia Total Score (ITT)		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Valbenazine (25-75 mg/day)*	45	8.0 (3.5)	-2.6 (1.2)	-2.4 (-3.7, -1.1)
Placebo	44	7.9 (4.5)	-0.2 (1.1)	

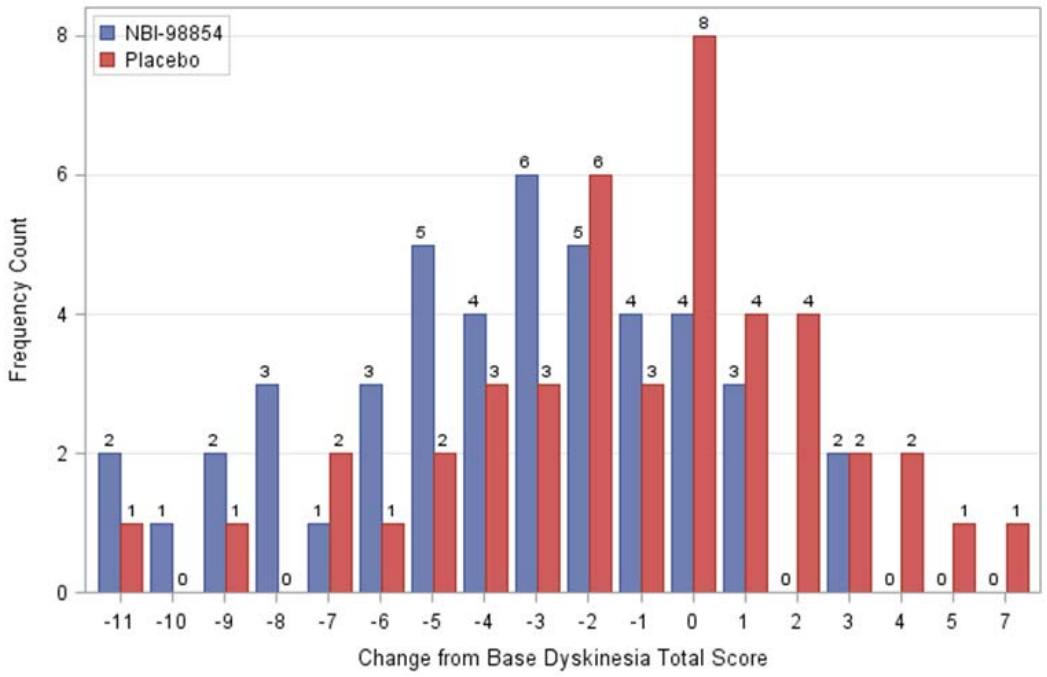
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval

[a] Difference (drug minus placebo) in least-squares mean change from baseline

* Doses statistically significantly superior to placebo

Dr. Birkner's plot of the frequency of responses by treatment group shows a clear drug effect, with the better responses (left) dominated by subjects in the valbenazine group (Figure 6; note that the *y*-axis shows numbers of patients, not percent of patients). If a response is defined as improvement of 3 points or better, the response rates were 60% vs 30% in the valbenazine and placebo groups, respectively.

Figure 6: Study 1202 – AIMS, Frequency of Change from Baseline at Week 6 (NBI-98854 = Valbenazine)



Results for the 2° efficacy measure, CGI-TD, are shown in Table 7.

Table 7: Study 1202 – Change from Baseline in CGI-TD Summary at Week 6

	Placebo	Valbenazine
CGI-TD	**N=44**	**N=45**
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 (67.7)
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: At explained by the review team, the applicant had several 2° endpoints in this study and no pre-specified plan for controlling the Type-I error rate. The finding on CGI-TD was not replicated in Study 1304 (b) (4) The finding does, however, add to the evidence of efficacy for the drug.

Efficacy Summary – Study 1202:

This study serves as confirmatory evidence of efficacy for valbenazine. Dose-response cannot be assessed because of the flexible-dose design, but the majority of patients were on the 75 mg/day dose at the Week 6 efficacy assessment. The information on the 2° endpoint is not fully interpretable, given that lack of a prospectively delineated statistical plan to control the Type-I error rate.

Patients treated with valbenazine (dose titrated from 25, to 50, to 75 mg every 2 weeks based on therapeutic response and tolerability) (n=89) achieved a mean 2.4-point greater reduction in AIMS total score at Week 6 compared to placebo patients (95% confidence interval: -3.7, -1.1). The majority of valbenazine patients (69%) were titrated to the 75 mg dose by the end of the study, and the mean daily dose was 64 mg. This dose is relatively close to the dose tested in Study 1304 (80 mg/day); therefore, this study substantiates findings of Study 1304.

Study 1202 had a number of limitations; however, a number of analyses performed by the statistical review team confirmed that the results are robust.

Study 1201

Study 1201 was a randomized, double-blind, placebo-controlled study in 109 adult patients with TD. This was the first phase 2 study in the sponsor's TD development program, and it did not demonstrate a statistically significant result on change from baseline in the AIMS, the 1° endpoint, *p*=0.3. The 1° endpoint had been assessed with on-site raters, which, in retrospect, may not have been optimal. An exploratory analysis using central review of video recordings, blinded to treatment and sequence, showed a stronger trend towards a treatment effect, and was the basis for the use of central rating in subsequent studies (Studies 1202 and 1304).

Conclusions: Efficacy

I agree with the reviews of the Division and Biostatistics and with the Division Director, that the applicant has submitted substantial evidence of efficacy for valbenazine for the treatment of TD in adults.

The Division prospectively agreed to use of the 1° endpoint, items 1 through 7 of the AIMS Total Dyskinesia Score, prior to study initiation, and this scale was developed to measure symptoms of TD.

As noted by Dr. Mathis, there was a fair amount of discussion among the staff with respect to the amount of change in the AIMS that would be clinically meaningful, but all agreed that any statistically significant decrease in abnormal involuntary movements may be meaningful for patients.

The 2° endpoint, CGI-TD, was not statistically significantly decreased in Study 1304, the only study with a prospective plan to control the Type-I error rate. (b) (4)

Importantly, because the efficacy of 80 mg/day exceeded that of 40 mg/day, and given the apparent lack of dose-limiting side effects (see below), it is reasonable to ask whether a daily dose of more than 80 mg/day would lead to improved efficacy. Achievement of greater efficacy would constitute a significant public health benefit, and the applicant has agreed to study this question under a postmarketing-commitment.

8. Safety

The safety review was conducted by Brian Miller, and considered in light of what is known about tetrabenazine, another VMAT2 inhibitor approved in 2008 for the treatment of chorea associated with Huntington's disease. As noted above, valbenazine's active metabolite is an enantiomer of tetrabenazine's active metabolite.

The applicant focused on the 6-week controlled portions of studies 1201, 122, and 1304 for their safety analyses. Dr. Miller noted, however, that the studies differed in potentially important ways: Study 1201 included a forced dose reduction, Study 1303 was a fixed-dose study, and Study 1202 used a dose-titration design. In all of these studies, subjects originally randomized to placebo were switched to drug after 6 weeks. Thus, Dr. Miller analyzed each of the 3 studies separately, and then compared results across the trials for consistency of effect.

Dr. Miller also constructed various custom MedDRA queries, combining similar and related preferred terms, e.g., his grouping “balance disorders/fall” includes the preferred terms: balance disorder, ataxia, dizziness, fall, and gait disturbance.

Dr. Stone analyzed the placebo-controlled periods (through Week 6) of Studies 1201, 1202, and 1304 together to gain an understanding of the overall pattern of adverse events and to construct an adverse event table.

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. The majority of exposure was at doses of 40 mg/day (108 patient-years) and 80 mg/day (123 patient-years). The Division concluded that exposure was adequate for a disease with near orphan-range prevalence.

The demographics of the safety population are summarized in Table 8.

As noted by Dr. Miller, the population includes a range of patients with respect to age, gender, and race, and seems reasonably representative of a typical patient population with longstanding schizophrenia who would have TD. Approximately 90% of subjects were taking an antipsychotic drug (19% typical; 74% atypical).

Safety Results

Because the numbers of deaths, dropouts, and serious adverse events were small, they were difficult to interpret. There were 4 deaths and 22 (generally unrelated) serious adverse events in the controlled database of studies 1201, 1202, and 1304 – too few to support any conclusions with respect to drug causality. None of the deaths or serious adverse events was interpreted as being suggestive of causality.

Significant Adverse Events

Dr. Miller confirmed differences in somnolence and balance disorders/falls in the controlled safety database. There was a considerable difference in somnolence (11% on drug vs. 4% on placebo), which merited a warning in Section 5 of labeling. The frequency of somnolence was similar in males and females.

One might think that somnolence would mostly occur early, because of habituation. As shown in an analysis of time-to-first event, however, somnolence was not exclusively an early adverse event; some was delayed (Figure 7). (It should be appreciated that the valbenazine dose was titrated up in some patients, and this analysis does not account for increases in dose.)

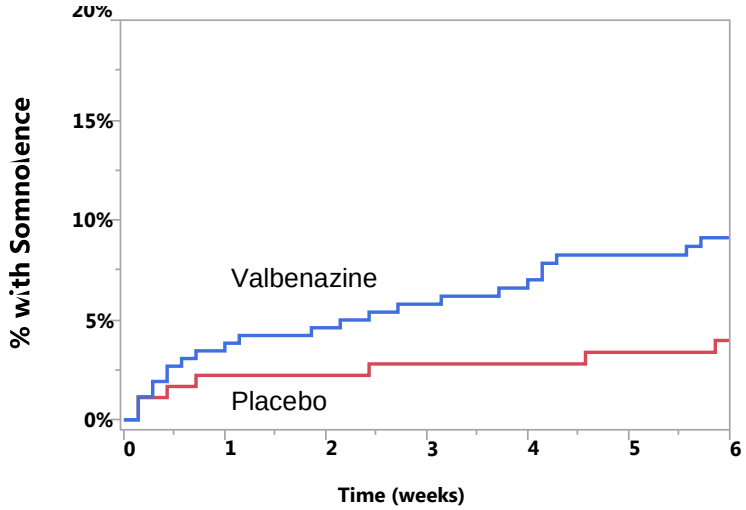
Table 8: Demographics of the Safety Database

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 of Latino(%)	70.5%
Weight (kg)	Mean	81.6
	Min	41.8
	Max	156
	S.D.	17.5
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%
Geography	USA	97.1%
	Canada	1.3%
	Puerto Rico	1.4%
Total N		613

Source: Dr. Miller, Clinical Review, Studies 1201, 1202, 1304, and 1402.

Close examination of assessments of depression and suicidality, including analyses of data from the Columbia Suicide Severity Rating Scale (C-SSRS), did not show evidence of worsening in the drug group. The data were consistent with the baseline rate of suicide in the schizophrenic/ schizoaffective disorder population (the estimated lifetime risk of suicide is 5% in patients with schizophrenia).

Figure 7: Time to Event for Somnolence – Studies 1201, 1202, and 1304



All Adverse Events:

Dr. Muñiz includes the following in his review: "Marc Stone, M.D., used a random effects logit model to account for the differences in randomization across the three 6-week controlled trial periods in order to derive a summary AE profile for labeling for TEAEs occurring at an incidence of ≥2% and greater than placebo."

Table 9, from Dr. Muñiz's review, is similar to the table that will be included in labeling.

Table 9: Treatment-emergent Adverse Events across Three Controlled-trial Periods

Adverse Reaction	*Placebo (%)*	*Valbenazine (%)*
Nervouse System Disorders		
Anticholinergic effects	4.9	5.5%
Balance disorders/fall	2.2%	3.8%
Akathsia	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: Created by Brian Miller from adverse event files for Studies 1201, 1202, and 1304 (AE.xpt)

My own findings from the adverse event datafile were consistent with those in Table 9, with the exception of anxiety. Through Week 6 of Studies 1201, 1202, and 1304, I found 6 unique subjects with anxiety (including the preferred terms "nervousness" and "panic attack" along with anxiety), and all were on valbenazine at the time of their adverse event. The frequency was 2.3% (vs. 0% in placebo).

As noted by Dr. Miller, valbenazine's metabolites bind extensively to the pigmented region of the eye. A 64 year-old female who had been on valbenazine for 57 days had adverse events of nuclear cataract, branch retinal vein occlusion, and macular

Table 10: Anxiety as an Adverse Event in Valbenazine-treated Subjects in the Controlled Portion of Studies 1201, 1202, and 1304

Subject	treatment	verbatim term	preferred term
XXX-3009	80 mg	INCREASED ANXIETY	ANXIETY
XXX-3001	80 mg	ANXIETY	ANXIETY
XXX-3001	40 mg	INCREASED ANXIETY	ANXIETY
XXX-3003	80 mg	NERVOUSNESS	NERVOUSNESS
XXX-2006	<40 mg	PANIC ATTACK	PANIC ATTACK
XXX-3006	80 mg	SYMPTOMS OF PANIC	PANIC ATTACK

edema (these adverse events were non-serious and all were rated 'mild' in severity). This constellation of adverse events seems unlikely to be a consequence of any retinal effects of the drug. Another subject had blurred vision (rated mild) from day 41 to day 100 of valbenazine treatment. As a single event, this is difficult to interpret.

Mean drug effects on lab parameters for Studies 1201, 1202, and 1304 were analyzed during the controlled period using a mixed-effects logistic regression, as performed by Dr. Stone. Paradoxical signals for increased blood glucose and decreased hemoglobin A1C were found, rendering interpretation difficult. There was a clear signal for increased prolactin, but no prolactin-related adverse events (e.g., galactorrhea) were observed. (Most of these patients were on antipsychotics, a class of drugs with known potential to increase prolactin.)

In the Thorough QT Study (TQT), the largest upper bound of the 2-sided 90% CI for the mean difference between valbenazine 160 mg and placebo ($\Delta\Delta$ QTcF) was 11.7 ms. Given the concern that accumulation of metabolites could add to QT prolongation, especially in CYP2D6 poor metabolizers, labeling will include a warning for QT Prolongation. (Of note, in the controlled

Safety Conclusions:

The main safety concerns are somnolence, akathisia, falls, and QT prolongation (the latter under certain circumstances). The Division found no evidence of a drug effect on instruments designed specifically to assess suicidal ideation/behavior or depression, and no patterns were evident in the adverse events to suggest worsening depression or a suicide risk. The risks of somnolence and QT prolongation will be included in the Warnings and Precautions Section of labeling, with the other risks described in Section 6 (Adverse Reactions).

Although valbenazine's metabolites are known to bind to pigmented structures in the eye, the pattern of ocular adverse events did not suggest toxicity.

9. Advisory Committee Meeting

The NDA was not presented to an Advisory Committee; no one on the review team thought that a public discussion was needed prior to taking an action. Although valbenazine is a new molecular entity, its mechanism of action is similar to that of tetrabenazine, a previously

approved drug. In addition, the primary endpoint is well accepted, the effect size was clear, and there were no controversies or major safety issues identified that would affect approval.

10. Pediatrics

This NDA did not include pediatric data. In their initial Pediatric Study Plan (iPSP), the Applicant requested a drug-specific waiver for neonates, infants, children, and adolescents, on the basis that clinical studies in these age groups would be highly impractical, given that the number of patients is very small. TD, although not unheard of in children, is very rare, because prolonged treatment with antipsychotics is required in most cases to produce the disease. For the very rare patient with TD under the age of 18, the treatment is to discontinue the offending medication and anticipate resolution of symptoms. In summary, a study of TD in children would be highly impracticable because of its rarity. The labeling will be clear that valbenazine is approved for adult patients with TD.

11. Other Relevant Regulatory Issues

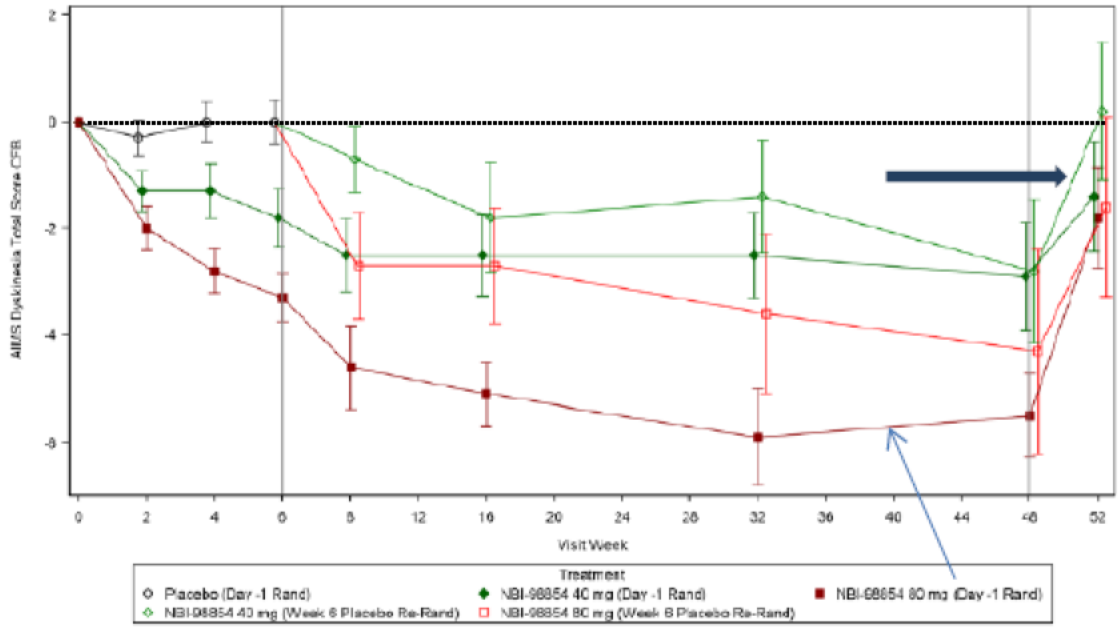
The Office of Scientific Investigations (OSI) audited 5 sites based upon enrollment numbers and dates of most recent inspections. The recommendation from OSI was to consider the data to be acceptable and the studies to have been conducted adequately.

There were no financial conflicts of interest reported that would call any of the study results into question (in fact, none were reported).

The Division of Risk Management assessed the need for a Risk Evaluation and Mitigation Strategy (REMS) and determined that a REMS was not necessary to ensure that the benefits of valbenazine outweigh its risks. Specifically, all consider that the risks of QT prolongation and somnolence can be managed adequately with a warning in labeling and a patient package insert.

The Controlled Substances Staff review drew attention to non-clinical data suggesting a withdrawal syndrome, along with concern about a rebound effect following withdrawal of valbenazine in some clinical studies. For example, in Study 1304, at Week 52, after discontinuation of valbenazine, the point estimate for the mean AIMS of the 40-mg group exceeds its baseline value (Figure 8, thick arrow; horizontal dotted line at zero added by me).

Figure 8: Study 1304 – Evidence of Rebound



Data Source: Figure 14.2.1.2.

I see some weakness, however, in this line of reasoning. First, there are 4 valbenazine groups at the end of this study, and all patients discontinued the drug abruptly at Week 48. Selecting one valbenazine group out of four represents a multiplicity problem. Second, although the point estimate of the AIMS exceed zero in this treatment group, the error bars widely straddle both sides of zero. Moreover, the pattern of adverse events reported after discontinuation of valbenazine was unremarkable. Finally, if present, an increase in symptoms to a level slightly worse than baseline would not necessarily be clinically important.

In any case, the Division agreed with the Controlled Substance Staff to request a systematic evaluation of clinical dependence and withdrawal. They recommend evaluation of subjects as they complete Studies 1304 and 1402 (presently ongoing). They also recommend evaluation of patients for signs and symptoms of clinical dependence and withdrawal for 3 weeks after the abrupt discontinuation of valbenazine. The applicant has agreed to conduct this study as a post-marketing requirement (PMR).

12. Labeling

Labeling has been negotiated with the applicant.

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

Based upon recommendations from the Clinical Pharmacology review team, there are a number of recommendations for patients taking various CYP inhibitors and inducers, as well as CYP2D6 poor metabolizers.

The applicant had originally proposed (b) (4) which we removed. (b) (4)

There is a warning for dose reduction to avoid clinically important QT prolongation with use of strong CYP2D6 and CYP3A4 inhibitors, as well as in patients known to be CYP2D6 poor metabolizers. Such conditions are expected to result in higher concentrations of valbenazine and its metabolites, which could increase the QT interval.

The Adverse Reactions section of labeling has been modified to reflect appropriately pooled safety data.

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 depict response based on different changes in AIMS as well as change in AIMS as a function of time, including the 42-week extension period of Study 1304.

Because Study 1202 was conducted with doses that will not be approved (i.e., 25 to 75 mg), we decided not to include that study in the Clinical Studies section, although data from the study will be included in Adverse Reactions, Section 6.

The Applicant had proposed a Medication Guide initially, but the review team determined that this would not be necessary for safe use of valbenazine. There will be a Patient Package Insert to describe common adverse reactions and explain when, and under what circumstances, the patient should contact the prescriber.

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:

PMRs Under 505(o):

- 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 pharmacokinetics: A pharmacokinetic trial 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 (a major valbenazine metabolite) 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.

PMCs:

- Potential for improved therapeutic benefit at doses higher than the recommended dose of 80 mg/day: A (b) (4) randomized, (b) (4)- (b) (4) efficacy and safety trial should be conducted to test a dose of 80 mg and a higher dose (b) (4) in patients not demonstrating an adequate response to 80 mg. Depending on the findings from the clinical pharmacology trial to assess the effect of CYP2D6 inhibition, CYP2D6 poor metabolizers may be excluded from this trial to avoid exposure-related adverse events (e.g., QT prolongation).
- Assess persistence of drug effect: Conduct a randomized withdrawal study in patients who have had an adequate response to valbenazine, randomizing these stable patients to continue their current dose of valbenazine or switch to placebo. Stratify the randomization based on concomitant (continued) antipsychotic use.
- Directly assess clinical meaningfulness: Conduct a study to define the magnitude of change in AIMS total dyskinesia score that translates into functional improvement.

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

/s/

ELLIS F UNGER
04/11/2017