CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	CDR Javier A. Muñiz
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 209241
Applicant	Neurocrine Biosciences
Date of Submission	August 11, 2016
PDUFA Goal Date	April 11, 2017
Proprietary Name / Non-Proprietary Name	Ingrezza/valbenazine
Dosage form(s) / Strength(s)	40mg capsule
Applicant Proposed Indication(s)/Population(s)	Tardive dyskinesia in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	*Tardive dyskinesia in adults*

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Valbenazine is a new molecular entity not currently marketed anywhere in the world for any indication. Its mechanism of action is thought to be related to its inhibition of vesicular monoamine transporter 2 (VMAT2). Valbenazine was developed for the treatment of tardive dyskinesia (TD), an iatrogenic hyperkinetic movement disorder usually resulting from long-term antipsychotic exposure. Although TD is not life-threatening, it can cause considerable social and functional impairment.

There are no currently approved options for the treatment of TD. Evidence for off-label treatments options is limited. Discontinuing or changing antipsychotic treatment is frequently unfeasible due to the underlying psychiatric condition. TD symptoms often persist and may even worsen after the offending drug has been discontinued.

Clear evidence of efficacy for valbenazine in the treatment of TD has been presented in two pivotal studies. The primary efficacy endpoint in these studies was the change in the Abnormal Involuntary Movement Scale (AIMS) total dyskinesia score from baseline to the end of Week 6, as assessed by central video raters who were blinded to treatment and visit sequence. It is anticipated that the majority of individuals with TD who take valbenazine 80 mg/day will experience a reduction in abnormal involuntary movement severity.

The Applicant has submitted sufficient data to adequately assess the safety profile of valbenazine. No clear safety signal has been identified to preclude the approval of this application and the risks (e.g., QT interval prolongation, somnolence, etc.) can be mitigated with appropriate product labeling.

The review team and I unanimously agree that the benefits of valbenazine in the treatment of TD outweigh the risks and we recommend that this application is approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• TD is characterized by involuntary athetoid or choreiform movements that develop in association with long term use of D2 dopamine receptor antagonist medications. • A detailed understanding of TD's biology remains incomplete. There is limited existing knowledge about genetic and other factors that predict the development and clinical course of TD. • Abnormal movements associated with TD can cause functional impairments (i.e., difficulties eating, intelligible speech, difficulty moving, increased risk of fall) as well as shame and social isolation for patients, due to their disfiguring appearance. • Risk factors for developing TD include older age, the use of first-generation/typical antipsychotics, and the development of acute extrapyramidal symptoms early in neuroleptic treatment. • The annual incidence of TD associated with typical antipsychotic exposure is estimated to be ~8.5% and the rate-ratio for atypical vs. typical antipsychotics is estimated to be ~0.68. The point prevalence of TD in the US population in 2013 has been estimated to be ~135,000, though the actual prevalence may be larger as many patients remain undiagnosed or misdiagnosed.	Although TD is not considered to be a life-threatening condition, it can have a significant impact on the quality of life of patients experiencing it.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• TD is frequently chronic in nature, particularly if continued neuroleptic treatment is necessary for management of the underlying condition.	
Current Treatment Options	• There are currently no FDA-approved treatments indicated for TD. • The primary treatment recommendations from the medical literature and professional society guidelines consist of early detection and modification of the neuroleptic regimen. • A number of off-label treatments for TD have been evaluated in clinical studies (e.g., benzodiazepines, anticholinergics, calcium channel blockers, GABA agonists, hormones, vitamins, essential fatty acids, herbs, etc.). There is little evidence supporting these approaches. • A small number of controlled studies suggest clonazepam, ginkgo biloba, amantadine, and tetrabenazine might have some benefit on TD symptoms; however, these studies have small sample sizes and other methodological issues that limit the strength of evidence. • Botulinum toxin administration is occasionally used as a treatment for focal orofacial TD, but evidence supporting this treatment is limited to case series and small open-label studies.	There are no FDA-approved treatments for this condition. There is a very limited body of supportive evidence for off-label treatments. Discontinuing or changing antipsychotic treatment is frequently unfeasible and is not considered to be widely effective for resolving TD symptoms.
Benefit	• Evidence for the effectiveness of valbenazine was provided by two pivotal studies; the primary endpoint for these studies was the change from baseline to the end of Week 6 on the Abnormal Involuntary Movement Scale (AIMS) total dyskinesia score. • Study 1304 was a Phase 3 trial in which 234 subjects with moderate to severe TD were randomized to receive valbenazine 40 mg/day, 80 mg/day, or placebo. ○ Valbenazine 80 mg/day was found to be significantly superior to placebo, with a least-squares mean difference vs. placebo of -3.1. • Study 1202 was a Phase 2 trial in which 102 subjects with moderate to severe TD were randomized to receive flexible-dose valbenazine (25-75 mg/day, titrated according to efficacy and tolerability) or	The efficacy of valbenazine for the treatment of TD has been established. The majority of individuals with TD who take valbenazine 80 mg/day are expected to experience an appreciable reduction in abnormal involuntary movement severity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo. ○ Valbenazine was found to be significantly superior to placebo, with a least-squares mean difference vs. placebo of -2.4. • Data from the pivotal efficacy studies were considered to be persuasive for several reasons: ○ The primary endpoint was scored by central video raters who were blinded to treatment and visit number; this would reduce the sequence/expectancy bias and inter-rater variability associated with on-site raters at each study center. ○ Subjects were generally not allowed to modify or discontinue medications for other psychiatric and medical conditions, so valbenazine effects were unlikely to be confounded by concomitant medications. ○ There was very limited subject attrition during the 6-week placebo-controlled treatment period. ○ In Study 1304, the 42-week extension period showed a dose-efficacy response for 80 vs. 40 mg/day valbenazine, and TD symptoms appeared to recur following treatment discontinuation. • One limitation of the pivotal efficacy data was that Study 1202 used flexible dosage that did not include the 80 mg/day dose; however, the majority of subjects received 75 mg/day for the two weeks of treatment prior to the primary efficacy endpoint. Overall, the trial design for this Study 1202 and Applicant analyses were generally consistent with guidance from the Agency and discrepancies did affect the overall conclusions about benefit. • The primary efficacy endpoint, the AIMS is commonly used in research and clinical settings for the purpose of assessing the presence and severity of TD. One limitation of the primary efficacy endpoint is the lack of consensus as to what would constitute a clinically meaningful change in AIMS score. ○ The Applicant conducted an analysis assessing the concordance of the AIMS change from baseline (CFB) at the	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	end of Week 6 with the Clinical Global Impression-TD (CGI-TD) score; this analysis suggested that the AIMS CFB associated with valbenazine treatment roughly correlated with a global impression of "very much" or "much improved." ○ While the AIMS measure consists of assessing the severity of involuntary movements across several body regions, it would have also been relevant to assess the functional impact of reducing TD for patients; however, the functional impact is thought to be heterogeneous. At this time it is considered to be acceptable, on face, that a significant reduction of abnormal involuntary movements will be clinically meaningful to patients.	
Risk	• The safety database was adequate and consisted of 613 subjects representing a wide variety of ages, medication use, and concurrent diagnoses. • Evidence from the premarket development demonstrated a clear profile for the following adverse events of somnolence (11%), balance disorders/falls (3.8%), and akathisia (2.7%). Suicidal ideation/behavior and depression did not show a clear association with valbenazine treatment in the development program, as supported by a lack of worsening on instruments measuring suicidality (C-SSRS) and depression (CDSS, MADRS). Minor laboratory abnormalities observed in controlled trials consisted primarily of increased blood glucose and prolactin, with the former additionally appearing as an adverse event. • The QT team identified a dose-response relationship with valbenazine concentration and prolongation of the QT interval. The degree of prolongation was considered only to be potentially clinically significant in patients taking a strong CYP2D6 or CYP3A4 inhibitor, poor metabolizers, or for those who have a cardiac arrhythmia associated with a prolonged QT interval.	These adverse events are not life-threatening, generally do not result in hospitalization, and can be mitigated via labeling. Somnolence, which occurs at a rate twice that of placebo and in over 10% of patients, will be labeled as a Warning & Precaution. To inform clinicians of risks associated with QT prolongation in certain sub-populations, valbenazine will be labeled with a Warning & Precaution, in addition to specific language in labeling directing clinicians to assess the QT interval prior to increases in dosage in sub-populations at increased risk.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The product will be labeled to describe adverse reactions and laboratory abnormalities due to valbenazine occurring in pooled, controlled trials and for the single, placebo-controlled, fixed dose study (Study 1304). Additionally, adverse reactions will be summarized in a patient package insert in order to better inform patients. • The Applicant did not adequately assess withdrawal, dependence, and tolerance in valbenazine. Therefore, the agency will require these to be assessed in a PMR, with a recommendation that these assessments be added to ongoing studies.	These risk mitigation strategies will clearly communicate the risks to clinicians and patients. Post-marketing requirements will address undefined risks of withdrawal, dependence, and tolerance.

2. Background

Valbenazine (NBI-98782; proposed proprietary name: Ingrezza) is a new molecular entity not currently marketed in the US or elsewhere for any indication. The Applicant, Neurocrine Biosciences, developed valbenazine for the treatment of tardive dyskinesia (TD). Valbenazine was granted Fast Track designation in January 2012 and Breakthrough Therapy designation in October 2014.

TD is an iatrogenic hyperkinetic movement disorder that can manifest following the sustained use of drugs which block dopaminergic receptors, most notably antipsychotics. Signs and symptoms of TD can include involuntary movements of the orofacial region, trunk, and extremities. These abnormal movements can cause functional impairment (e.g., unintelligible speech, difficulty moving, etc.) and be distressing to patients. Symptoms frequently persist even after discontinuing antipsychotic medications. There are currently no FDA-indicated treatments for TD and there is little data supporting the efficacy of off-label treatments.

Valbenazine is an inhibitor of vesicular monoamine transporter 2 (VMAT2), which is an integral membrane transporter that transports monoamines, including dopamine, from the cytosol into synaptic vesicles. Inhibiting VMAT2 decreases the quantity of neurotransmitter molecules released by presynaptic neurons during synaptic transmission. Although the exact mechanism of action of valbenazine is not known, the Applicant hypothesizes that modulating dopaminergic tone in the striatum by inhibiting VMAT2 will reduce the signs and symptoms of TD. Three metabolites of valbenazine also bind VMAT2 with moderate to relatively high affinity; [+]-alpha-dihydrotetrabenazine (NBI-98782), M10b (NBI-679006), and M14 (NBI-136110). Of note, NBI-98782 is 40-fold more potent than valbenazine and is considered the primary moiety contributing towards effectiveness. NBI-98782 is also a metabolite of the drug Xenazine (tetrabenazine, NDA 021894), approved for the treatment of chorea associated with Huntington's disease.

The proposed dosage form for valbenazine is a 40 mg capsule, which is the recommended initial dose. If necessary, after one week the dose is to be titrated to the recommended dose of two capsules (80 mg) once a day. The maximum recommended daily dosage is 80mg.

3. Product Quality

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

The Office of Process and Facilities (OPF) review team found each of manufacturing and testing sites acceptable for the functions listed in this application. The environmental assessment (EA) team found the categorical exclusion claim from an EA accordance with 21 CFR Part 25.31(b) to be acceptable. The Biopharmaceutics review team found the proposed dissolution method acceptable for release and stability testing. Although a Biopharmaceutics Classification System (BCS) designation was not requested, the biopharmaceutics team considered the drug product to be Class I (high permeability, high solubility). The Applicant more conservatively considered it to be Class III (low permeability, high solubility) due to lack of data on bioavailability.

One notable quality review issue is that there are significant differences between the (b) (4) drug product used in Phase 3 studies and the proposed commercial product. However, a bioequivalence study successfully bridged these formulations and *in vitro* performance results (including dissolution data) supported this bridge.

The drug product reviewer, Rao Kambhampati, PhD, determined that the stability data submitted with this application supported a (b) (4) month instead of the requested (b) (4) month product expiry period.

The OPQ review team recommends for the action letter to include the following points:

1. The stability data supports a (b) (4) month product expiry period.
2. Highlight the Applicant's previous commitment to add bulk density, tapped density, optical rotation tests, and acceptance criteria to the drug substance specification.

4. Nonclinical Pharmacology/Toxicology

Darren Fegley, PhD, was the primary nonclinical reviewer for this application; he recommends approval.

Valbenazine is extensively metabolized in rats, dogs, and humans with little unchanged drug excreted via biliary or renal pathways. *In vivo* radiolabeled mass balance studies conducted in rats, dogs, and humans demonstrated that metabolism was qualitatively, although not quantitatively, similar across the species. The primary difference in metabolism is related to the extent of ester hydrolysis of valbenazine to form NBI-98782 ([+]-alpha-dihydrotetrabenazine), which is significantly greater in the rat than in dog, mouse, or human. Due to NBI-98782's significantly higher affinity for VMAT2 relative to valbenazine, this metabolic difference may account for the increased sensitivity of rats to valbenazine effects noted in the nonclinical studies.

Valbenazine-related material was highly distributed to the pigmented region of the eye, suggesting extensive melanin binding. A similar distribution to pigmented skin was not observed. Because rat studies were conducted in albino animals, no valbenazine treatment-related eye findings were noted in the dog or pigmented mouse, and no phototoxicity was observed in BALB/c 3T3 mouse fibroblasts. The clinical significance of the extensive distribution of valbenazine-related material to the eye remains unclear, according to Dr. Fegley.

Rats were the most sensitive species in the pivotal toxicology studies, with mortality and excessive morbidity observed at exposures roughly equivalent to the maximum recommended human dose (MRHD) of 80 mg based on both area under the curve (AUC) and mg/m^2. In general, other nonclinical species (CD-1 mice and Beagle dogs) tended to tolerate higher exposures of valbenazine, with no adverse effects occurring at doses two to five times the MRHD based on both AUC and mg/m^2 and no mortality or excessive morbidity at therapeutically relevant exposures. Dr. Fegley notes that exposure to the primary pharmacologically active circulating metabolite in human, [+]-alpha-dihydrotetrabenazine, was similar at the no observed adverse effect level (NOAEL) and maximum tolerated doses across nonclinical species.

Safety pharmacology studies found valbenazine moderately inhibits the hERG channel (IC50 ~ 2 μM) and produces moderate QTc prolongation in dogs at a dose 6 times the MRHD of 80 mg/day based on mg/m^2. There were no other adverse cardiovascular effects found in dogs at doses up to 12.5 times the MRHD based on mg/m^2.

Across all nonclinical species, the central nervous system (CNS) was the primary target organ for toxicity. Signs consistent with depletion of monoamines from the CNS (e.g., decreased activity, ataxia, trembling, and ptosis) were noted in rats, mice, and dogs. Rodents exhibited increased activity at valbenazine trough levels and for a couple of days following drug cessation, suggesting a potential withdrawal phenomenon. Although no specific studies were conducted to address this potential phenomenon, no clear signs of withdrawal were reported during the human clinical trials. In his review, Dr. Fegley notes that "valbenazine administration was also associated with tremors and convulsions in both rats and dogs. In rats, self-resolving myoclonic jerking or clonic convulsions generally lasting < 1 minute were noted at doses approximately equivalent to the MRHD of 80 mg based on mg/m^2. This seizure-like activity was late developing, requiring at least 2 months of dosing, was not associated with tmax, but instead with handling (dosing, detailed clinical examinations, etc.), and was not observed following dosing cessation. In addition, extensive neuropathology examinations were undertaken in these studies and no CNS lesions were noted. Taken together these findings suggest that the convulsions are the result of chronic administration and that this process appears to be reversible." Dr. Fegley also notes that similar effects in rats were noted with tetrabenazine, another VMAT2 inhibitor, suggesting that this effect may be common to this class of drugs. In dogs, there were periods of significant tremor in proximal muscles (head, neck, shoulders) with no associated electroencephalogram abnormalities or neuropathology lesions in doses at doses ≥ 2 times the MRHD of 80 mg based on mg/m^2.

Death occurred after doses > 35 mg/kg/day which is at least 15 times the MRHD on mg/m^2. The toxicological significance of these findings in dogs is unclear at this time.

Valbenazine did not increase tumors in rats treated orally for 91 weeks in doses up to 2 mg/kg/day (0.24 times the MRHD based on mg/m^2). Similarly, valbenazine did not increase tumors in hemizygous Tg.rasH2 mice treated orally for 26 weeks in doses up to 75 mg/kg/day (4.6 times the MRHD based on mg/m^2). Valbenazine was not mutagenic in the *in vitro* bacterial reverse mutation test (Ames) or clastogenic in the in vitro mammalian chromosomal aberrations assay in human peripheral blood lymphocytes or in the *in vivo* rat bone marrow micronucleus assay. Valbenazine did not produce structural abnormalities, functional impairment, or alterations in growth in rats or rabbits at doses up to 12 times the MRHD based on mg/m^2.

In a fertility study, rats were treated orally with valbenazine in doses up to 10 mg/kg/day (1.2 times the MRHD based on mg/m^2) prior to mating and through mating, for a minimum of 10-weeks (males) or through Day 7 of gestation (females). Valbenazine delayed mating in both sexes which led to lower number of pregnancies and disrupted estrous cyclicity at a 10 mg/kg/day dose. However, valbenazine had no effects on sperm parameters (e.g., motility, count, density) or on uterine parameters (e.g., corpora lutea, number of implants, viable implants, pre-implantation loss, early resorptions and post-implantation loss) at any dose. Valbenazine administration increased the incidence of stillbirths and postnatal pup mortality at doses below the MRHD based on mg/m^2. In addition, valbenazine and the metabolites, NBI-98782 and NBI-136110, were detected in fetuses as well as in milk and in pups following administration to pregnant or lactating rats. These data indicate risk to benefit should be considered when administering valbenazine to pregnant or breastfeeding women as fetal and infant exposure are likely to occur.

Dr. Fegley notes that all impurities in drug substance and/or product present at levels above the qualification threshold have been adequately qualified in nonclinical studies.

5. Clinical Pharmacology

The review team from the Office of Clinical Pharmacology recommends approval of this application.

The following is a summary of the clinical PK features of valbenazine and NBI-98782:

- **Absorption:** The median T_{max} of valbenazine ranged from 0.5 to 1 hour whereas the T_{max} for NBI-98782 ranged from four to eight hours. The absolute oral bioavailability (BA) of valbenazine is ~ 49%. Ingestion of a high-fat meal decreased valbenazine mean C_{max} by about 47% and mean AUC by about 13 %. The mean C_{max} and mean AUC of NBI-98782 decreased by about 18% and 6%, respectively.

- **Distribution:** The plasma protein bindings of valbenazine and NBI-98782 were > 99% and ~64%, respectively. The mean steady state volume of distribution of valbenazine was 92 L.
- **Elimination:** Mean total systemic clearance for valbenazine was 7.2 L/hr. Elimination half-lives of valbenazine and NBI-98782 ranged from 15 to 22 hours.
- **Metabolism:** Valbenazine is extensively metabolized by hydrolysis to form NBI-98782 and by oxidative metabolism, primarily by CYP3A4/5, to form mono-oxidized valbenazine and other minor metabolites. NBI-98782 is further metabolized mainly by CYP2D6 and CYP3A4.

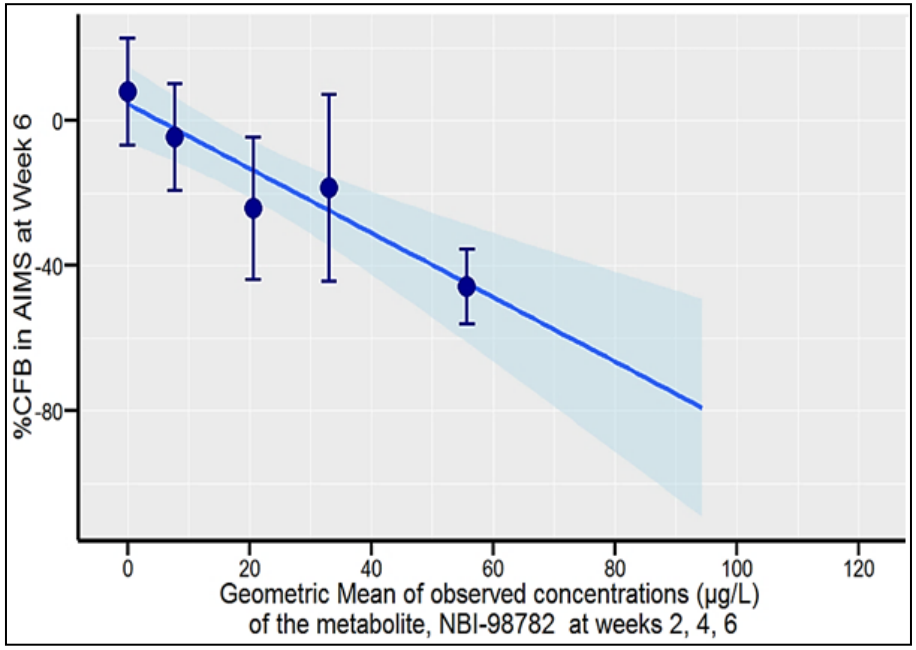
The OCP review team agrees with the proposed dosing regimen; 40 mg daily for 1 week as titration to the recommend dose of 80 mg daily. For some patients, however, adequate clinical response is achieved at 40 mg dose. Given that various adverse events are exposure-dependent, the OCP review team recommends labeling language that a dose of 40 mg daily may be considered for some patients.

Based on the data submitted with the application, the OCP review team recommends for the dose of valbenazine to be reduced by half in patients with moderate to severe hepatic impairment (Child-Pugh score 7 to 15). Similarly, the dose of valbenazine should be reduced by half when administered with a strong CYP3A4 inhibitor. It is also recommended to avoid concomitant use of strong CYP3A4 inducers. CYP2D6 is a major metabolic enzyme for the active metabolite NBI-98782; thus, significant changes in exposure to NBI-98782 are expected in patients receiving a strong CYP2D6 inhibitor or in CYP2D6 poor metabolizers (PMs). However, no dedicated study was conducted in patients receiving a concomitant strong CYP2D6 inhibitor. In addition, the exposure data obtained from the CYP2D6 PMs in the development program are variable and the OCP review team had concerns with various key aspects of the Sponsor's population PK analyses (e.g., studies included in the PopPK analyses included rich and sparse sampling design, administration of valbenazine without regard to food, etc.), limiting the reliability of the Sponsor's conclusions on the impact of CYP2D6 inhibition. Although no significant exposure increase is anticipated in patients with mild to moderate renal impairment, it has been shown that the CYP2D6-mediated clearance can be decreased in patients with severe renal impairment. Therefore, the OCP review team recommends for a dedicated post-marketing study in patients with severe renal impairment to be required. The team also recommends a post-marketing requirement (PMR) for a PK study to quantify the impact of CYP2D6 inhibition on the exposures of the parent compound and major metabolites.

In the pivotal Study 1304, PK sampling occurred at Weeks 2, 4, and 6. The OCP review team conducted an exposure-response analysis for efficacy, using the percentage of change from baseline in the Week 6 AIMS total dyskinesia score as the efficacy measure and the geometric mean concentrations of [+]α-dihydrotetrabenazine (NBI-98782) as the exposure variable (see OCP-reviewer-constructed Figure 1). This analysis showed an exposure-efficacy response relationship that did not appear to plateau in the tested dose

range. Therefore, the OCP review team proposes a post-marketing commitment (PMC) trial to assess whether a higher dose of valbenazine confers additional therapeutic benefit for patients with TD. The OCP review team concluded that substantial evidence of effectiveness was demonstrated by the registration trials, and a significant dose/exposure-response relationship indicated that higher dose/exposure is associated with higher reduction in the AIMS total score.

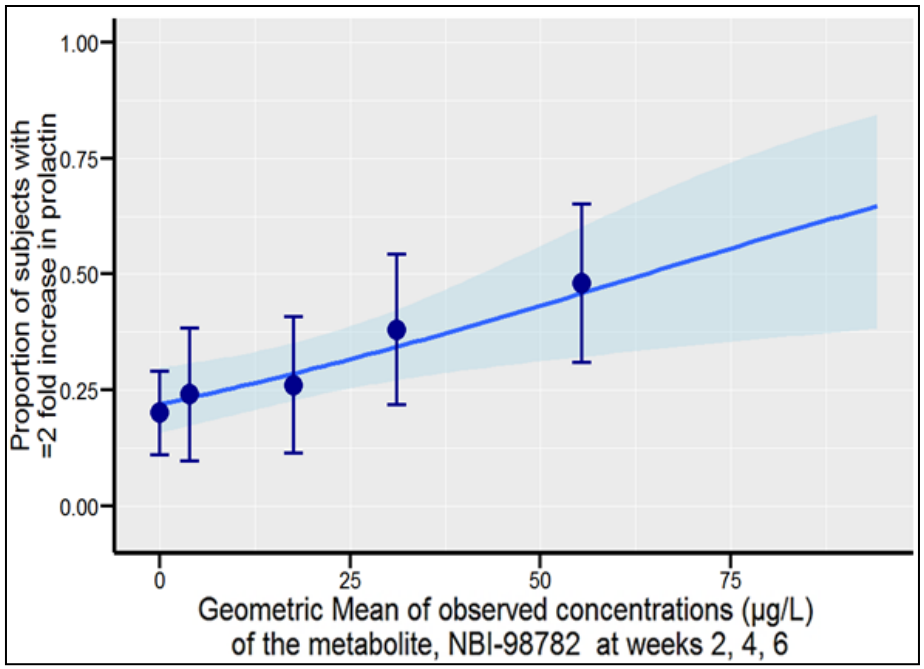
Figure 1: Exposure-Response Analysis for Efficacy, Study 1304



[Source: OCP Review, Figure 28, p. 50]

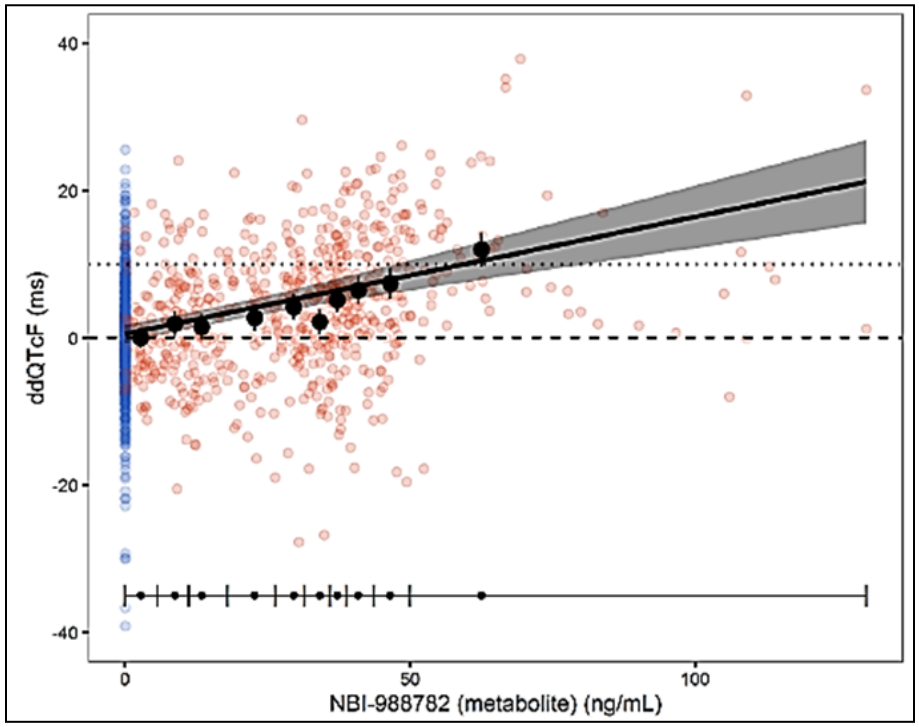
A similar safety exposure-response analysis was performed by the OCP team, assessing the proportion of subjects with a ≥2-fold increase in prolactin levels at Week 6 (Figure 2). This analysis suggests that greater drug exposure confers a greater increase in prolactin levels; this could theoretically be associated with adverse reactions such as oligomenorrhea or galactorrhea. Additionally, an exposure-response analysis of clinical data from two healthy subject studies revealed a positive correlation in QTc interval with the plasma concentration of α-dihydrotetrabenazine (Figure 3); patients taking a 80 mg valbenazine dose may have a mean (95% upper bound) QTc prolongation of 6.7 (8.4) msec, and patients taking an 80 mg dose with increased exposure (e.g., taking a concomitant strong CYP3A4 or CYP2D6 inhibitor) may have a mean QTc prolongation > 10 msec.

Figure 2. Exposure-Response Analysis for Prolactin Elevation, Study 1304



[Source: OCP Review, Figure 30, p. 56]

Figure 3: Exposure-Response Analysis for QTc Prolongation



[Source: QT review by Dr. Nan Zheng and Dr. Lars Johannesen]

According to the QT data reviewed by Dr. Nan Zheng and Dr. Lars Johannesen, NBI-98782 causes concentration-dependent increases in the QTc interval. However, based on the exposures in patients who received 80 mg doses, QT prolongation was modest and considered acceptable. Although many antipsychotics prolong the QTc interval to some extent and this medication class is expected to be used concomitantly in a large proportion of patients with TD, the safety profile of the recommended dose of 80 mg seems acceptable in the general population.

As discussed in Section 3, there are significant differences between the to-be-marketed formulation and the formulation used during the clinical trials. Upon review of the pivotal relative BA trial comparing these formulations, the OCP review team also agrees that bioequivalence has been demonstrated. Thus, similar effectiveness and safety profiles are expected between the two.

Finally, the OCP review team recommends a PMC for an *in vitro* study to assess the induction potential of NBI-136110 on CYP2B6 enzyme, citing the Drug Interaction Guidance recommendations for the evaluation of CYP enzyme induction potential for major circulating moieties.

6. Clinical Microbiology

No clinical microbiology data was submitted with this application.

7. Clinical/Statistical- Efficacy

Michael Davis, MD, PhD, was the primary clinical reviewer for this NDA; he recommends approval. The efficacy claim for the treatment of TD is based on the results of two trials (Study 1202 and Study 1304).

Individual Study Results

Study 1202

Study 1202 was a Phase 2, randomized, double-blind, placebo-controlled, dose titration trial to assess the safety, tolerability, and efficacy of valbenazine in the treatment of TD. It was conducted in 29 US sites, including Puerto Rico. The primary efficacy endpoint measure was the change from baseline to Week 6 on the AIMS dyskinesia total score (sum of AIMS items 1-7). Subjects were adults, aged 18-85, with moderate to severe tardive dyskinesia and an underlying diagnosis of schizophrenia, schizoaffective disorder, or gastrointestinal disorder Eligible subjects were randomized (1:1) to receive valbenazine or placebo treatment, with randomization stratified by underlying disease category and concomitant use of valproic acid and derivatives (due to prior observations that valproic acid may reduce exposure to valbenazine and its active metabolite, NBI-98782). Subjects who were randomized to receive valbenazine received a starting dose of 25 mg by mouth daily. The valbenazine dose could be adjusted in increments of 25 mg every two weeks to a maximum of 75 mg daily, based on efficacy and tolerability. The titration design did not allow for a formal dose comparison, since subjects who responded to treatment at a lower dose were not escalated to the next higher dose.

Importantly, the Applicant instituted the use of blinded central video AIMS raters and revised the AIMS scoring descriptors (Table 1) during the conduct of Study 1202, in an effort to improve scoring consistency. These changes were submitted with Amendment 2 of the protocol, before study completion and database lock. The Division agreed with these changes, with input from the Clinical Outcomes Assessment team. In addition to being blinded to treatment arm, the central raters were also blinded to visit sequence, thus

reducing the potential for expectancy bias. The central video raters were neurologists with movement disorder expertise. Two central raters reviewed each video and needed to reach a consensus in order to provide an AIMS score. On-site raters (whose scores were used in secondary/exploratory analyses) used the original AIMS descriptors in Study 1202, whereas the central raters used the revised AIMS descriptors.

Table 1: AIMS Score Descriptors Used by On-Site vs. Central Video Raters

Score	Descriptors Used by the On-Site Rater	Descriptors Used by the Central Video Raters
0	**None**	**None**: No dyskinesia
1	**Minimal**: Given when there is some movement, but you are not sure that it is TD. May be at upper extreme of normal range	**Minimal** or slight dyskinesia: Low amplitude, present during some but not most of the exam
2	**Mild**: Rated if movements are definitely TD, however slight	**Mild** dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam)
3	**Moderate**: Assigned when there is an increase in amplitude and frequency of movements	**Moderate** dyskinesia: Moderate amplitude and present during most of exam
4	**Severe**: Rated if movements are constant, very noticeable, unsightly. Sharp increase of amplitude and frequency	**Severe** dyskinesia: Maximal amplitude and present during most of exam

[Source: Study 1202 CSR; Table 5, p. 44]

A total of 205 subjects were screened for the study and 102 were randomized; 51 were assigned to placebo and 51 to valbenazine. The percentage of subjects completing the study was high (88.2% overall) and similar between treatment groups. See Table 3 for a summary of patients included in each pre-specified analysis set; the Applicant pre-specified that the per protocol (PP) analysis set would be used for evaluating the primary efficacy endpoint. Dr. Davis writes in his review that "it is noted 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."

Table 2: Study 1202 - Analysis Set Disposition

Analysis Set	Placebo (N=51) n (%)	NBI-98854 (N=51) n (%)	All Subjects (N=102) n (%)
Safety Analysis Set			
Subjects included	49 (96.1)	51 (100.0)	100 (98.0)
Subjects excluded	2 (3.9)	0	2 (2.0)
Reason for exclusion			
Did not receive study drug	2 (3.9)	0	2 (2.0)
Intent-to-Treat Analysis Set			
Subjects included	44 (86.3)	45 (88.2)	89 (87.3)
Subjects excluded	7 (13.7)	6 (11.8)	13 (12.7)
Reason for exclusion:			
Did not have an evaluable central AIMS video raters' CFB AIMS dyskinesia total score during the double-blind treatment	5 (9.8)	6 (11.8)	11 (10.8)
Multiple reasons	2 (3.9)	0	2 (2.0)
Per Protocol Analysis Set			
Subjects included	44 (86.3)	32 (62.7)	76 (74.5)
Subjects excluded	7 (13.7)	19 (37.3)	26 (25.5)
Reason for exclusion:			
Important protocol deviation	0	1 (2.0)	1 (1.0)
NBI-98854 treated subject with no quantifiable plasma concentration at Week 6	0	11 (21.6)	11 (10.8)
Multiple reasons	7 (13.7)	6 (11.8)	13 (12.7)

[Source: Study 1202 Clinical Study Report, Table 7, p. 71; NBI-98854 = valbenazine]

Overall, Dr. Davis concludes that protocol violations identified in the study report were infrequent and would not appear to bias the interpretation of results in favor of valbenazine treatment. Similarly, the demographic characteristics of the ITT population (e.g., race, sex, age, CYP2D6 genotype classification, etc.) do not limit study generalizability. The most common concomitant medications taken during double-blind treatment were related to the underlying psychiatric illnesses (e.g., anticholinergics such as benztropine for the treatment of EPS, antidepressants, anticonvulsants for mood stabilization, antipsychotics) and medications related to cardiovascular disease (e.g., lipid lowering medications and antihypertensives).

The Applicant defined the primary efficacy endpoint as the AIMS dyskinesia total score CFB at Week 6, based on the central raters' assessments, using the PP analysis set. As Dr. Davis points out, this is not optimal in a pivotal study because removing poor compliers

could bias the interpretation of efficacy results. The clinical review focused on the Applicant-defined ITT analysis set, which was modified from a true ITT population in that it excluded subjects who did not receive any study medication or did not have any post-baseline AIMS assessments. This is acceptable but not ideal, as the tendency for subjects to not return for post-baseline AIMS assessments might not be random.

The following table provides a summary of the Applicant's primary efficacy endpoint analysis.

Table 3: Applicant's Primary Efficacy Endpoint Analysis (ITT); Study 1202

Study Number	Treatment Group	Primary Efficacy Measure: AIMS Dyskinesia Total Score (ITT)		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1202	Valbenazine (25-75 mg/day)* [n=45]	8.0 (3.5)	-2.6 (1.2)	-2.4 (-3.7, -1.1)
	Placebo [n=44]	7.9 (4.5)	-0.2 (1.1)	--

[Source: Biostatistics review, Table 10, p. 19]
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.

Patients treated with valbenazine achieved, on average, a 2.4 point greater reduction in the AIMS total score at the end of Week 6 compared to patients treated with placebo (95% CI: -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 dose at week 6 was 64.4 mg/day. The biostatistics reviewer, Thomas Birkner, PhD, was able to replicate the AIMS dyskinesia total score data based on a dataset containing the seven components of the AIMS dyskinesia total score.

The secondary efficacy endpoint Clinical Global Impression of Change-Tardive Dyskinesia (CGI-TD) achieved nominal statistical significance at week 6 (see table below). Dr. Birkner was able to confirm these results. CGI-TD was not pre-specified in a multiple testing procedure.

Table 4: Applicant's Secondary Endpoint Results; Study 1202

Study Number	Treatment Group	Key Secondary Efficacy Measure: Clinical Global Impression of Change (Week 6)	
		LS Mean (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1202	Valbenazine (25-75 mg/day)	2.2 (0.3)	-0.8 (-1.2, -0.5)
	Placebo	3.1 (0.3)	--

[Source: Biostatistics review, Table 12, p. 20]
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 performed additional analyses related to the primary efficacy measure, based on the fact that there were 12 subjects (five receiving valbenazine and seven receiving placebo) who were randomized but discontinued during the double-blind period. Because they did not have a central AIMS rating at the end of Week 6, they were not included in the "ITT" analysis set. Dr. Birkner performed a tipping point analysis by imputing incrementally worse scores for the excluded valbenazine subjects, while imputing either no change or minimal improvement scores for the excluded placebo subjects. The conclusion from this analysis was that the excluded valbenazine subjects would have to worsen by 9-10 points on the AIMS total dyskinesia score to overturn the statistical significance of the primary efficacy measure. Observing such a worsening was deemed unlikely, given the highest observed worsening of three points among completers who received valbenazine.

Dr. Birkner did not perform subgroup analyses for Study 1202 due to small overall sample size (ITT population of 89) and the dose titration design.

In summary, Dr. Birkner concludes: "With the majority of subjects being titrated to the 75 mg dose at the end of Study 1202 and this subset showing a treatment effect in an exploratory analysis this reviewer is satisfied as far as replication of the positive result of the 80 mg dose in the Phase 3 study is concerned. Changes in the planned analysis from the original protocol (MMRM to ANCOVA) led to the 'ITT set' being a completer set. Fortunately in this therapeutic setting the number of discontinuations during the double-blind phase was modest. An exploration of the patient efficacy trajectories prior discontinuation and the results of a tipping point analysis lend some confidence to the results obtained from the 'ITT'/Completer set.

Study 1304

Study 1304 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study designed to evaluate the efficacy, safety, and tolerability of two doses of valbenazine, compared to placebo. It was conducted in 63 sites in North America and Puerto Rico. The primary efficacy endpoint was the change from baseline to Week 6 on the AIMS dyskinesia total score (sum of AIMS items 1-7). The key secondary endpoint was the CGI-TD. This study included a six-week double-blind, placebo-controlled, treatment period followed by a 42-week extension period. Subjects were adults, aged 18-85, with moderate or severe TD and an underlying diagnosis of schizophrenia, schizoaffective disorder, or mood disorder, stable on their medication for at least 30 days prior to randomization. Eligible subjects were initially randomized (1:1:1) to receive daily doses of valbenazine 40 mg, 80 mg, or placebo. Subjects who were randomized to receive 80 mg daily were titrated in a blinded manner, receiving 40 mg daily for the first week, following by 80 mg daily. Investigators were permitted to decrease subjects' dose for tolerability reasons one time during the study, and subjects who could not tolerate the adjusted dose were discontinued from the study. To maintain the study blind, subjects who were receiving valbenazine 40 mg daily or placebo were to receive their current dose following a dose "decrease." After six weeks of double-blind treatment, subjects were re-consented to enter the 42-week extension period. During this period, all subjects received valbenazine, though subject and investigator were blinded to the actual dose. Subjects who were initially randomized to receive valbenazine continued their current dose, and those who were initially randomized to receive placebo were re-randomized (1:1) to receive either valbenazine 40 mg or 80 mg daily (with the latter subjects receiving 40 mg daily for the first week as titration).

A total of 546 subjects were screened for the study and 234 were randomized (76 to valbenazine 40mg, 80 to valbenazine 80mg, and 76 to placebo). The most common reason for screen failure was not meeting TD entry criteria. Of the 234 randomized subjects, 205 (87.6%) completed the 6-week placebo-controlled period; this included 91% of subjects assigned to placebo, 82.9% of subjects assigned to valbenazine 40 mg, and 88.8% of subjects assigned to valbenazine 80 mg. Interestingly, the lower rate of completion in the valbenazine 40 mg group was mostly attributable to reasons of adverse events and withdrawal of consent. The majority of subjects who completed the placebo-controlled 6-week period entered the 42-week extension period (97% of placebo completers, 98% of valbenazine 40 mg completers, and 96% of valbenazine 80 mg completers). Three subjects who were initially randomized to valbenazine 80 mg daily had a dose-reduction during the 6-week period so were included in the valbenazine 40 mg group in the extension period. Overall, the completion rate was not as high in the extension period as the initial 6-week treatment period, but given that the duration was much longer, this is not unexpected. As Dr. Davis and Dr. Birkner point out, this loss of subjects affects the interpretability of the long-term efficacy results due to attrition bias, as only 121 out of the initial 234 randomized patients (61.1%) completed the entire study. There was no clear relationship of valbenazine dose with whether subjects completed the extension period. The ITT sample included 225 subjects; of the nine subjects who were randomized but not included in the efficacy analysis set, two subjects withdrew and seven subjects had no post-randomization AIMS data. The treatment arm assignments of the nine subjects excluded from the ITT analysis set were placebo (n=2), valbenazine 40 mg (n=6), and valbenazine 80 mg (n=1).

The primary efficacy endpoint (Change from Baseline to Week 6 in AIMS Dyskinesia Total Score) achieved statistical significance at alpha=0.05 for the 80 mg Valbenazine dose ($p < 0.0001$). Table 5 below presents the LS mean point estimate of the change and of the placebo-subtracted difference, with the patients treated with Valbenazine 80 mg on average improving by approximately 3 points more than the placebo treated patients. While valbenazine 40 mg had a nominally significant p value, it was not considered statistically significant because its statistical test was lower in the pre-specified multiple testing sequence than a non-significant statistical test. In this study, valbenazine 40 mg and valbenazine 80 mg treatment groups were nominally statistically superior to placebo (p=0.0313 and p=0.0010, respectively) by Week 2, suggesting that onset of therapeutic benefit from valbenazine may occur earlier than six weeks. It should be noted that all AIMS component scores improved over time with valbenazine treatment, suggesting that drug effects are not limited to specific muscle groups.

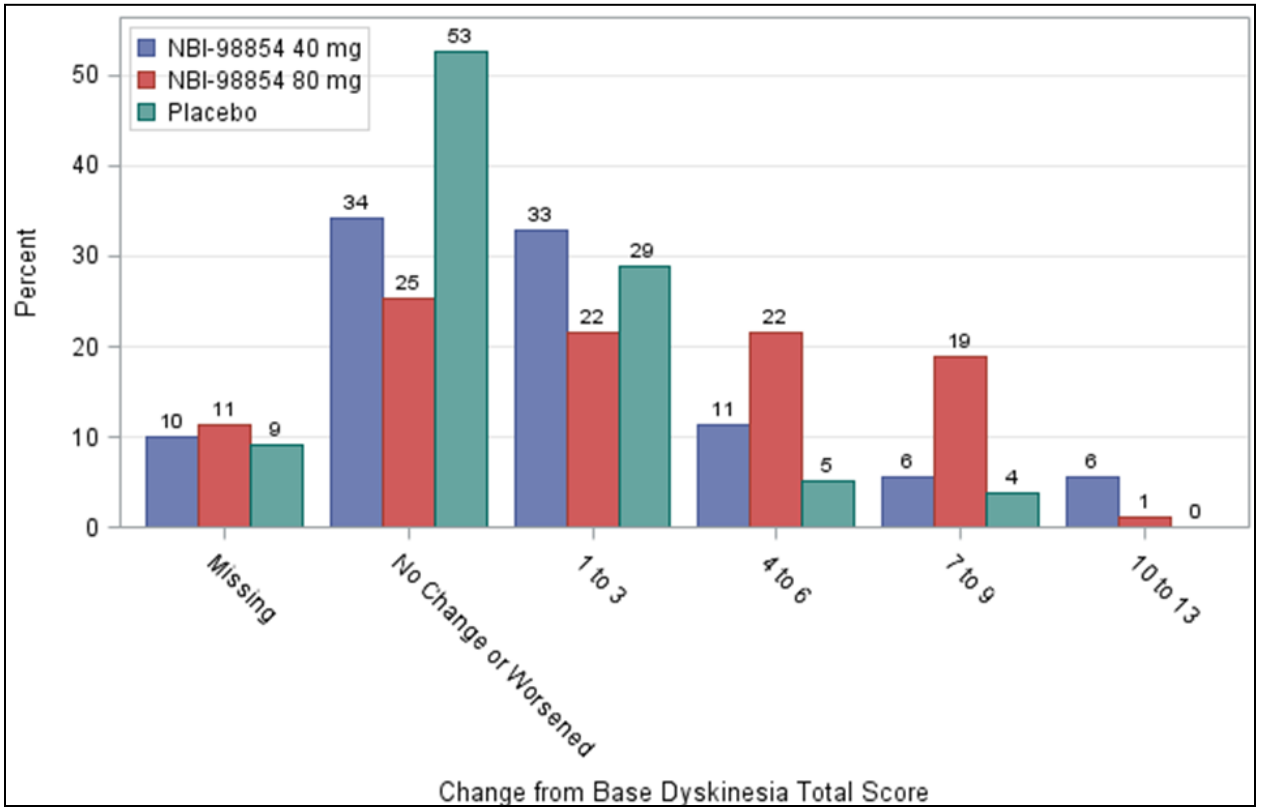
Table 5: Applicant's Primary Efficacy Results; Study 1304

	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

Dr. Birkner prepared a response histogram (see figure below) in order to better visualize the proportion of subjects who achieved various thresholds of AIMS score changes. This analysis shows that at the end of Week 6, 42% of subjects receiving valbenazine 80 mg had ≥ 4 reduction on the AIMS total dyskinesia score, as compared to 9% of subjects receiving placebo.

Figure 4: Percent of Patients with Specified Magnitude of AIMS Total Score Improvement at the end of Week 6; Study 1304



[Source: Created by Dr. Thomas Birkner, Biostatistics review, Figure 4, p. 33]

Dr. Davis performed exploratory analyses for the effects in demographic subpopulations and by baseline characteristics. Although the study was not powered to assess subgroup effects and any statistical comparisons would be limited by multiplicity concerns, subjects who were not using antipsychotic medications appeared to have a better response than those using antipsychotic medications; however, there were a limited number of subjects in the former group. Subjects with schizophrenia or schizoaffective disorder appeared to have a modestly poorer response than those with mood disorders, which might be related to antipsychotic use, as ~70% of subjects with schizophrenia or schizoaffective disorder were taking antipsychotics vs. ~30% of subjects with mood disorders. Subgroup analyses conducted by Dr. Birkner did not reveal any concerning trend. Although limited by the sample size, all subgroups improved in the AIMS CFB at Week 6 for the 80mg dose.

Dr. Davis notes that the mean change from baseline in the AIMS total dyskinesia score continued to decrease at each visit during the 6-week placebo-controlled period for both doses of valbenazine, with no evidence of tolerance or a response plateau. The data from the extension period suggest additional improvement may occur over time, with a maximal AIMS CFB of approximately -5 for the 80 mg valbenazine dose. Persistence of drug effect was evaluated at the end of the valbenazine extension treatment. At the end of Week 48, subjects were withdrawn from active valbenazine treatment and returned four weeks later for a final assessment. Subjects demonstrated a worsening in AIMS score after discontinuing valbenazine treatment but, on average, did not worsen beyond their baseline. This suggests that 42-48 weeks of valbenazine treatment may not worsen the underlying TD process but that continued treatment may be necessary to maintain treatment benefit. The residual mean improvement in AIMS total dyskinesia score at Week 52 (off treatment) raises the question of whether valbenazine might have some benefit on the underlying disease process, as most subjects continued to receive antipsychotic treatment throughout the study. While there are factors that limits the interpretability of these findings in the long-term extension phase (e.g., lack of placebo control, high subject attrition over the 48-week period, etc.), other factors provide some confidence in these findings (e.g., the use of central video AIMS raters blinded to visit number and treatment dose, the 40 mg valbenazine dose provided an internal active control to which the 80 mg dose could be compared to, etc.).

The mean CGI-TD at Week 6 was pre-specified as a key secondary efficacy endpoint. For multiplicity correction, the Applicant pre-specified a fixed sequence of tests, with the CGI-TD for the valbenazine 80 mg dose vs. placebo as the second test and the CGI-TD for the valbenazine 40 mg dose vs. placebo as the fourth test. Overall, the mean CGI-TD at all post-baseline visits in all three treatment groups was <4, indicating that on average, all subjects were assessed as having some global improvement over the course of the study. Both doses of valbenazine were associated with a lower mean CGI-TD score than the placebo group but the key secondary efficacy endpoint did not reach statistical significance (p=0.0560 for the valbenazine 80 mg group at Week 6 vs. placebo and p=0.0742 for the 40 mg dose). Nominal p values were <0.05 for both valbenazine dose groups at Week 4.

Dr. Birkner concludes that "Study 1304 provides strong statistical evidence for the 80 mg dose on the primary efficacy endpoint. The primary efficacy endpoint for the 40 mg dose cannot be declared statistically significant due to the failure of the 80 mg dose on the secondary efficacy endpoint, which is located above in the fixed testing sequence."

Additional Studies

Study 1402 is a long-term open-label study that is yet to be completed at the time of this review; therefore, it will not be further discussed in this section.

The Applicant also submitted Study 1201 as supportive evidence for efficacy but this study had methodological issues that were addressed in the pre-specified analysis plan for subsequent Phase 2/3 trials discussed above (i.e., Study 1202, 1304, and 1402). These

issues included inconsistent AIMS scoring across the large number of on-site raters, AIMS item score descriptors that were less sensitive for detecting change, and sequence/expectancy bias introduced by raters' knowledge of how long subjects had been receiving study treatment. Additionally, the dose of valbenazine was 100mg daily for two weeks. After the initial two weeks, the dose was reduced to 50mg daily for the next four weeks. This dosing paradigm made the findings of this study difficult to interpret.

Integrated Summary of Efficacy

The AIMS' validity has been established by comparisons to other similar instruments and it has been widely used in clinical and research settings for the purpose of assessing the presence and severity of TD. Although the AIMS is a reasonable choice for a primary efficacy measure, its limitations include the need for a trained and experienced rater and the lack of consensus as to what would constitute a meaningful change in AIMS score. The general primary efficacy endpoint measure for the studies used to support valbenazine's efficacy was the change from baseline to the end of Week 6 on the AIMS dyskinesia total score (sum of AIMS items 1-7). The following table, constructed by Dr. Davis, summarizes the three trials which used this primary efficacy endpoint: Study 1201 (submitted as supportive evidence), Study 1202, and Study 1304.

Table 6: Summary of Controlled Studies Evaluating 6-Week Efficacy Endpoints

Trial ID[1]	N=	Population	Dosing Regimen	Pre-specified Primary Efficacy Endpoint	Pre-specified Analytic Methods	Notes
1201	109	Adults (age 18-65) with Schizophrenia or Schizoaffective Disorder and TD	3 groups (1:1:2): valbenazine 50 mg daily; valbenazine 100 mg daily x 2 weeks, then 50 mg daily; and placebo	AIMS dyskinesia total score Week 6 CFB (on-site AIMS raters), ITT analysis set	Comparison between pooled valbenazine 50+100 mg groups vs. placebo; ANCOVA model	Non-significant (p=0.2966); post hoc analysis using central video raters also did not reach significance (p=0.0663)
1202	102	Adults (age 18-85) with Schizophrenia, Schizoaffective Disorder, Mood Disorder, or Gastrointestinal Disorder and TD	2 groups (1:1): valbenazine 25-75 mg daily flexible dose (according to efficacy and tolerability) and placebo	AIMS dyskinesia total score Week 6 CFB (central raters), PP analysis set	Comparison between valbenazine group and placebo group; ANCOVA model	Significant (p<0.0001); analysis using ITT analysis set was also significant (p=0.0005)
1304	234	Adults (age 18-85) with Schizophrenia, Schizoaffective Disorder, or Mood Disorder and TD	3 groups (1:1:1): valbenazine 40 mg daily, valbenazine 80 mg daily, and placebo	AIMS dyskinesia total score Week 6 CFB (central raters), ITT analysis set	Comparison between valbenazine dose group and placebo group, MMRM analysis; sequential testing for multiplicity	Significant for valbenazine 80 mg dose vs. placebo (p<0.0001). Valbenazine 40 mg dose had nominal p=0.0021 but was non-significant, because previous test in sequence (CGI-TD) was non-significant (p=0.0560)

[Source: Constructed by Dr. Davis, Table 45 of valbenazine's Clinical Review
[1]4-digit numbers are prefaced by NBI-98854- for the full trial identifier.
mITT = modified intent to treat; PP=per protocol; CFB=change from baseline

In his review, Dr. Davis notes that the subject populations were relatively similar between studies. The increase of the maximum age to 85 for Studies 1202 and 1304 did not have a significant effect on the mean and median ages of the study populations (mid-50's). The ineligibility of subjects with gastrointestinal illness for Study 1304 likewise does not have a significant impact, as there was only one subject in this group in the Study 1202 intention-to-treat (ITT) analysis set. Study 1201 did not include subjects with mood disorders and neuroleptic-induced TD, but there was no reason to suspect that the specific underlying psychiatric illness would affect the treatment-sensitivity of neuroleptic-induced TD and there were reasonable proportions of subjects with mood disorders in subsequent Phase 2/3 studies.

Other important differences between the three studies that affect the interpretation of the primary efficacy measure were:

- Differences in dosing regimens between studies.
- Differences in statistical analysis plans (e.g., Study 1202 pre-specified the use of the PP analysis set for the primary efficacy endpoint; Studies 1201 and 1202 used analysis of covariance (ANCOVA) methods, and Study 1304 used mixed effect model repeat measurement (MMRM) methods for evaluating statistical significance).
- Differences in AIMS scoring methods (Study 1201 pre-specified the use of on-site rater AIMS data, which employed AIMS scoring descriptors prior to revision).

The baseline AIMS total dyskinesia and 6-week CFB scores are summarized in the table constructed by Dr. Davis below. On-site baseline AIMS scores were significantly higher (in Study 1201) than the centrally-rated AIMS baseline scores; this may reflect the impact of the revised AIMS score descriptors as well as the central raters being blind to visit number. It is also notable that the AIMS CFB placebo response was greater with the on-site raters in Study 1201; this may be due to the raters not being blind to visit number (sequence bias) as well as the pre-revision AIMS item descriptors. The mean AIMS CFB at 6 weeks was in the -3 to -4 range in both studies 1202 and 1304 (valbenazine 80 mg treatment group).

Table 7. Comparison of 6-week AIMS Baseline and Change Scores Across Controlled Studies

Study*	Treatment Group (N=)	AIMS Baseline mean (SEM)	AIMS CFB mean (SEM)
1201 on-site[1]	Placebo (N=54)	15.3 (0.6)	-2.4 (0.5)
1201 on-site[1]	Valbenazine 50+100 mg pooled (N=53)	14.6 (0.7)	-3.1 (0.6)
1201 post hoc[2]	Placebo (N=46)	8.5 (0.7)	-0.5 (0.4)
1201 post hoc[2]	Valbenazine 50+100 mg pooled (N=40)	7.8 (0.6)	-1.3 (0.5)
1202	Placebo (N=44)	7.9 (0.7)	-1.1 (0.6)
1202	Valbenazine 25-75 mg pooled (N=45)	8.0 (0.5)	-3.6 (0.5)
1304	Placebo (N=76)	9.9 (0.5)	0 (0.4)
1304	Valbenazine 40 mg (N=70)	9.8 (0.5)	-1.8 (0.5)
1304	Valbenazine 80 mg (N=79)	10.4 (0.4)	-3.3 (0.5)

[Source: Created by Dr. Mike Davis using data from Clinical Study Reports for Studies 1201, -1202, and -1304 ITT Analysis Sets
AIMS=AIMS total dyskinesia score (sum of Items 1-7); CFB=change from baseline
*4-digit numbers are prefaced by NBI-98854- for the full study identifier
1On-site rater scores using AIMS score descriptors pre-revision
2Post hoc central rater scores using modified AIMS descriptors; Applicant's mITT analysis set excluded subjects without AIMS scores or detectable α-dihydrotetrabenazine plasma levels at Week 6

Because there is no accepted criterion as to what is considered a clinically meaningful change in AIMS score, the Applicant conducted an analysis assessing the concordance of the AIMS dyskinesia CFB at Week 6 with the CGI-TD score (see table below). Subjects who were assessed as being much or very much improved at Week 6 had mean and median changes from baseline of -3.4 and -3.0 on the AIMS dyskinesia total score. This is roughly equivalent to the mean changes associated with valbenazine treatment (either titrated up to 75 mg/day or 80 mg/day fixed dose) as well as the Applicant's "AIMS Responder" definition of a ≥50% decrease in AIMS total dyskinesia score. Dr. Davis notes that this analysis has some limitations, as the on-site CGI-TD raters were not necessarily the same at each visit, were not blinded to visit number, and had additional efficacy-related information in Study 1202 that may have influenced their CGI-TD ratings (authorization to increase study treatment dose by independent AIMS raters). Altogether, however, it seems reasonable that a -3 to -4 decrease in the AIMS total dyskinesia score would represent a clinically meaningful change in TD symptoms.

Table 8: AIMS Dyskinesia CFB at 6 Weeks by CGI-TD Category (ITT analysis sets, Phase 2/3 controlled studies)

	Categorization 1		Categorization 2	
Statistic for AIMS Dyskinesia Total Score Change from Baseline at Week 6	**CGI-TD=1, 2[a] (N=108)**	**CGI-TD>2 (N=265)**	**CGI-TD=1, 2, 3 (N=269)**	**CGI-TD>3 (N=104)**
Mean (SD)	-3.4 (4.0)	-0.9 (3.4)	-2.2 (3.8)	0.0 (3.1)
SE	0.39	0.21	0.23	0.31
Median	-3.0	0.0	-2.0	0.0
Min, max	-13, 8	-12, 8	-13, 8	-8, 8

[Source: Integrated Summary of Efficacy, Table 38, p. 82]
The AIMS scores were from blinded, central AIMS video raters and the CGI-TD scores were from on-site investigators who were blind to treatment by not to visit number.
[a]CGI-TD scores: 1="very much improved", 2="much improved", 3="minimally improved", 4="no change", 5="minimally worse", 6="much worse", 7="very much worse.

Dr. Davis conducted an exploratory analysis of the AIMS in order to further assess the clinical meaningfulness of treatment effects. He points out that a clinician might consider a patient's TD symptoms to be well-controlled if there are no body parts with abnormal movement severity greater than "minimal" (corresponding to a score of 1 on the AIMS). As displayed in the table below, valbenazine treatment (80 mg dose in Study 1304 and flexible-dose treatment in Study 1202) was associated with ~34% of subjects meeting this remission criterion at Week 6, as compared to ~19% of subjects receiving placebo. "By this measure, the number needed to treat (NNT), calculated using the change in the proportion of subjects meeting the criterion from baseline to Week 6, is ~4-5. If an adequate treatment response was considered to be having no body parts with abnormal movement severity greater than 'mild' (corresponding to a score of 2 on the AIMS), ~72% of subjects receiving valbenazine met this criterion at the end of Week 6 as compared to ~51% of subjects receiving placebo (however, a much larger proportion of subjects met this criterion at baseline)."

Table 9: Studies 1202 and -1304, Exploratory Remission Criteria, ITT Analysis Set

	Baseline			Week 6		
Treatment	No	Yes	% Yes	No	Yes	% Yes
Placebo	109	13	10.7	92	21	18.6
Valbenazine	120	5	4.0	75	39	34.2

[Source: Created by Dr. Mike Davis using responder dataset created by Dr. Douglas Warfield in which subjects met responder criteria if they scored no more than "minimal" on any individual body area, as assessed by blinded central video raters. Subjects include those in the ITT analysis set from Studies 1202 (all) and 1304 (placebo and valbenazine 80 mg groups).]

8. Safety

The safety review for this application was completed by Brian Miller, MD, MBA, MPH; he did not find any safety signal that would preclude approval of this NDA.

The valbenazine development program consisted of fourteen Phase 1 studies, four Phase 2 studies, and two Phase 3 studies. Based on Dr. Miller's pooling of the safety data, a total of 785 subjects received at least a single dose of the drug, 241 subjects were exposed to at least six months, and two subjects were exposed to longer than 12 months. Given the estimated TD population size in the US (less than 135,000 individuals), Dr. Miller concludes that the size of the safety database is adequate; I concur with his assessment.

The demographic features of the safety population (constructed from Studies 1201, 1202, 1304, and 1402) are summarized in the following table created by Dr. Miller.

Table 10: Demographic features of the 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: Created by Dr. Brian Miller from the demographics datasets (DM.xpt) for Studies 1201, 1202, 1304, and 1402]

With the exception of an underrepresentation of Asians, the population appears well balanced and representative of a typical US patient with longstanding schizophrenia.

Concomitant medications were grouped according to primary and secondary pharmacologic activity. A summary of these is provided in Table 11.

Table 11: Concomitant Medications for the 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: Created by Dr. Brian Miller from the concomitant medications datasets (CM.xpt) for Studies 1201, 1202, 1304, and 1402 (medication properties as classified by Dr. Miller)]

Notably, three out of four patients were on an antipsychotic mediation. Over half of the patients were also on an anticholinergic drug while a third of them were on benzodiazepines. Few patients were on stimulants, and only one patient was on a dopamine agonist.

There were four deaths in the valbenazine development program. One of these occurred in a subject receiving placebo and another one was clearly unrelated to the study drug. Pertinent information (e.g., no autopsy report, limited hospitalization information, etc.) is unavailable to make a certain determination; however, these deaths are highly unlikely to be related to the study drug.

Dr. Miller reviewed all serious adverse events (SAEs) and summarized his observations for every case report form. Dr. Miller concludes: "There was no discernible pattern of SAEs in Studies 1201 and 1202, and the SAEs were deemed unlikely to be due to the study drug. In the controlled period of Study 1304, nearly all SAEs occurred in subjects receiving the study drug. Upon close examination of the SAEs, it is apparent that they are likely due to pre-existing medical conditions or other events otherwise not

attributable to the study drug (e.g. acute hepatitis occurring in a subject who previously had hepatitis A, hepatitis C, acute hepatitis otherwise not specified and who is concurrently taking both acetaminophen and alcohol)." Dr. Miller notes that there appears to be a clear dose-dependent response in the overall rate of SAEs, declining with dose of study drug. Given the boxed warning in tetrabenazine, Dr. Miller identified suicidal ideation (SI) and suicidal attempts (SA) as SAEs of high interest. There were 14 SAEs of SI or SA in Dr. Miller's safety database. SI/SA occurred concurrently with exacerbation of underlying psychiatric disease in eight of these events. However, many of these "exacerbation of underlying disease" cases appear to be due to the subject discontinuing their antipsychotic medication.

In Dr. Miller's safety database, the AEs of greatest incidence and clinical significance leading to study discontinuation are akathisia, altered mental status (AMS), depression, elevated liver function tests, EPS (non-akathisia), exacerbation of underlying psychiatric disease, rash, SI/SA, and somnolence. Of note, there was no significant difference in time to event between placebo and drug groups. In order to better examine differential rates of events, incidence for the AEs leading to discontinuation was calculated by dose. The 50 mg dose exposure group and events were pooled with the 40 mg dose exposure group and events for the purposes of analysis.

Table 12: Incidence of AEs Resulting in Study Discontinuation by Dose

	Incidence (Events per 100 Person-Years)		
AE	*Placebo*	*40 - 50 mg*	*80 mg*
Akathisia	-	1.6	-
AMS	-	2.4	-
Depression	-	1.6	-
Elevated LFTs	-	2.4	-
EPS - Non-Akathisia	-	0.8	0.8
Exacerbation of Underlying Psychiatric Disease	10.2	2.4	1.6
Rash	1.1	4.8	-
SI/SA	-	4.0	4.9
Somnolence	-	1.6	2.4

[Source: Created by Dr. Brian Miller from adverse event and exposure safety population datasets]

In his review of all significant AEs, Dr. Miller concluded that there was no consistent trend of between valbenazine and placebo. Marc Stone, MD, 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 (see Table 13 below).

Table 13: TEAEs Across Three Controlled-Trial Periods

Adverse Reaction	*Placebo (%)*	*VBZ (%)*
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: Created by Dr. Brian Miller from adverse event files for Studies 1201, 1202, and 1304 (AE.xpt)]

Somnolence occurred at rate more than two and half times in valbenazine-treated patients when compared with placebo. This particular AE will be discussed further in the labeling section. Dr. Miller also highlighted balance disorders/falls and akathisia as safety signals.

Mean drug effects on lab parameters for Studies 1201, 1202, and 1304 were analyzed during the controlled period via a mixed-effects logistic regression by Dr. Stone. Based upon this, signals for increased blood glucose, decrease hemoglobin A1C, and increased prolactin were found. Although a clear signal for elevate glucose was found in some patients, an inexplicable decrease in hemoglobin A1C was also found in other patients. It is also important to note that no prolactin-related TEAEs (e.g., galactorrhea) were observed, and that many of these patients are and will continue to be on antipsychotics (a class that is known to potentially increase prolactin), regardless of elevations on prolactin. Table 14 shows the incidence and the odds of an abnormally high (as defined in the protocols) result for drug relative to no drug, all with statistically significant p-values.

Table 14: Laboratory Parameters Significantly affected by Valbenazine

	Incidence		Odds Ratio		
Lab Parameter	*Drug*	*No drug*	*Ratio*	*95% CI*	*P-value*
Glucose	3.50%	2.00%	1.77	1.33 - 2.38	< 0.0005
Hemoglobin A1C	31.20%	39.60%	0.69	0.53 - 0.90	0.007
Prolactin	6.00%	2.00%	3.17	2.24 - 4.47	< 0.0005

[Source: Created by Dr. Brian Miller from Dr. Marc Stone's analysis]

Study 1401 was a thorough QT (TQT) study conducted during product development which was reviewed by the QT team. It evaluated the potential of 160 mg of valbenazine (twice the maximum recommended dose but not considered adequately supratherapeutic by the QT team) to prolong the QT interval compared to moxifloxacin, a positive control. Notably, the highest upper bound for the 90% confidence interval was 11.7 ms (8.9 ms at 8 hours, 90% CI 6.1 – 11.7 ms), exceeding the regulatory ceiling of 10 ms. The QT team examined the individual values for each study, noting that for both Study 1401 and Study 1301 (a QT study exploring up to single doses of 300 mg), no QTcF values above 480 ms were observed. Furthermore, no ΔQTcF values for either study were above 60 ms for valbenazine 160 mg or 300 mg doses. Finally, the QT team had concerns regarding the accumulation of NBI-98782 and its effects on the QT interval in CYP2D6 PMs. The potential for QT interval prolongation will be addressed under labeling recommendations.

Dr. Miller analyzed data from the Columbia-Suicide Severity Rating Scale (C-SSRS), the Barnes Akathisia Rating Scale (BARS), the Simpson-Angus Scale (SAS), the Positive and Negative Syndrome Scale for Schizophrenia (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), the Young Mania Rating Scale (YMRS), and the Montgomery-Asberg Depression Rating Scale (MADRS) instruments. He concluded that suicidal ideation appears to occur at rates similar to the background rate of suicidal ideation in the intended patient population (e.g., patients with schizophrenia, schizoaffective disorder, etc.). Overall, these data suggest that valbenazine treatment does not worsen symptoms of schizophrenia, mania, or depression.

In summary, no safety signal was identified that would preclude the approval of this application. The risks identified in Dr. Miller's safety analyses (i.e., QT interval prolongation, somnolence, balance disorders/falls, and minor prolactin and blood glucose abnormalities) can be mitigated with appropriate product labeling.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application. Although valbenazine is a new molecular entity, the evaluation of the safety data did not reveal particular safety issues that were unexpected for this class of drugs (VMAT2 inhibitors), and the design and results of the efficacy trials did not pose particular concerns.

10. Pediatrics

This application 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 impracticable, as the number of patients is very small. Given that TD tends to occur with long-term exposure to antipsychotics and that older age is one of the known risk factors, we agree that a dedicated study in pediatric patients will be unfeasible. Furthermore, Dr. Davis' medical literature review suggests that when TD symptoms occur in the pediatric population, symptoms appear to be reversible upon discontinuation of the offending agent.

11. Other Relevant Regulatory Issues

Good Clinical Practices Audit

Five study sites were inspected by the Office of Scientific Investigations (OSI). These sites were identified for a Good Clinical Practices (GCP) audit based on relative importance of the study to the NDA and on the number of subjects per site. No special concerns were identified for protocol violations or investigators' conflict of interests. Overall, the data submitted by the Applicant in support of this application are acceptable.

Analysis of Tetrabenazine's Postmarketing Safety Data

NBI-98782 is 40-fold more potent than valbenazine as a VMAT2 inhibitor and is considered the primary moiety contributing towards effectiveness. As previously discussed in the background section, NBI-98782 is also a metabolite of tetrabenazine and the two drugs share several other metabolites. Dr. Miller conducted an evaluation of the postmarketing safety data for tetrabenazine because of the overlapping metabolites with valbenazine, its boxed warning for depression and suicidality, its reports of off-label use to treat TD, and its existence as the only other approved drug in its class. Dr. Miller did not identify any new safety signals that could impact valbenazine's approval or labeling.

12. Labeling

At the time of this review, the Agency and the Applicant are on the third round of labeling negotiations.

The following are some of the labeling revisions proposed by the review team:

1. Dosing regimen: We agree with the revised proposed dosing regimen (identical to the dosing regimen in Study 1304): 40 mg daily for a week as titration to the recommend dose of 80 mg daily. For some patients, however, adequate clinical response is achieved at 40 mg dose. Given that various adverse events are exposure-dependent, the review team recommends language to reflect that a dose of 40 mg daily may be considered for some patients.
2. CYP Inhibitors/Inducers: The OCP review team recommends revisions to be included regarding dosing recommendations for patients with concomitant use with strong CYP3A4 or CYP2D6 inhibitors, or CYP3A4 inducers.
3. Risk of QT prolongation: Revisions are being proposed to more clearly describe the relationship between valbenazine and prolongation of the QT interval. Specifically, language was added noting that in patients taking a strong CYP2D6 or CYP3A4 inhibitor or who are poor metabolizers, valbenazine concentrations may be higher, resulting in clinically significant QT prolongation, and a dose reduction may be necessary. In order to mitigate this risk, language instructing clinicians to assess the QT interval prior to increasing the valbenazine dose was added.
4. Adverse reactions: This section was extensively revised.
    - The clinical trial experience section was modified to describe the pooling of the three pivotal controlled studies used to support the Agency's labeling recommendations and the associated characteristics of the patient population (i.e., age, diagnoses, ethnicity, race, concomitant medications).
    - An adverse reaction table for the pooled Studies was inserted, as below:

Table 15: AEs in Three Placebo-Controlled Studies of 6-weeks Treatment Duration [redacted] ≥2% of Subjects and >Placebo

Adverse Reaction	*Placebo (n = [redacted] (%)*	*INGREZZA (n = [redacted]) (%)*
General Disorders		
Somnolence	4.2%	10.9%
Nervous System Disorders		
Anticholinergic effects	4.9%	5.4%
Balance disorders/fall	2.2%	4.1%
Headache	2.7%	3.4%
Akathisia	0.5%	2.7%
Gastrointestinal Disorders		
Vomiting	0.6%	2.6%
Nausea	2.1%	2.3%
Musculoskeletal Disorders		
Arthralgia	0.5%	2.3%

[Source: Created by Dr. Brian Miller (adapted from analysis by Dr. Marc Stone)]

- Adverse reactions occurring at ≥1% incidence and greater than placebo were also listed.
- A sentence was added describing a dose-related increase in prolactin observed during controlled trials.
- A sentence was added describing a dose-related increase in alkaline phosphatase and bilirubin

5. Clinical Studies:
   - Because Study 1202 was conducted with doses that will not be approved (i.e., 25-75mg) it will not be included in the Clinical Studies section.
   - Descriptors for AIMS scores (0-4) were added, with the rationale that this may be helpful for clinicians to interpret study data (who may be familiar with descriptors from other versions of the AIMS).

Although the Applicant submitted a Medication Guide (MG), the review concluded that it is not necessary. Kimberly Updegraff, PharmD, the Division's Associate Director for Labeling, recommended for the MG to be converted into a Patient Package Insert (PPI). The PPI will describe common adverse reactions and when patients should bring them to the attention of their physician.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The need for a REMS was evaluated by the Division of Risk Management (DRISK). DRISK determined that a REMS was not needed because the risks associated with valbenazine use (e.g., risk of QT prolongation) could be adequately managed with labeling and the Division agreed with their recommendation.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
The OCP review team has the following PMR recommendations:

1. Effect of CYP2D6 inhibition: A PK 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 PMs.
2. Effects of severe renal impairment on PK: A PK trial to assess the exposures of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose.

The OCP review team has the following PMC recommendations:

1. Potential for improved therapeutic benefit at doses higher than the recommended dose of 80mg: A (b) (4) randomized, (b) (4) efficacy and safety to test doses of 80mg and higher in patients not demonstrating adequate response to the maximum recommended dose. Pending findings from the clinical pharmacology trial to assess the effects of CYP2D6 inhibition, CYP2D6 PMs may be excluded from this trial to avoid the risk of QT prolongation.
2. Evaluate the induction potential of NBI-136110 on CYP2B6: An *in vitro* study to assess the induction potential of NBI-136110 on CYP2B6 enzyme, citing the Drug Interaction Guidance recommendations for the evaluation of CYP enzyme induction potential for major circulating moieties.

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/s/

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04/05/2017

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04/06/2017