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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Integrated Review

NDA or BLA Number	209241
Link to EDR	\\Cdsesub1\evsprod\NDA209241
Submission Date	August 11, 2016
Submission Type	Priority
Brand Name	INGREZZA™
Generic Name	Valbenazine
Dosage Form and Strength	40 mg Capsule
Route of Administration	Oral
Proposed Indication	Tardive Dyskinesia (TD)
Applicant	Neurocrine Biosciences, Inc.
Associated IND	111591
OCP Review Team	Di Zhou, PhD., Huixia Zhang, PhD., Gopichand Gottipati, PhD., Jeffrey Kraft, PhD., Hao Zhu, PhD., Kevin Krudys, PhD., Christian Grimstein, PhD.
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1. EXECUTIVE SUMMARY

This is an original NME NDA submitted by Neurocrine Biosciences, Inc. on August 11, 2016. The Applicant is seeking approval of INGREZZA (Valbenazine), a selective vesicular monoamine transporter 2 (VMAT2) inhibitor, for the treatment of patients with tardive dyskinesia (TD). Currently, there is no FDA approved product for this indication. The Division of Psychiatry Products has granted valbenazine fast track designation (January 2012) and breakthrough therapy designation (October 2014).

The clinical development program included 14 Phase 1 clinical pharmacology trials (i.e., absolute and relative bioavailability, single- and multiple-ascending dose, pivotal bioequivalence, food effect, mass balance, drug interaction, hepatic impairment and QT studies), 4 Phase 2 trials (two exploratory, one pivotal dose-titration, and one supportive) and 2 Phase 3 efficacy/safety trials (one pivotal fixed-dose, one supportive). In addition, population PK and exposure-response analyses reports were included in the submission.

Key review issues include (1) the appropriateness of the dosing instruction in general patients and (2) recommendations in specific patient populations (i.e., CYP2D6 poor metabolizers and severe renal impairment), and patients receiving concomitant medications (i.e., strong CYP2D6 inhibitors).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209241. This NDA is considered approvable from a clinical pharmacology perspective. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Substantial evidence of effectiveness was demonstrated by the registration trials. Significant dose/exposure-response relationship further indicated that higher dose/exposure is associated with higher reduction in the Abnormal Involuntary Movement Scale (AIMS) total score.

General dosing instructions	1. Overall, the proposed dosing in the general patient population is acceptable. • As tested in the registration trials, the initial dose of valbenazine is 40 mg once daily. After one week, the dose should be increased to the recommended dose of 80 mg once daily. • As shown in the registration trials, some patients may achieve adequate clinical response at 40 mg dose. Given that various adverse events are exposure-dependent there may be a merit for these patients to continue at the dose of 40 mg 2. Further exploration of doses beyond 80 mg in a clinical trial is recommended based on the fact that dose/exposure-response relationship has not reached plateau at the currently recommended dose range (See Section 1.2). 3. Valbenazine can be administered with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dosage adjustment is recommended in subgroups of patients based on relevant PK studies, the established exposure-response relationships, and the understanding of the mechanism of drug elimination. • Reduce daily dose by half, when coadministered with a strong CYP3A4 inhibitor. • Consider dose reduction based on tolerability, when coadministered with a strong CYP2D6 inhibitor or for a known CYP2D6 poor metabolizer. • Avoid concomitant use with strong CYP3A4 inducers. • Reduce daily dose by half for patients with moderate or severe hepatic impairment. • No dose adjustment for patients with mild to moderate renal impairment. Dosing instructions of valbenazine (1) for patients with severe renal impairment, and (2) for patients receiving a CYP2B6 inducer are pending further investigation (See Section 1.2).
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed formulation is expected to show similar effectiveness and safety profiles as compared to the clinical trial formulation. The exposures following the administration of the to-be-marketed formulation and the clinical trial formulation were found to be similar (i.e., meeting bioequivalence criteria), based on a relative bioavailability study, whose data are deemed acceptable by the Office of Study Integrity and Surveillance (OSIS).

1.2 Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐PMC ☑PMR	Effect of CYP2D6 inhibition	CYP2D6 is considered as a major metabolic enzyme for the active metabolite NBI-98782. However, there is no dedicated drug-drug interaction study in the presence of a strong CYP2D6 inhibitor to quantify the impact of increase in exposures of NBI-98782. Additionally, the precise-magnitude of the difference in exposures of NBI-98782 of CYP2D6 PMs and non-PMs was inconclusive because the observed trends varied between significantly higher exposures in a few individuals and no difference in exposures	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 (PMs) should be conducted.

☑PMC ☐PMR	Potential for improved therapeutic benefit at doses higher than the recommended dose of 80 mg	Given the safety/tolerability findings in study 1304 and the observation that the dose/exposure response relationships for efficacy has not reached plateau within the tested dose range of 80 mg, it is necessary to assess whether a higher dose would confer additional therapeutic benefit for patients with TD, especially for patients not reaching optimal clinical response at the currently recommended dose level (i.e., 80 mg).	A (b) (4) randomized, (b) (4), efficacy and safety trial should be conducted to test doses of 80 mg and a higher dose (b) (4) in patients not demonstrating adequate response at the dose of 80 mg. Depending on the findings from the clinical pharmacology trial to assess the effect of CYP2D6 inhibition, CYP2D6 PMs may be excluded from this trial to avoid exposure-related adverse events (e.g., QT prolongation).
☐PMC ☑PMR	Effect of severe renal impairment on PK	Significant increase in exposure of a CYP2D6 substrate in patients with severe renal impairment has been reported (see Reference 1). CYP2D6 is considered as a major metabolic enzyme for the active metabolite NBI-98782. Exposure change of NBI-98782 has not been assessed in the current program. Lack of this information will not ensure a safe use of valbenazine in severe renal impairment patients.	A pharmacokinetic trial should be conducted to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose.

☑PMC ☐PMR	Evaluate the induction potential of NBI-136110 for CYP2B6	The Drug Interaction Guidance recommends evaluation of CYP enzyme induction potential for the major circulating moieties. The induction potential of NBI-136110 has not been evaluated for CYP2B6.	An *in vitro* study should be conducted to assess the induction potential of NBI-136110 on CYP2B6 enzyme.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Valbenazine (NBI-98854) is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor. Upon oral administration, valbenazine is metabolized to an active metabolite, α dihydrotetrabenazine (NBI-98782), which is a more potent VMAT2 inhibitor. As VMAT2 inhibitors, both valbenazine and NBI-98782 are believed to cause reversible reduction of dopamine release at the presynaptic nerve terminal by selectively inhibiting presynaptic VMAT2. Other major circulating metabolites such as NBI-136110 and NBI-679006 are formed via oxidative metabolism, but with much less pharmacological activity. The following is a summary of the clinical pharmacokinetic features of valbenazine and NBI-98782:

Absorption: Following oral administration, the median Tmax of valbenazine ranged from 0.5 to 1.0 hours. NBI-98782 gradually forms and reaches Tmax at 4 to 8 hours. The absolute oral bioavailability of valbenazine is ~ 49%. Ingestion of a high-fat meal decreased valbenazine mean Cmax by about 47% and mean AUC by about 13 %. The mean Cmax 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 92L.

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. Following the administration of a 50 mg single oral dose of radiolabeled valbenazine, approximately 60% and 30% of the total radioactivity was recovered in urine and feces, respectively. Less than 2% of the total radio activity was excreted as unchanged valbenazine or NBI-98782 in either urine or feces.

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.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The initial oral dosing is 40 mg once daily. The dose should be increased to the recommended dose of 80 mg once daily after one week, based on therapeutic response and tolerability. For some patients, adequate clinical response is achieved at 40-mg dose. Given that various adverse events are exposure-dependent, there may be a merit for these patients to continue at the dose of 40 mg.

2.2.2 Therapeutic individualization

Patients Concomitantly Receiving CYP3A Inhibitors: In a dedicated drug-interaction study, concomitant use of ketoconazole (a strong CYP3A4 inhibitor) increased both valbenazine and NBI-98782 Cmax by ~1.5 fold and AUC by ~2-fold. Therefore, valbenazine dose should be reduced by half in patients with a concomitant strong CYP3A4 inhibitor use. No dose reduction of valbenazine is recommended in patients with concomitant weak and moderate CYP3A4 inhibitor uses.

Patients Concomitantly Receiving CYP2D6 Inhibitors or CYP2D6 PMs: CYP2D6 is a major metabolic enzyme for the active metabolite NBI-98782. Significant exposure change of NBI-98782 in patients receiving a strong CYP2D6 inhibitor or in CYP2D6 PMs is anticipated. 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 there are several major concerns with the sponsor's population PK analyses (please refer to Appendix 4.2 for further details). Therefore, there is inconclusive evidence with regards to the precise magnitude of difference in exposures of NBI-98782 in CYP2D6 PMs versus non-PMs. Hence, no specific dosage adjustment regarding magnitude change can be provided at this point of time. However, based on the understanding of the metabolic pathway and exposure-response relationships, dosage reduction based on clinical response should be considered when coadministered with a strong CYP2D6 inhibitor or for a known CYP2D6 poor metabolizer.

Patients Concomitantly Receiving CYP3A Inducers: In a dedicated drug-interaction study, concomitant use of rifampin (a strong CYP3A4 inducer) decreased valbenazine Cmax and AUC by about 30% and 70%, respectively, and decreased NBI-98782 Cmax and AUC by about 50% and 80%, respectively. Therefore, use of valbenazine in patients on a concomitant strong CYP3A4 inducer should be avoided.

Hepatic Impairment: Valbenazine is extensively metabolized. Based on the results from a dedicated hepatic impairment study, a modest increase (<1.5 fold) in valbenazine and NBI-98782 Cmax and AUC was observed in subjects with mild hepatic impairment. A greater increase in

valbenazine and NBI-98782 Cmax (up to 2.5 fold) and AUC (up to 3.4 fold) was observed in subjects with moderate or severe hepatic impairment. Therefore, dose reduction by half in patients with moderate or severe hepatic impairment is recommended.

Renal Impairment: The change of valbenazine and NBI-98782 exposure in renal impairment patients has not been evaluated. Based on the results from a mass balance study, an average of 1.8% of the administered dose was excreted as unchanged drug in urine. In addition, low level of NBI-98782 was excreted in urine, which on average is equivalent to 1.6% of valbenazine dose. Given the absolute bioavailability is about 50%, renal clearance is not the major elimination pathway. Therefore, no significant exposure increase is anticipated in patients with mild to moderate renal impairment. Hence, no dose adjustment for patients with mild to moderate renal impairment is necessary.

It has been shown that the CYP2D6-mediated clearance can be decreased in patients with severe renal impairment. Since CYP2D6 is involved in the metabolism of NBI-98782, it is unclear if the exposure of NBI-98782 will be affected in severe renal impairment patients. The Applicant will be required to conduct a dedicated post-marketing study in severe renal impairment patients.

2.3 Outstanding Issues

- The exposure-response analysis suggests that the doses beyond 80 mg may provide additional therapeutic benefit to patients. It may be important to explore doses greater than 80 mg in the future.

- The effect of CYP2D6 inhibition, either in the presence of strong CYP2D6 inhibitors or in PMs has not been adequately characterized. The evidence with regards to the precise magnitude of difference in exposures of NBI-98782 when the CYP2D6 function is completely inhibited or compromised is inconclusive. This may impact labeling statements regarding dose adjustment as well as QT prolongation analysis in this population.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

- The initial dose for INGREZZA is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients.

- Reduce INGREZZA dose by half, when INGREZZA is coadministered with a strong CYP3A4 inhibitor.

- Consider dose reduction based on tolerability, when coadministered with a strong CYP2D6 inhibitor.
- Avoid concomitant use of INGREZZA with strong CYP3A4 inducers.
- The recommended dose for patients with moderate or severe hepatic impairment (Child-Pugh score 7 to 15) should be reduced by half.
- No dose adjustment for patients with mild or moderate renal impairment.
- INGREZZA can be taken with or without food.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

INGREZZA contains valbenazine, a selective vesicular monoamine transporter 2 inhibitor. INGREZZA capsules are intended for oral administration only. Each capsule contains 73 mg of valbenazine tosylate, which is equivalent to 40 mg of valbenazine free base.

INGREZZA is indicated for the treatment of tardive dyskinesia (TD) in adult patients. There is no currently approved product for this indication. Valbenazine has received both fast-track and breakthrough therapy designations.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The mechanism of action of valbenazine for the treatment of tardive dyskinesia is unknown. It is believed that upon oral administration, valbenazine is metabolized to a more potent active metabolite NBI-98782. Both valbenazine and its active metabolite are VMAT2 inhibitors that cause reversible reduction of dopamine release at the presynaptic nerve terminal by selectively inhibiting presynaptic VMAT2.
Active Moieties	NBI-98782 is the active moiety, which is 40-fold more potent than valbenazine.
QT Prolongation	Valbenazine causes an increase in the QTc interval. An exposure-response analysis of clinical data from two healthy subject studies revealed a positive correlation in QTc interval with the plasma concentration of the active metabolite. Based on exposure-response modeling, patients taking a 80-mg dose may have a mean (95% upper bound) QTc prolongation of 6.7

	(8.4) msec. Patients taking a 80-mg dose with increased exposure (e.g., taking a concomitant strong CYP3A4 or CYP2D6 inhibitor) may have a mean QTc prolongation beyond 10 msec.	
General Information		
Bioanalysis	Valbenazine and active moieties were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as appendix 4.1.	
Drug exposure at steady state following the therapeutic dosing regimen	The AUC0-24 and Cmax (mean± SD) based on Study NBI-98854-1503 in healthy subjects at the 80 mg daily dose (N=21) on Day 14 were 6150 ± 1510 ng·h/mL and 916 ± 220 ng/mL, respectively for valbenazine; and 695 ± 227 ng×h/mL and 39.4 ± 12.9 ng/mL, respectively for NBI-98782.	
Maximum tolerated dose or exposure	Single Dose	300 mg in healthy subjects
	Multiple Dose	100 mg QD for 8 days in healthy volunteers
Dose Proportionality	AUC and Cmax of valbenazine and NBI-98782 increased approximately proportionally when the INGREZZA dose was increased from 40 mg to 300 mg.	
Accumulation	The accumulation factors are 1.5 fold for valbenazine, 2.3 fold for NBI-98782, respectively.	
Absorption		
1. Absolute BA: Mean (CV): 48.6% (10.3%). 2. Tmax: Valbenazine: 0.5 to 1 hours; NBI-98782: 4 to 8 hours. 3. Food effect (high-fat): Ingestion of a high-fat meal decreased valbenazine Cmax by ~ 47% and AUC by ~13 %. The Cmax and AUC of NBI-98782 Cmax and AUC decreased by about 18% and 6%, respectively.		
Distribution		
1. Volume of Distribution: Valbenazine: 92 L. 2. Plasma Protein Binding: Valbenazine: >99%; NBI-98782: ~64% 3. Blood to Plasma Ratio: Valbenazine ~0.75		
Elimination		

1. Clearance: Valbenazine has a mean total plasma systemic clearance of 7.2 L/hr.
2. Mean Terminal Elimination half-life: Valbenazine and NBI-98782: 15 - 22 hours.
3. Primary metabolic pathway(s): Mass balance study showed that approximately 60% and 30% radioactivity was recovered in urine and feces, respectively. Less than 2% was excreted as unchanged valbenazine or NBI-98782 in either urine or feces. The results indicated that renal clearance is not the major elimination pathway.
4. Metabolism, CYP3A4/5 and CYP2D6 involved
5. Transporter: Valbenazine and NBI-98782 are unlikely to inhibit the transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3) at clinically relevant concentrations.
6. Inhibitor/Inducer to CYP enzymes: Valbenazine and NBI-98782 are unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4/5 or induce CYP1A2, CYP2B6 and CYP3A4/5 at clinically relevant concentrations.

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

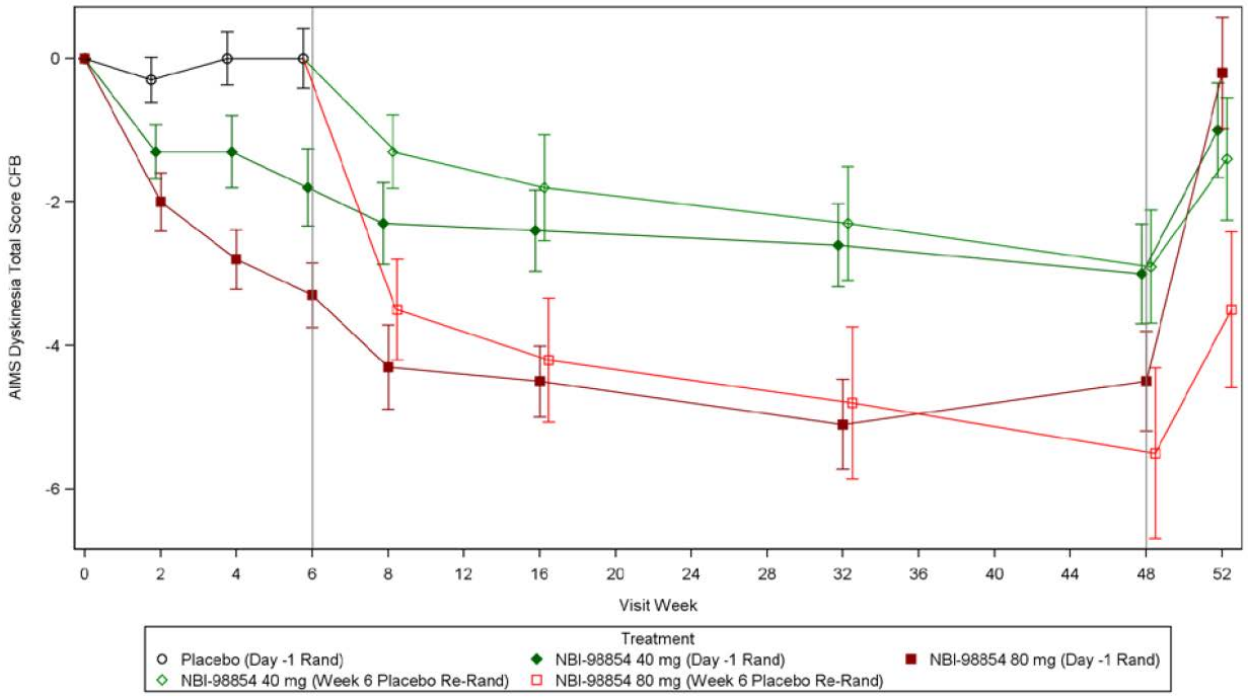
The evidence of effectiveness is primarily supported by the reduction in the Abnormal Involuntary Movement Scale (AIMS) total score data relative to baseline as compared to the placebo group from one Phase 3 trial, Study NBI-98854-1304 (1304). Results from one Phase 2 trial, Study NBI-98854-1202 (1202) provided supportive evidence of effectiveness of valbenazine. The results from an internal exposure-response relationship analysis using the Phase 3 data were consistent with the observed dose-response relationship and thus provided additional supportive evidence

In the Phase 2 trial, Study 1202, which is a randomized, double-blinded, placebo-controlled trial, valbenazine doses were titrated to subject's optimal dose of 25 mg, 50 mg, or 75 mg QD. The study enrolled patients who were medically stable with a clinical diagnosis of Schizophrenia or Schizophrenia disorder, or mood disorder, with TD. The titration design did not allow for a formal dose comparison, since the subjects who responded to treatment at a lower dose were not escalated to the next higher dose. However, a significant reduction in the AIMS total score relative to baseline was observed in the valbenazine-treated group compared to the placebo group at end of week 6. Additionally, in the Phase 3 trial, Study 1304, which is a randomized, double-blinded, parallel-group, placebo-controlled trial with fixed-dose design, the efficacy, safety and tolerability of 40 mg and 80 mg QD were evaluated in a population with similar characteristics as Study 1202 described above. A clear trend in the dose-response was observed in the primary efficacy endpoint at end of week 6 at the tested dose levels (**Figure 1**). While the higher dose (80 mg) met the pre-specified statistical criteria for the primary efficacy endpoint, owing to the sponsor's statistical analysis plan of testing 80 mg on the secondary efficacy

endpoint prior to 40 mg on the primary efficacy endpoint, the latter had only a significant nominal p-value.

Furthermore, in the open-label safety extension phase of Study 1304, when the patients originally assigned to the placebo cohort during the controlled study period (6 weeks) were re-randomized to either (a) 40 mg for next 42 weeks or (b) 40 mg during week 7 and titrated to 80 mg for next 41 weeks, the trend in the reduction in AIMS seems to persist (**Figure 1**). Upon discontinuation at the end of 48 weeks, the observed AIMS seems to revert back, but does not seem to reach and/or get worse off than the values at baseline within 4 weeks. (*Please refer to the statistical review by Dr. Thomas Birkner and clinical efficacy review by Dr. Mike Davis for further details about the pivotal efficacy data*)

Figure 1: Study 1304: LS Means (±SEM) Change from Baseline in AIMS Total Score by Visit and Treatment Group (ITT Analysis Set) Including the Extension Phase

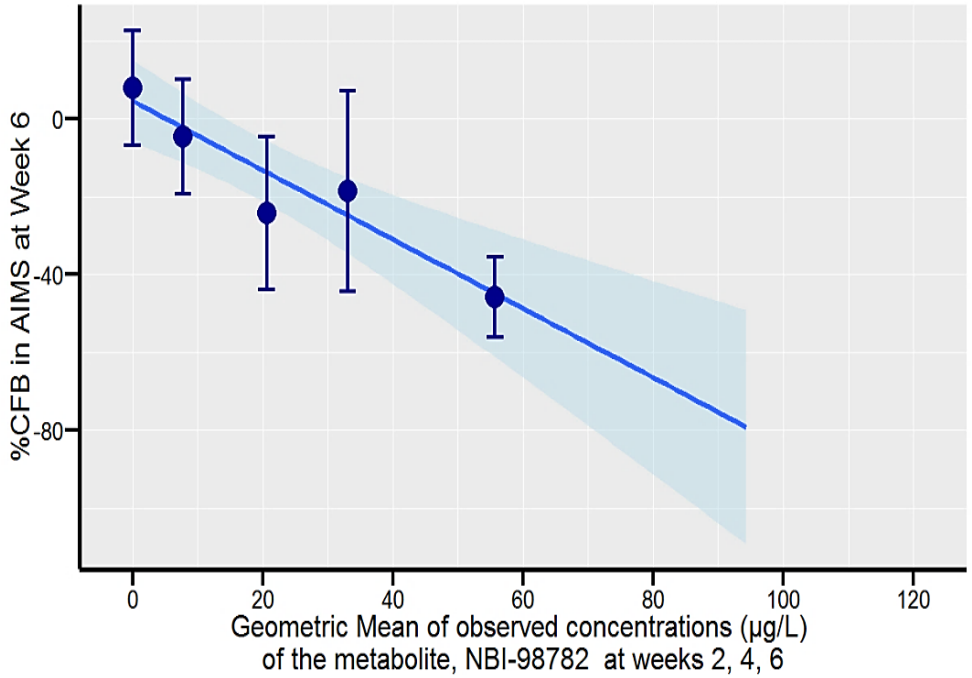


Note: The data in the first 6 weeks were obtained from Study 1304. The observations between Week 6 to Week 48 were obtained through the open-label extension phase. Between Week 48 and Week 52, all patients discontinued the treatment of Valbenazine.

Valbenazine is a selective VMAT2 inhibitor, which causes reversible reduction of dopaminergic release at the pre-synaptic nerve terminals and is the presumed mechanism involved in treating TD. Valbenazine, upon oral administration results in the formation of the active metabolite NBI-98782, which is considered as the primary moiety contributing towards effectiveness.

An internal exposure-response analysis using the exposures, namely, geometric mean of the observed concentrations of NBI-98782 at weeks 2, 4, 6 and the percent reduction in the AIMS total score relative to the baseline was conducted using data from Study 1304. The results (**Figure 2**) were consistent with the observed dose-response relationship.

Figure 2: FDA's Exposure-Response Analysis using the Geometric Mean of the Observed Concentrations at Weeks 2, 4, 6 and %Change in AIMS Total Score from Baseline Results from Study 1304



3.3.2 Is the proposed general dosing regimen appropriate?

Yes. The proposed dosing regimen – starting dose of 40 mg QD and titrating to the recommended therapeutic dose of 80 mg QD after one week is appropriate. However, patients who achieve adequate clinical response at 40 mg QD can continue on this dose. The proposed dosing regimen is identical to that used in the pivotal phase 3 trial, Study 1304.

The results from the pivotal phase 3 trial, Study 1304, and the internal exposure-response analyses for efficacy (**Figure 2**) suggest that therapeutically recommended 80 mg is more effective than the 40 mg dose. Additional internal exposure-response analysis of the safety events suggested a significant relationship with the proportion of subjects with ≥2-fold increase in the prolactin concentrations (**Figure 3**) and QTc prolongation (**Figure 4**).

Figure 3: FDA's Exposure-Response Analysis using the Geometric Mean of the Observed Concentrations at Weeks 2, 4, 6 and Proportion of Subjects with ≥2-fold Increase in Prolactin Concentrations from Study 1304

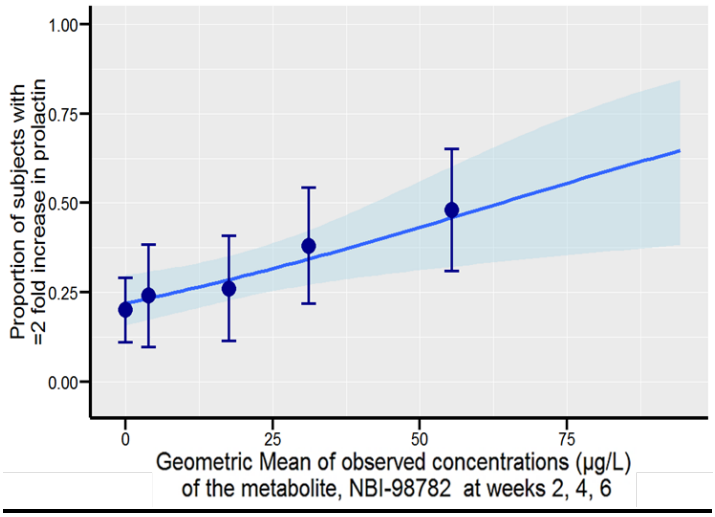
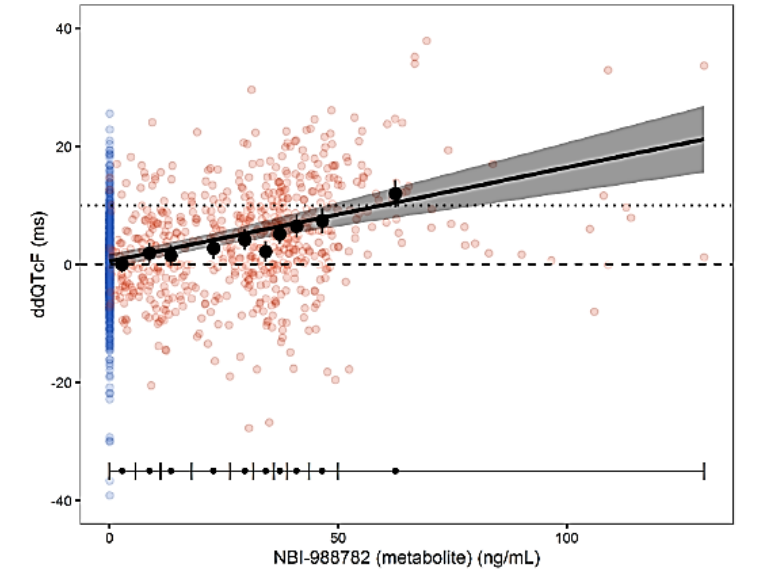


Figure 4: FDA's Exposure-Response Analysis for QTc Prolongation



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

It was noted that the TD patients who were on background neuroleptic therapy (dopamine receptor blocking agents) showed higher baseline prolactin levels. The effect of chronic administration of valbenazine on serum prolactin concentrations in humans has not been studied

previously. While a significant relationship was found between the exposures and the proportion of subjects who had ≥2-fold increase in prolactin concentrations in Study 1304, no such relationship with the proportion of subjects who had ≥4-fold increase in prolactin concentrations (there were very few individuals who had this adverse event). Based on our discussion with the clinical review team, the clinical relevance and consequences of ≥2-fold increase in prolactin concentrations is not fully understood. Based on an internal C-QT analysis (please refer to the QT review by Dr. Nan Zheng and Dr. Lars Johannesen for further details), it was found that 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. Overall, the safety profile of therapeutically recommended dose of 80 mg seemed acceptable in the general population.

It has been shown in Study 1304, some patients may demonstrate adequate clinical response in managing TD at the dose of 40 mg. Given some of the AEs are exposure-dependent (**Figure 3** and **Figure 4**), for these patients, there may be merit to continue the dose of 40 mg to avoid unnecessary risk for additional AEs.

In addition, as shown in Study 1304, the dose of 80 mg appears to be reasonably safe and well tolerated. The dose/exposure-response for effectiveness (**Figure 2**) does not seem to reach plateau within the tested dose range up to 80 mg. Therefore, it seems reasonable to assess whether a higher dose would confer additional therapeutic benefit for patients, especially for those who have not demonstrated sufficient clinical response at the dose of 80 mg. Hence, we recommend a post-marketing study to explore this further (please see section 1.2 for more details).

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes.

Body Weight, Age, Gender, Race

No dosage adjustment is necessary based on body weight, age, gender, race and BMI. As stated previously (and discussed in detail in Appendix 4.2), we believe there are several major issues with the sponsor's population PK analyses and so consequently the covariate analysis cannot be used to support their conclusion that these factors do not influence valbenazine pharmacokinetics. However, based on the dosing regimen used in the pivotal phase 3 trial, Study1304, as well as the supportive phase 2 trial, Study 1202, where the doses were administered without adjusting for body weight, age, gender, race and BMI, and since the general population in which valbenazine is intended to be administered is expected to have characteristics similar to the population studied in 1202 and 1304, no dose adjustment strategies are warranted based on these covariates.

CYP2D6

Based on the *in vitro* studies, NBI-98782 is a substrate for CYP2D6. Increased exposure of NBI-98782 is anticipated in patients with compromised (i.e., CYP2D6 PMs) or inhibited (i.e., CYP2D6 inhibitors) CYP2D6 function. However, with the current submission, the sponsor did not adequately characterize the impact of losing CYP2D6 function on NBI-98782 exposure either in CYP2D6 poor metabolizers (PMs) or in a dedicated drug-drug interaction study in the presence of concomitant strong CYP2D6 inhibitors. As mentioned previously, since we believe there are several major issues with the sponsor's population analyses, their finding of a 2-fold higher exposure in PMs versus. non-PMs is unreliable. Additionally, the dataset used in the population PK analyses consists of a total of only 16 PMs, of which 13 PMs are in studies with sparse sampling (n = 10 in study 1304, n=3 in study 1202) and only 2 PMs were administered the therapeutically recommended dose (80 mg). The sponsor provided exposure data of NBI-98782 in an additional 7 PMs, 4 of which were from phase 1 healthy volunteer studies and 3 were adolescent patients with Tourette's Syndrome. Overall, the limited data showing large variability makes it difficult to assess the precise magnitude of the differences in the exposures of NBI-98782 in PMs vs. non-PMs. Dose reduction may be needed depending on magnitude of the interaction and the safety/tolerability for PMs or subjects who take concomitant CYP2D6 inhibitors. Therefore, we recommended a post-marketing study to quantify the impact of CYP2D6 inhibition on the exposures of NBI-98782 (see section 1.2 for more details), which will help to improve confidence in the labeling recommendation. The current recommendation is to consider dose reduction based on tolerability in patients who are known to be CYP2D6 PMs or patients receiving a strong CYP2D6 inhibitor as a comedication. An additional note, which is contextual is that, based on the c-QT analysis, it seems very important to characterize the QT effect in CYP2D6 PMs especially if higher doses were to be explored (recommended as a PMC study, see section 1.2 for more details). (*Please refer to the QT review by Dr. Nan Zheng and Dr. Lars Johannesen for further details*)

Hepatic impairment

In subjects with mild hepatic impairment, there was a modest increase (<1.5 fold) in valbenazine and NBI-98782 Cmax and AUC0-inf. A greater increase in valbenazine and NBI-98782 Cmax (up to 2.5-fold) and AUC0-inf (up to 3.4-fold) was observed in subjects with moderate or severe hepatic impairment (**Table 1**). Therefore, a dosage reduction by half is recommended in moderate or severe hepatic impairment patients.

Table 1. Valbenazine, NBI-98782, and NBI-136110 Hepatic Impairment Group Geometric Mean Ratios for AUC0-inf and Cmax

Parameter Comparison	C_{max} (ng/mL)		$AUC_{0-\infty}$ (ng×hr/mL)	
	Ratio[a]	90% CI[b]	Ratio[a]	90% CI[b]
NBI-98854				
Mild vs. Normal	1.4	0.89, 2.3	1.2	0.89, 1.7
Moderate vs. Normal	2.0	1.1, 3.5	1.9	1.2, 2.8
Severe vs. Normal	2.5	1.6, 3.9	2.4	2.0, 2.9
NBI-98782				
Mild vs. Normal	1.2	0.98, 1.5	1.2	0.95, 1.6
Moderate vs. Normal	2.1	1.4, 3.2	2.8	1.6, 4.8
Severe vs. Normal	2.2	1.7, 2.7	3.4	2.7, 4.3
NBI-136110				
Mild vs. Normal	1.1	0.84, 1.4	1.1	0.89, 1.3
Moderate vs. Normal	1.3	0.91, 1.9	1.4	0.95, 2.1
Severe vs. Normal	1.6	1.3, 1.9	1.9	1.6, 2.3

[a] Ratio of the geometric least-squares (LS) means was based on an analysis of variance model using log transformed (base 10) data
[b] 90% CI for the geometric mean ratio was based on the LS means using log transformed (base 10) data.

Source: Table 38 of Clinical Pharmacology Summary Aid

Renal impairment

The change of valbenazine exposure in renal impairment patients was not evaluated. Based on the results from a mass balance study, an average of only 1.8% of the administered dose excreted as unchanged drug in the urine. Low levels of NBI-98782 were excreted in the urine, which on average is equivalent to 1.6% of valbenazine dose. Given the absolute bioavailability is about 50%, renal clearance is not the major elimination pathway. Therefore, no significant exposure increase is anticipated in patients with mild to moderate renal impairment. Hence, no dose adjustment for patients with mild to moderate renal impairment is necessary.

It has been shown that the CYP2D6-mediated clearance can be decreased in patients with severe renal impairment (**Reference** 1). Since CYP2D6 is involved in the metabolism of NBI-98782, it is unclear if the exposure of NBI-98782 will be affected in severe renal impairment patients. The Applicant will be required to conduct a dedicated post-marketing study in severe renal impairment patients.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No clinically relevant food effect has been identified. Valbenazine can be administered with or without food. As shown in Section 1.1, dosage adjustment may be needed for patients receiving strong CYP3A4 or CYP2D6 inhibitors. In addition, concomitant use of valbenazine with strong CYP3A4 inducers should be avoided. Valbenazine inhibits intestinal P-glycoprotein (P-gp), yielding moderate increase in digoxin exposure. No significant CYP3A inhibition of valbenazine

has been identified. Based on *in vitro* studies, valbenazine is unlikely to cause clinically significant pharmacokinetic drug interactions with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, and CYP3A4/5 or BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3. The induction potential for NBI 136110 is pending further investigation. Our recommendations are based on the following findings.

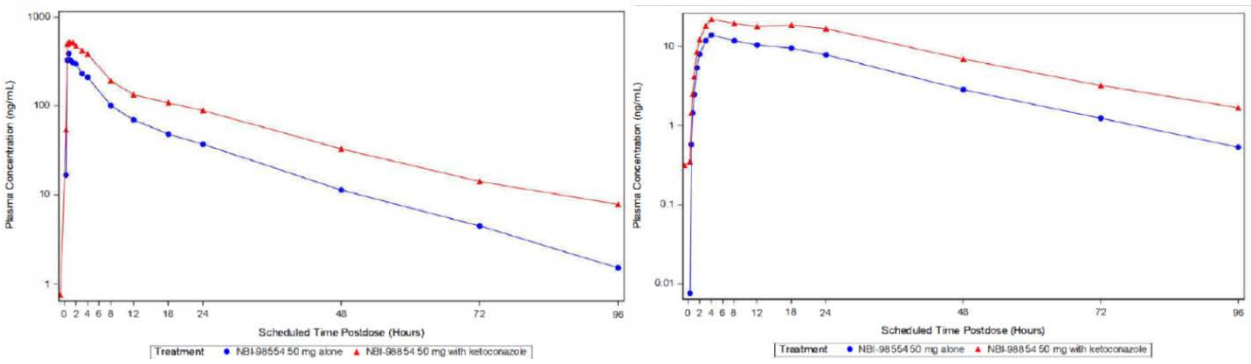
Effect of CYP3A4 Inhibitors and Inducers on Valbenazine

Strong CYP3A4 Inhibitor: As shown in **Table 2** and **Figure 5**, coadministration of ketonconazole led to an approximate 1.5-fold and 2-fold increase in the Cmax and AUC0-inf, respectively, for valbenazine. Similar effect was observed for NBI-98782. Exposure changes for the other metabolite, NBI136110, are shown in **Table 2** as well. Based on the results, a dose reduction by half is recommended when valbenazine is coadministered with a strong CYP3A4 inhibitor.

Table 2. PK parameters (arithmetic mean±SD) of NBI-98854, NBI-98782, and NBI-136110 following a single oral 50-mg dose of NBI-98854 alone or with ketoconazole to healthy subjects

Moiety	PK parameters	NBI-98854 +ketoconazole (T, n=24)	NBI-98854 alone (R, n=24)	Geomean Ratio (T/R, 90% CI)
NBI-98854	C_{max} (ng/mL)	624±221	425±176	151.1 (140.6,162.3)
	T_{max} (hr)*	0.75(0.5, 2.0)	0.75(0.48, 1.5)	-
	AUC_{last}(hr*ng/mL)	7100±2260	3420±1230	-
	AUC_{inf} (hr*ng/mL)	7340±2360	3470±1240	213.7 (203.6,224.3)
	$T_{1/2}$(hr)	20±3.1	16±2.2	-
NBI-98782	C_{max} (ng/mL)	23.4±10.4	14.1±5.48	162.9 (153.8, 172.5)
	T_{max} (hr)*	4.0 (4.0, 24)	4.0 (4.0, 18)	-
	AUC_{last}(hr*ng/mL)	880±488	435±246	-
	AUC_{inf} (hr*ng/mL)	935±534	450±262	206.7 (198.4, 215.4)
	$T_{1/2}$(hr)	21±3.3	18±2.4	-
NBI-136110	C_{max} (ng/mL)	8.05±3.31	37.8±14.0	21.6(18.8, 24.8)
	T_{max} (hr)*	18 (2.0, 48)	4.0 (1.5, 24)	-
	AUC_{last}(hr*ng/mL)	567±223	1210±333	45.6(41.8, 49.7)
	AUC_{inf} (hr*ng/mL)	NA	1330±376	-
	$T_{1/2}$(hr)	NA	28±5.3	-
*median (min,max) -source: Tables 2, 3, 4, 5, 6, and 7 of 1302 study report				

Figure 5. Mean (+SD) Plasma Concentration Versus Time for NBI-98854 (left) and NBI-98782 (right)- Treatment with NBI-98854 Alone or in Combination with Ketoconazole (N=24)



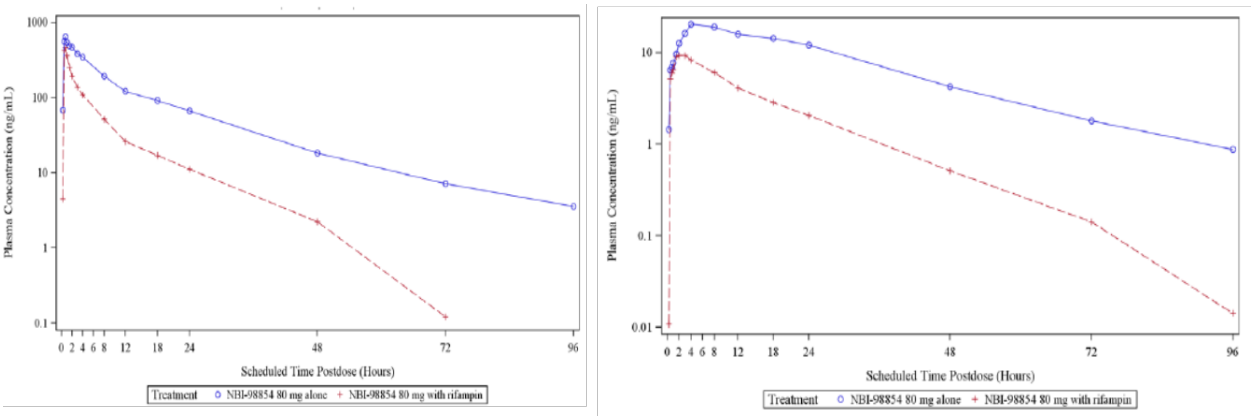
Source: Figure 2 and 3 of 1302 Study Report

Strong CYP3A4 Inducer: As shown in **Table 3** and **Figure 6**, coadministration of rifampin led to an approximate 30% decrease in Cmax and 70% decrease in AUC0-inf for NBI-98854; about 50% decrease in Cmax and 80% decrease in AUC0-inf for NBI-98782. Exposure changes for the other metabolite, NBI136110, are shown in **Table 3** as well. Based on the findings, concomitant use of valbenazine with strong CYP3A4 inducers should be avoided.

Table 3. PK parameters (mean±SD) of NBI-98854, NBI-98782, and NBI-136110 following a single oral 80-mg dose of NBI-98854 alone or with rifampin to healthy subjects

Moiety	PK parameters	NBI-98854 +Rifampin (T, n=11)	NBI-98854 alone (R, n=11)	Geomean Ratio (T/R, 90% CI)
NBI-98854	C_{max} (ng/mL)	542±299	795±386	68.2 (57.9,80.3)
	T_{max} (hr)*	0.75(0.5, 1.0)	0.75(0.5, 2.1)	-
	AUC_{last}(hr*ng/mL)	1670±555	5930±1180	-
	AUC_{inf} (hr*ng/mL)	1700±553	6020±1210	27.7 (25.5,30.1)
	$T_{1/2}$(hr)	10±2.1	16±2.3	-
NBI-98782	C_{max} (ng/mL)	11.2±5.8	21.5±4.6	48.5 (41.3, 56.9)
	T_{max} (hr)*	3.0 (0.5, 4.0)	4.0 (0.5, 18)	-
	AUC_{last}(hr*ng/mL)	153±43.9	665±193	-
	AUC_{inf} (hr*ng/mL)	156±43.9	689±203	22.8 (20.5, 25.4)
	$T_{1/2}$(hr)	12±1.7	19±2.3	-
NBI-136110	C_{max} (ng/mL)	81.5±24.6	59.8±16.9	139.5 (112.3, 173.3)
	T_{max} (hr)*	1.5(0.75, 2.1)	3.0 (2.0, 8.0)	-
	AUC_{last}(hr*ng/mL)	658±166	1890±451	-
	AUC_{inf} (hr*ng/mL)	663±166	2080±463	31.9 (28.9, 35.2)
	$T_{1/2}$(hr)	12±3.0	27±6.7	-
*median (min,max) -source: Tables 3, 4, 5, 6, 7, and 8 of 1502 study report				

Figure 6. Plasma Concentration Versus Time for NBI-98854 (left), NBI-98782 (right) - Treatment with NBI-98854 Alone or in Combination with Rifampin (N=11)

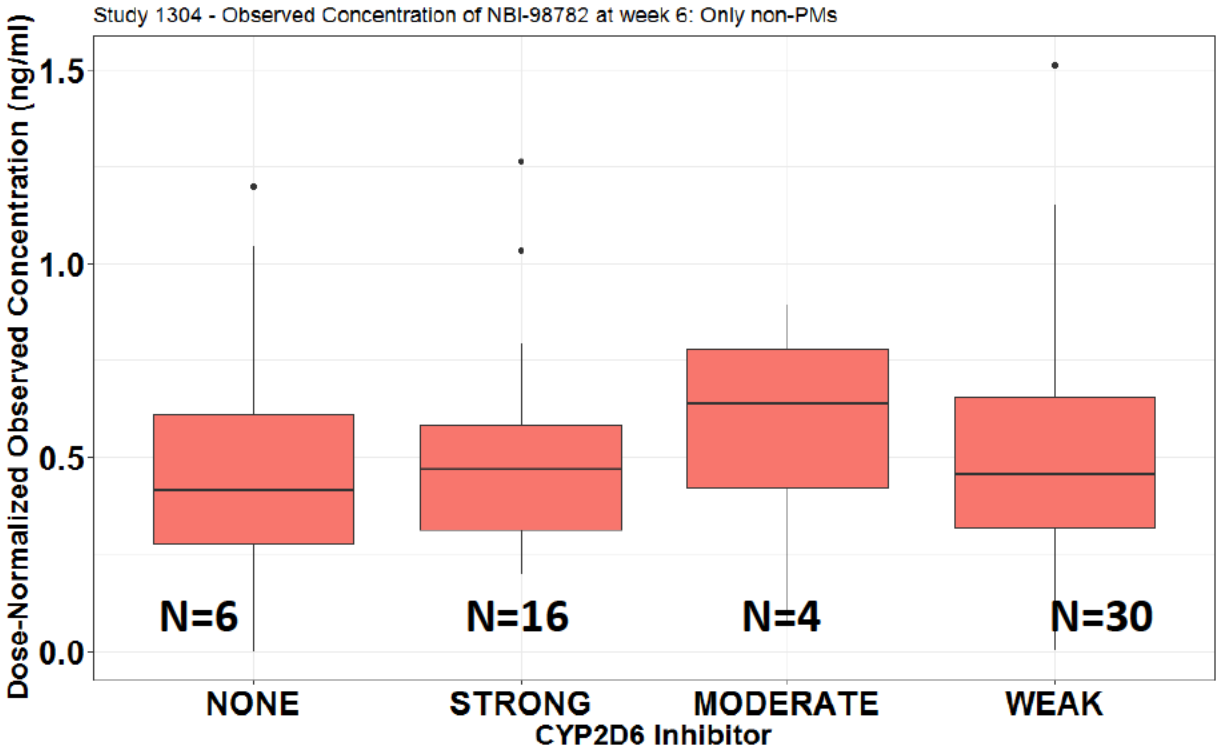


Source: Figure 2 and 3 of 1502 Study Report

Effect of CYP2D6 Inhibitors on Valbenazine

As stated previously in section 3.3.3, the sponsor did not conduct a dedicated DDI study to characterize CYP2D6 inhibition. In study 1304, the sponsor reported that the patients were on stable concomitant weak to strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, duloxetine, sertraline, bupropion), but details pertinent to the time of administration and their dose were lacking. When the dose-normalized exposures of NBI-98782 at week 6 in study 1304 were plotted, no obvious exposure differences in NBI-98782 were observed between subjects who were on weak, moderate and strong inhibitors (**Figure 7**). The recommended post-marketing study will help shed more light on the impact of CYP2D6 inhibition. The current recommendation is that valbenazine dose may be reduced based on tolerability, when coadministering with strong CYP2D6 inhibitors.

Figure 7: Dose-Normalized Observed Concentrations of NBI-98782 at Week 6 in non-PMs from Study 1304



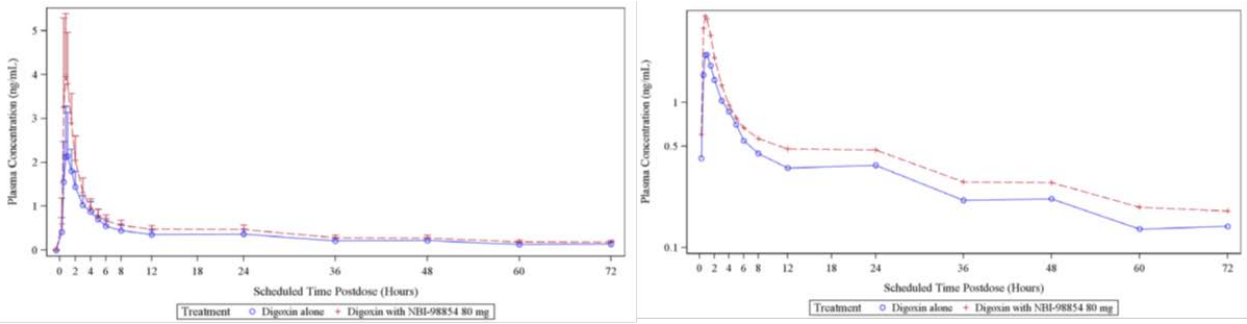
Effect of Valbenazine on Digoxin

As shown in **Table 4** and **Figure 8**, concomitant administration of digoxin and valbenazine led to an approximately 1.9-fold increase in Cmax and an approximately 1.4-fold increase in AUC0-inf of digoxin compared with administration of digoxin alone. Mean digoxin t½ was similar with and without valbenazine administration (35 and 36 hours, respectively). Median digoxin tmax was 0.25 hours shorter (0.75 hours vs. 1.0 hours) after administration of digoxin in combination with valbenazine than after administration of digoxin alone. Digoxin concentrations should be monitored when coadministering valbenazine with digoxin. Increased digoxin exposure may increase the risk of exposure related adverse reactions. Dosage adjustment of digoxin may be necessary based on digoxin concentration.

Table 4. PK Parameters (mean±SD) for Digoxin Alone Versus Digoxin in Combination with NBI-98854

PK parameters	Digoxin (R, n=17)	Digoxin + NBI-98854 (T, n=17)	Geomean Ratio (T/R, 90% CI)
C_{max} (ng/mL)	2.47±0.99	4.61±1.47	191.7(166.4, 220.8)
T_{max} (hr)*	1.0(0.75, 2.0)	0.75(0.5, 1.5)	-
AUC_{last}(hr*ng/mL)	23.4±6.36	31.8±5.35	-
AUC_{inf} (hr*ng/mL)	30.9±9.25	41.0±7.38	136.4(126.0, 147.6)
$T_{1/2}$(hr)	36±7.4	35±7.2	-
*median (min,max) -source: Tables 4 and 5 of 1503 study report			

Figure 8. Plasma Digoxin Concentration Versus Time – by Treatment with Digoxin Alone or in Combination with NBI-98854 (N=17) (Linear and Log Scales)



Source: Figure 2 of 1503 Study Report

Effect of Valbenazine on Midazolam

As shown in **Table 5**, **Table 6** and **Figure 9**, coadministration of midazolam with valbenazine did not significantly affect the PK of midazolam.

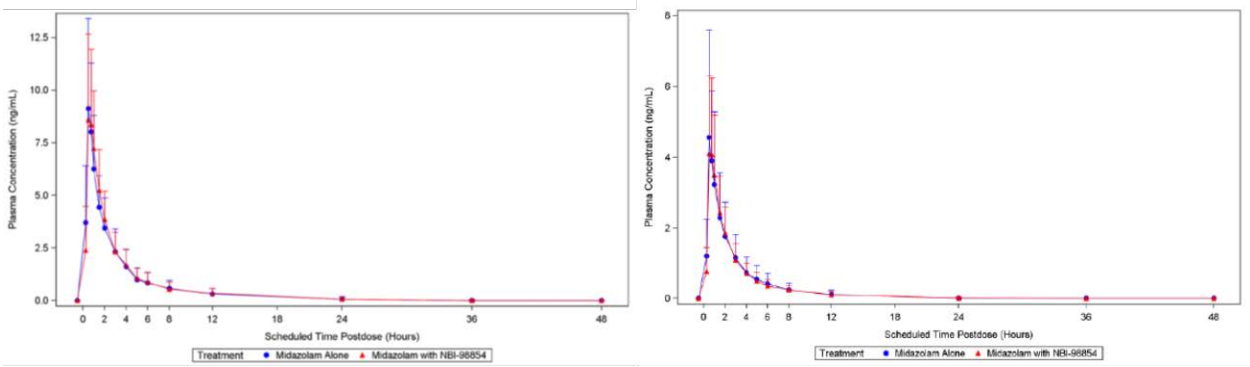
Table 5. Plasma Pharmacokinetic Parameters (Mean±SD) for Midazolam Alone Versus Midazolam in Combination with NBI-98854

PK parameters	Midazolam (R, n=12)	Midazolam + NBI-98854 (T, n=12)	Geomean Ratio (T/R, 90% CI)
C_{max} (ng/mL)	9.59±4.1	9.61±3.83	102.1(86.0, 121.2)
T_{max} (hr)*	0.5 (0.5, 1.0)	0.5 (0.5, 1.0)	-
AUC_{last}(hr*ng/mL)	22.5±13.9	23.4±11.1	-
AUC_{inf} (hr*ng/mL)	23.7±12.3	24.9±11.5	106.9(100.3, 113.9)
$T_{1/2}$(hr)	4.5±2.1	4.7±2.3	-
*median (min,max) -source: Tables 3 and 4 of 1507 study report			

Table 6. Plasma 1′-Hydroxymidazolam Pharmacokinetic Parameters for Midazolam Alone Versus Midazolam in Combination with NBI-98854

PK parameters	Midazolam (n=12)	Midazolam + NBI-98854 (n=12)
C_{max} (ng/mL)	4.82±2.86	4.55±2.17
T_{max} (hr)*	0.63 (0.5, 1.0)	0.5 (0.5, 1.0)
AUC_{last}(hr*ng/mL)	9.97±6.16	9.96 ±4.85
AUC_{inf} (hr*ng/mL)	10.9±6.55	10.8±5.20
$T_{1/2}$(hr)	3.4±1.6	4.0±2.6
*median (min,max) -source: Table 5 of 1507 study report		

Figure 9. Mean (+SD) Plasma Concentrations Versus Time for Midazolam (Left Panel) and 1-hydroxy Midazolam (Right Panel)– by Treatment with Midazolam Alone or in Combination with NBI-98854 (N=12)



Source: Figure 2 and 3 of 1507 Study Report

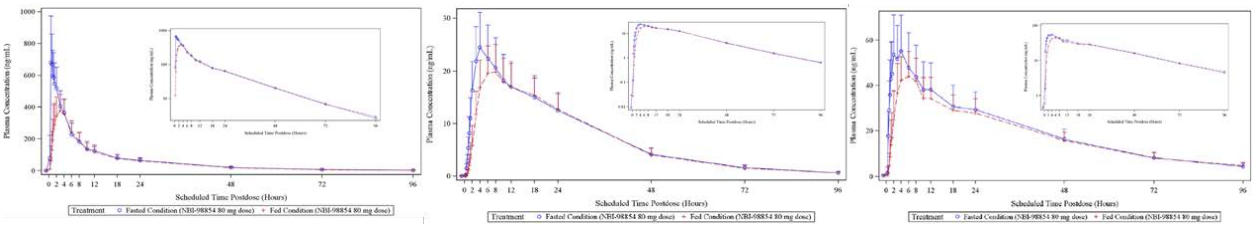
Effect of Food

As shown in **Table 7** and **Figure 10**, coadministration of NBI-98854 with high-fat and high-calorie meal causes an approximate 47% and 13% attenuation of the Cmax and AUC of valbenazine, respectively. The Cmax and AUC of NBI-98782 decreased by about 18% and 6%, respectively. Since the Cmax and AUC of the active metabolite NBI-98782 were largely unchanged in presence of food, the decrease in Cmax of valbenazine is not clinically relevant. Therefore, valbenazine may be administered with or without regard to meals.

Table 7 Summary of Pharmacokinetic Parameters (Mean±SD) for NBI-98854, NBI-98782 and NBI-136110 in Fasted and Fed Subjects.

Moiety	PK parameters	Fasted NBI-98854 (80mg) (N=24)	Fed NBI-98854 (80mg) (N=22)
NBI-98854	C_{max} (ng/mL)	769±230	409±112
	T_{max} (hr)*	0.63 (0.5, 2.0)	3.0 (1.3, 4.0)
	AUC_{last}(hr*ng/mL)	5950±1520	5130±1260
	AUC_{inf} (hr*ng/mL)	6010±1530	5200±1270
	$T_{1/2}$(hr)	16±1.6	16±1.9
NBI-98782	C_{max} (ng/mL)	25.1±6.55	20.5±5.35
	T_{max} (hr)*	4.0 (3.0, 8.0)	8.0 (4.0, 10)
	AUC_{last}(hr*ng/mL)	694±177	650±162
	AUC_{inf} (hr*ng/mL)	711±181	666±165
	$T_{1/2}$(hr)	17±2.0	17±1.8
NBI-136110	C_{max} (ng/mL)	57.4±17.0	46.1±10.7
	T_{max} (hr)*	4.0 (1.3, 6.1)	6.0 (2.0, 8.2)
	AUC_{last}(hr*ng/mL)	1910±486	1740±357
	AUC_{inf} (hr*ng/mL)	2080±514	1950±400
	$T_{1/2}$(hr)	26±4.3	29±5.8
*median (min,max) -source: Tables 9, 12 and 14 of 1504 study report			

Figure 10 Mean (+SD) NBI-98854 (Left), NBI-98782 (Middle) and NBI-136110 (Right) Plasma Concentration Versus Time in Fasted and Fed Subjects (Linear and Log Scales (inserted))



Source: Figure 2 and 3 of 1507 Study Report

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

The to-be-marketed formulation is not the same as the clinical trial formulation. The quantitative composition of the Phase-3 clinical and proposed commercial capsule drug products are provided in **Table 8**.

Table 8. Quantitative Composition Comparison of Phase-3 Clinical Capsule and Proposed Commercial Capsule Formulations

Component	Function	40 mg Phase-3 Capsule		40 mg Proposed Commercial Capsule	
		Weight (mg/unit)	% (w/w)	Weight (mg/unit)	% (w/w)
Valbenazine tosylate[a]	Active Ingredient	73.0[b]	(b) (4)	(b) (4)	(b) (4)
Mannitol[c]	(b) (4)	(b) (4)			
Partially pregelatinized starch					
Fumed silica					
Magnesium stearate[d]					
		(b) (4)			
(b) (4)	Capsule Shell	--	1 capsule		
(b) (4) gelatin capsules, Size 1; (b) (4) purple (b) (4) cap/ (b) (4) white opaque body; axially printed with 'VBZ' over '40' in black ink, on both the cap and body[f, g]	Capsule Shell			--	1 capsule

Source: Table 48 of Clinical Pharmacology Summary Aid

A pivotal relative bioavailability trial was performed to compare the two formulations. The results are summarized in **Table 9**. It is shown that the 90% CIs for the geometric mean ratios for AUC0-tlast, AUC0-inf, and Cmax of valbenazine for the to-be-marketed formulation compared with the clinical formulation were all within the bioequivalence range of 80% to 125% (100.2% to 106.9%, 100.1% to 106.6%, and 101.8% to 116.6%, respectively) (**Table 10**). In addition, the mean PK curves for NBI-98782 between the two formulations are most identical (**Figure 11**). Hence similar effectiveness and safety profiles are expected between the two formulations, based on similar exposures observed between the two formulations.

Table 9. Summary of Pharmacokinetic Parameters (Mean±SD) for NBI-98854, NBI-98782 and NBI-136110 by NBI-98854 Formulation

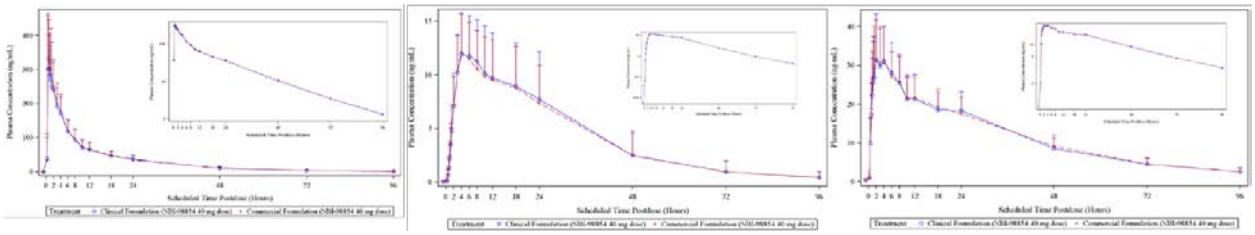
Moiety	PK parameters	Clinical Formulation NBI-98854 (40mg) (N=24)	Commercial Formulation NBI-98854 (40mg) (N=22)
NBI-98854	C_{max} (ng/mL)	349±131	376±118
	T_{max} (hr)*	0.50 (0.48, 2.0)	0.50 (0.50, 2.0)
	AUC_{last}(hr*ng/mL)	3000±849	3100±874
	AUC_{inf} (hr*ng/mL)	3040±857	3140±883
	$T_{1/2}$(hr)	16±2.1	15±2.3
NBI-98782	C_{max} (ng/mL)	12.8±4.10	12.4±3.58
	T_{max} (hr)*	4.0 (3.0, 12)	4.0 (4.0, 12)

	AUC_{last}(hr*ng/mL)	400±223	392±197
	AUC_{inf} (hr*ng/mL)	413±242	404±210
	$T_{1/2}$(hr)	17±2.3	17±2.7
NBI-136110	C_{max} (ng/mL)	34.6±10.5	33.7±9.84
	T_{max} (hr)*	4.0 (1.3, 6.1)	3.0 (1.5, 8.2)
	AUC_{last}(hr*ng/mL)	1100±282	1110±268
	AUC_{inf} (hr*ng/mL)	1200±317	1210±296
	$T_{1/2}$(hr)	26±3.4	26±4.2
*median (min,max) -source: Tables 7, 11 and 13 of 1504 study report			

Table 10. NBI-98854 Geometric Mean Ratios for Pharmacokinetic Exposure Parameters by NBI-98854 Formulation

Parameter	Ratio (%)[a] (Commercial Formulation vs Clinical Formulation)	90% Confidence Interval[b]
$AUC_{0\text{-tlast}}$ (ng×hr/mL)	103.5%	(100.2%, 106.9%)
$AUC_{0-\infty}$ (ng×hr/mL)	103.3%	(100.1%, 106.6%)
C_{max} (ng/mL)	108.9%	(101.8%, 116.6%)

Figure 11 Mean (+SD) NBI-98854 (Left), NBI-98782 (Middle) and NBI-136110 (Right) Plasma Concentration Versus Time by NBI-98854 Formulation (Linear and Log Scales (inserted))



Source: Table 8 of 1504 Study Report

Reference

1. Yoshida K, Sun B, Zhang L, Zhao P, Abernethy DR, Nolin TD, Rostami-Hodjegan A, Zineh I, Huang SM. Systematic and quantitative assessment of the effect of chronic kidney disease on CYP2D6 and CYP3A4/5. Clin Pharmacol Ther. 2016 Jul;100(1):75-87.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

4.2 Pharmacometrics Assessment: Population PK Analyses

4.2.1 Sponsor's Population PK analysis:

Population PK (PopPK) analyses were conducted by the sponsor to characterize the pharmacokinetics of Valbenazine (NBI-98854) and its active metabolite NBI-98782 following oral administration of valbenazine in healthy subjects and TD patients. Their key objectives were (i) to identify the intrinsic and extrinsic covariates that could potentially account for the interindividual PK differences and support the need for appropriate dose adjustment if necessary; and (ii) to derive the exposure metrics that can be used for subsequent exposure-response analyses of the efficacy and safety endpoints.

Data from two phase 1 studies (NBI-98854-901 and NBI-98854-1504), two phase 2 studies (NBI-98854-1201 and NBI-98854-1202) and one phase 3 study (NBI-98854-1304) were included in the analyses and described in **Table 11**.

Table 11: Summary of the characteristics of the studies used for PopPK analyses

Study ID	Subjects	Doses	Description of data
NBI-98854-901	Phase 1, Healthy subjects (N=30)	Single dose cohort: 75, 100, 125, 150 mg Multiple dose cohort 50, 100 mg	Single dose cohort: Rich PK collected at 15 minutes predose, and up to 12 hours postdose on days 1, 8, 15; single postdose PK sample collected on days 2-6, 9-13, 16-20 Multiple dose cohort: Rich PK at 15 minutes predose, and up to 12 hours postdose on days 1, 8; single pre-dose PK on days 2-7
NBI-98854-1504	Phase 1, Healthy subjects (N=48)	40, 80 mg	Rich PK collected at 45 min predose, and up to 24 hours postdose and single PK postdose sample on days 2-4
NBI-98854-1201	Phase 2, Patients (N=47)	50, 100 mg	Sparse PK: single PK sample collected 4-9 hours postdose at end of weeks 2, 6, 8, 12 and 14 or at early termination
NBI-98854-1202	Phase 2, Patients (N=42)	25, 50, 75 mg	Sparse PK: single PK sample collected 4-9 hours postdose at the end of weeks 2, 4, 6, 8 or at early termination
NBI-98854-1304	Phase 3, Patients (N=138)	40, 80 mg	Sparse PK: single PK sample collected at 4-9 hours postdose at the end of weeks 2, 4 and 6 during the placebo-controlled treatment period

Source: Adapted from Summary of Clinical Pharmacology Studies report, Table 36 on page 83-84

Overall, the final dataset for PopPK analyses consists of a total of 4793 PK samples from a total of 305 subjects who received at least one dose of valbenazine, of whom 78 were healthy subjects while 227 were TD patients. This dataset includes a total of only 16 PMs, of which 13 PMs are in studies with sparse sampling (n = 10 in NBI-98854-1304, n=3 in NBI-98854-1202) and only 2 PMs were administered the therapeutically recommended dose (80 mg). Although there was information about the specific use of CYP2D6 inhibitors (weak, moderate and strong), details pertinent to the time of administration and their dose were lacking. Two subjects were excluded from the analyses because their genotype information was missing and twenty more subjects were excluded for whom the concentration was reported as below quantification limit or missing after the dosing, and data points where time after dose was not recorded.

The PopPK data consisting of valbenazine and NBI-98782 were modeled simultaneously using non-linear mixed effects in NONMEM. The structural model developed by the sponsor consists of:

a) three-compartment model for the parent compound: whose absorption was described by first order absorption rate constant (Ka) with a lag time (t_{lag}), distribution characterized by apparent volumes of central (VCp) and peripheral compartments (VPp) and the inter-compartmental clearance (Qp) between them, elimination described by two apparent clearances, namely, conversion of valbenazine to NBI-98782 (CLpm) and the clearance of valbenazine from the systemic circulation (CLp);
b) two-compartment model for NBI-98782: formed from valbenazine (CLpm), distribution characterized by apparent volumes of central (VCm) and peripheral compartments (VPm) and the inter-compartmental clearance (Qm) between them, and elimination from the systemic circulation (CLm); and
c) residual error structure included both additional and proportional components.

Covariate identification was performed in a stepwise manner and body weight was retained as a covariate on apparent clearance and volume of distribution of valbenazine and only on the volume of distribution of NBI-98782 using allometry while fixing the coefficients to 1 and 0.75 for CL and Vd respectively. Additionally, CYP2D6 genotype status (PMs vs. Non-PMs) was included as a covariate on the elimination clearance (CLm) of NBI-98782 and was estimated to be *-0.50*, suggesting CLm for PMs was 50% lower than non-PMs. The parameter estimates of the final PopPK model are shown in **Table 12.**

Table 12 – Parameter estimates of the final PopPK model

Parameter	Units	Base Model (with t_{lag} BSV on t_{lag}): BM7		Final Model (Weight as allometry + Geno on CLm): C004	
		Estimate	BSV (%CV)	Estimate	BSV (%CV (shrinkage))
Apparent clearance of NBI-98854 (CLp)	L/hr/78kg[a]	10.7	72.2	10.7	71.3 (5.36%)
Apparent central volume of NBI-98854 (VCp)	L/78kg	166	71.6	152	61.8 (31.3%)
Absorption rate constant (Ka)	/hr	7.66	69.2	6.59	74.5 (56.4%)
Apparent inter-compartmental clearance of NBI-98854 (Qp)	L/hr/78kg	14.2	NE	15.0	NE
Apparent peripheral volume of NBI-98854 (VPp)	L/78kg	118	28.9	134	26.7 (53.8%)
Apparent clearance of NBI-98854 to NBI-98782 (CLpm)	L/hr/78kg	4.40	26.7	4.28	27.1 (29.1%)
Apparent clearance of NBI-98782 (CLm)	L/hr/78kg	29.7	33.6	29.5	28.3 (30.4%)
Apparent central volume of NBI-98782 (VCm)	L/78kg	272	NE	276	NE
Apparent inter-compartmental clearance of NBI-98782 (Qm)	L/hr/78kg	3.76	82.4	1.49	1.31 (67.3%)
Apparent peripheral volume of NBI-98782 (VPm)	L/78kg	67.3	NE	74.1	NE
t_{lag}	hr	0.161	56.6	0.185	34.6 (54.2%)
Effect of genotype in CLm		NA		-0.502	
Additive residual error for NBI-98854	µg/L	1.79		0.573	
Proportional residual error for NBI-98854		23.1%		23.4%	
Additive residual error for NBI-98782	µg/L	0.388		0.0887	
Proportional residual error for NBI-98782		22.5%		23.0%	

[a] 78 kg is the median body weight of the population.

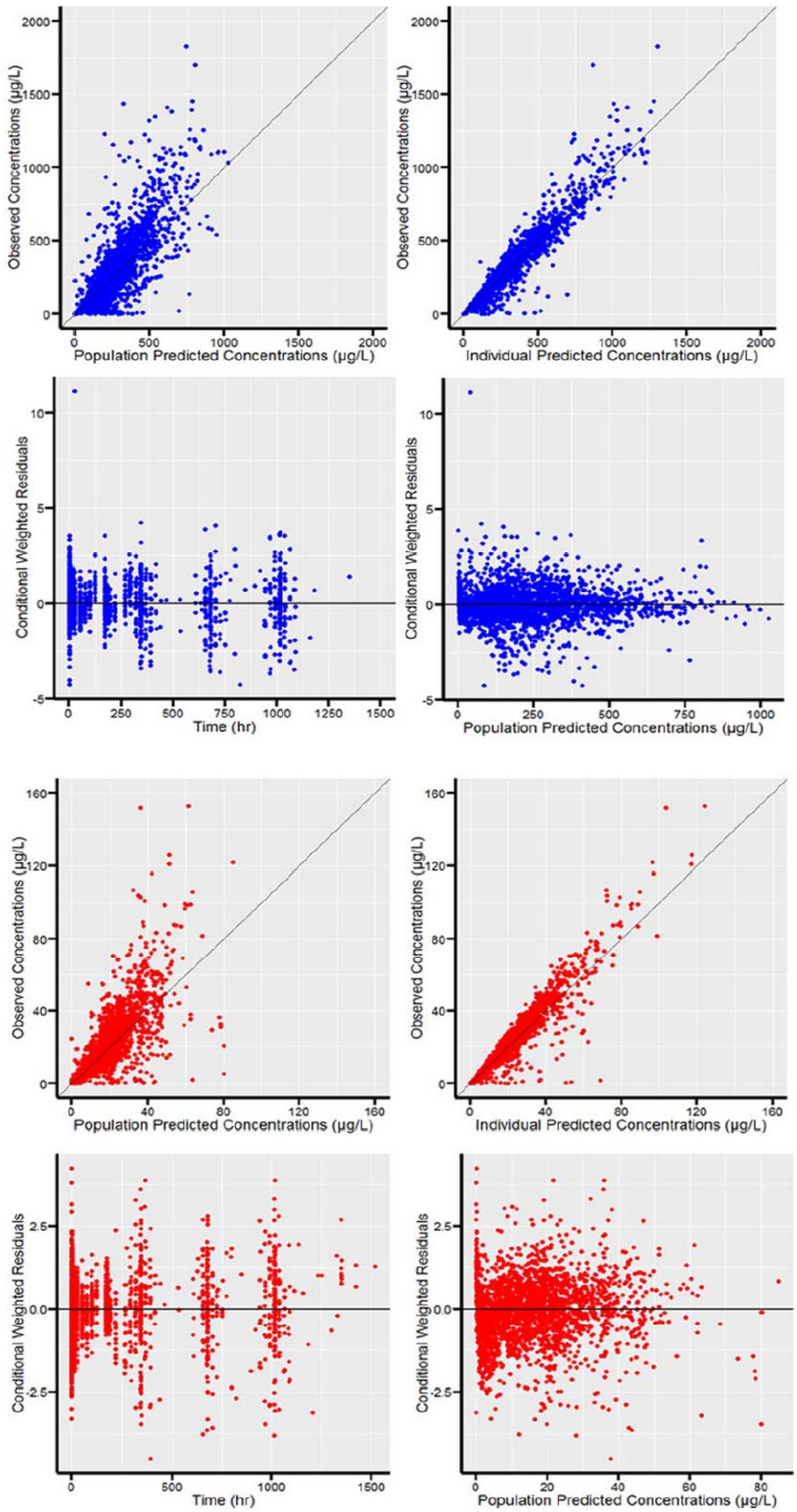
Note: The data were rounded to 3 significant figures.

Ka=first order absorption rate constant; t_{lag}=delay between time of dosing and time of appearance of measurable concentration of test article; CLp=NBI-98854 clearance from the systemic circulation; CLpm=NBI-98854 chemical transformation or metabolism into NBI-98782; CLm=clearance of NBI-98782; Qp=inter-compartmental clearance of NBI-98854; Qm=inter-compartmental clearance of NBI-98782; VCp=apparent volume of the central compartment of NBI-98854; VPp=apparent volume of the peripheral compartment of NBI-98854; VCm=apparent volume of the central compartment of NBI-98782; VPm=apparent volume of the peripheral compartment of NBI-98782; NE=not estimated; BSV=between subject variability; NA=not applicable.

Source: Population PK report(2016-PK-056) Table – 4 on Page 43

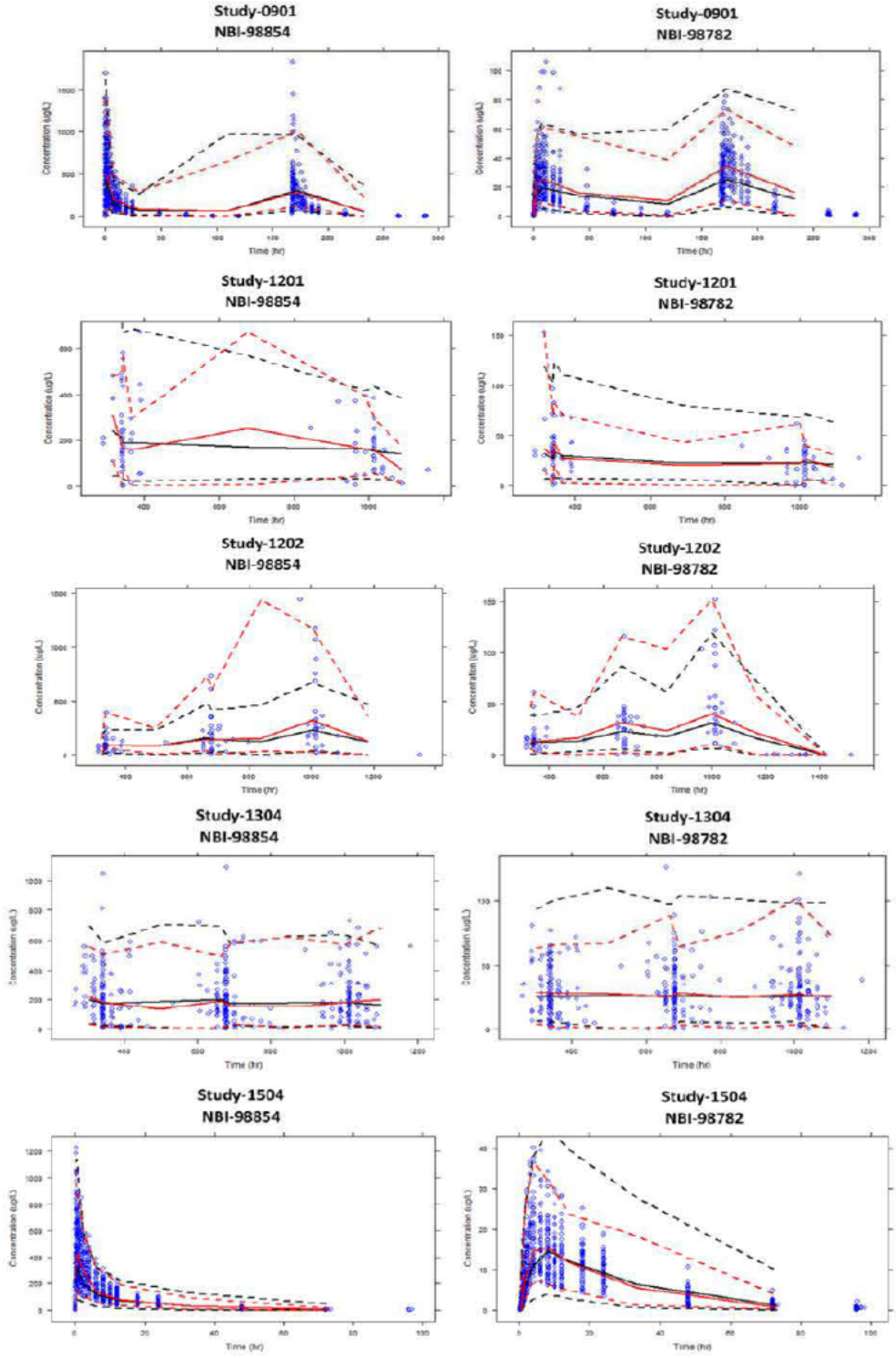
The qualification of the final PopPK model was performed using the goodness of fit plots, shown in **Figure 12** .Furthermore, the individual predictions from simulation of 500 replicates with same design using the population means and variability from the final PopPK model were overlaid with the observed data and visualized using Visual Predictive Check (VPC) shown in **Figure 13**.

Figure 12 – Goodness of fit plots for the final population PK model



Blue: Valbenazine, Red: NBI-98782;
Source: Population PK report(2016-PK-056) Table – 12 & 13 on Page 65 & 66

Figure 13: VPC of the final population PK model stratified based on the study



Note: open blue circles represent observed data; red solid and dotted lines represent the 2.5th, 50th and 97.5th percentiles of the observed data; black solid and dotted lines represent the 2.5th, 50th and 97.5th percentiles of the predicted data.

Source: Population PK report(2016-PK-056) Figure 21 on Page 73 & 74

Reviewer's comments:

*The sponsor modeled the PK data of both the Valbenazine and NBI-98782 simultaneously from all the studies listed in **Table 11**, which included both rich and sparse sampling designs. There are a few major issues with sponsor's PopPK analyses. Firstly, sparse PK samples were collected within 4-9 hours window post-dose from the phase 2 and 3 studies, and consequently, adequate characterization of model parameters from just a single observation close to 'Cmax' may be difficult and inaccurate, since it can be highly sensitive to the sampling timepoint. Furthermore, it should be noted that in studies 1201, 1202 and 1304, valbenazine was administered without regard to food and the sponsor reports impact of food on Cmax of Valbenazine (lowered by 40%), which in turn decreases NBI-98782 presumably. Owing to these factors, the results from the PopPK model should be interpreted with caution. This was also noted previously in the pre-NDA meeting minutes (02-04-2016, in response to question 8), when we expressed concern with accurately estimating the Cmax,ss using the sparse PK sampling scheme, especially when the doses were administered without regard to food. Secondly, the model parameter estimates shown in **Table 12** indicate that there is high between-subject variability and high shrinkage values for several of them. Additionally, the uncertainity in the estimation of these parameters was not reported and there are concerns with successful minimization and convergence to obtain the standard errors from the variance-covariance matrix upon re-running the sponsor's final PopPK model. This further raises concerns about the identifiability of the model and reliability of its parameter estimates.*

The covariate modeling results suggest that although the body weight was found to be a significant covariate on clearance of both valbenazine and NBI-98782, the magnitude of this impact (an approximate change of 20-30% in CL across the observed weight) was considered moderate and since the efficacy was similar across the different weight subgroups, it was not clinically meaningful. Based on this finding, the sponsor proposed not to adjust the doses based on the body weight. As mentioned above, since there are major issues with respect to the characterisitcs of the data and the development of the PopPK model, these analyses do not support the rationale for not adjusting the dose based on body weight. However, since the doses were not adjusted in any of the pivotal or supportive trials, similar dosing recommendation to not adjust for BW seems appropriate.

Additionally, CYP2D6 metabolizer status was found to be significant covariate on the clearance of NBI-98782, with PMs showing ~50% lower clearance than non-PMs. The sponsor did not find specific trends in the random effects for clearance of NBI-98782 and use of concomitant administration of mild, moderate or strong inhibitors of CYP2D6, and therefore, no further evaluation was conducted. Based on these findings, the sponsor proposed that the dose may be reduced to 40 mg when adding a strong CYP2D6 inhibitor to a stable valbenazine dose. The sponsor did not conduct a dedictated drug-drug interaction study using a strong CYP2D6 inhibitor (or in individuals who are PMs vs. non-PMs) to investigate its clinical impact and the recommendation was based solely on the estimate from the PopPK analyses, which has some

major issues described above. Owing to these reasons, there appears to be inconclusive evidence with regards to the precise magnitude difference in exposures of NBI-98782 in PMs vs. non-PMs, to support this labeling recommendation.

4.2.2. Reviewer's Analysis

Introduction

There are inherent limitations with the characteristics of the data and the PopPK analyses as described in detail above. Consequently, the reliability on the results of the PopPK model to support dosing recommendations seems inaccurate, specifically in the sub-population who are CYP2D6 PMs or subjects who are on concomitant medications which include strong CYP2D6 inhibitors. The reviewer performed independent analysis to assess the impact of CYP2D6 metabolizer status and concomitant use of CYP2D6 inhibitors on the exposures of NBI-98782 from the entire clinical development program of valbenazine.

Objective

- To evaluate the magnitude of the impact of CYP2D6 poor metabolizer status and concomitant use of CYP2D6 inhibitors on the exposures of NBI-98782

Datasets

Datasets used in the analyses are summarized in the **Table 13** below.

Table 13: Analysis Datasets

Study Number	Name	Link to EDR
2016-PK-056	pkmstrf.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\2016-pk-056\analysis\legacy\datasets
2016-PK-056	pkmstrfm.xpt	
NBI-98854-801	pk801.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-0801\analysis\legacy\datasets
NBI-98854-1102	pk1102.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-1102\analysis\legacy\datasets
NBI-98854-1203	pk1203.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-1203\analysis\legacy\datasets
NBI-98854-1204	pk1204.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-1204\analysis\legacy\datasets
NBI-98854-1302	pk1302.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-1302\analysis\legacy\datasets
NBI-98854-1403	pk1403.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-1403\analysis\legacy\datasets
NBI-98854-1203	pk1203.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\nbi-98854-1203\analysis\legacy\datasets

Software

The statistical software R version (3.3.1) were utilized for dataset compilation, analyses and generation of plots.

Methods

The observed concentrations of NBI-98782 were explored based on the CYP2D6 genetic polymorphism status, namely, poor-metabolizer (PMs) or non-PM (e.g., intermediate, rapid, ultra-rapid metabolizers, etc.) and concomitant CYP2D6 inhibitors as available from the studies included in the PopPK analyses dataset. Additionally, as noted in the late-cycle meeting minutes (07-02-2017, in response to question 2), the sponsor sent more information with respect to the PMs from other studies from their valbenazine development program in late-cycle meeting response (02-15-2017). These were also analysed in a similar way

Results

The observed concentrations of NBI-98782 in PMs relative to the NMs in various studies are shown in **Figures 14-18, 20-25** and dose-normalized concentrations in subjects who were non-PMs and on concomitant use of CYP2D6 inhibitors in study 1304 at week 6 is shown in **Figure 19**

Figure 14: Observed concentrations of NBI-98782 in Study 901 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

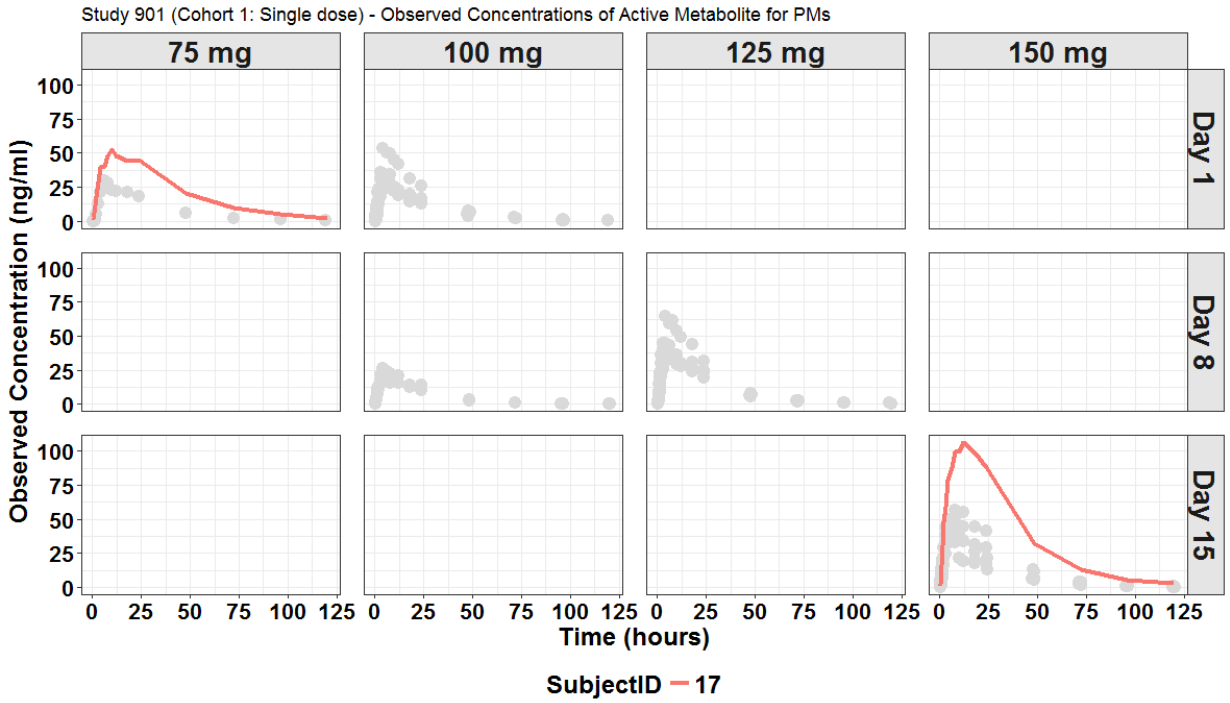


Figure 15: Observed concentrations of NBI-98782 in Study 901 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

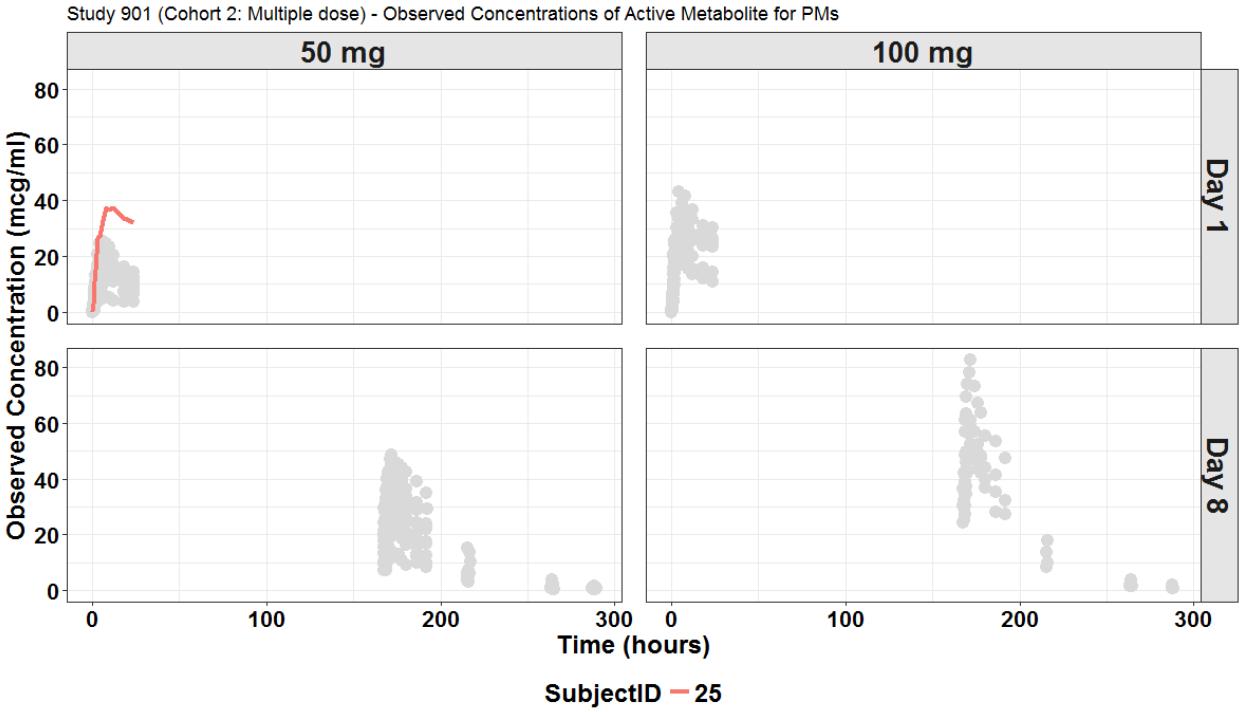


Figure 16: Observed concentrations of NBI-98782 in Study 1504 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

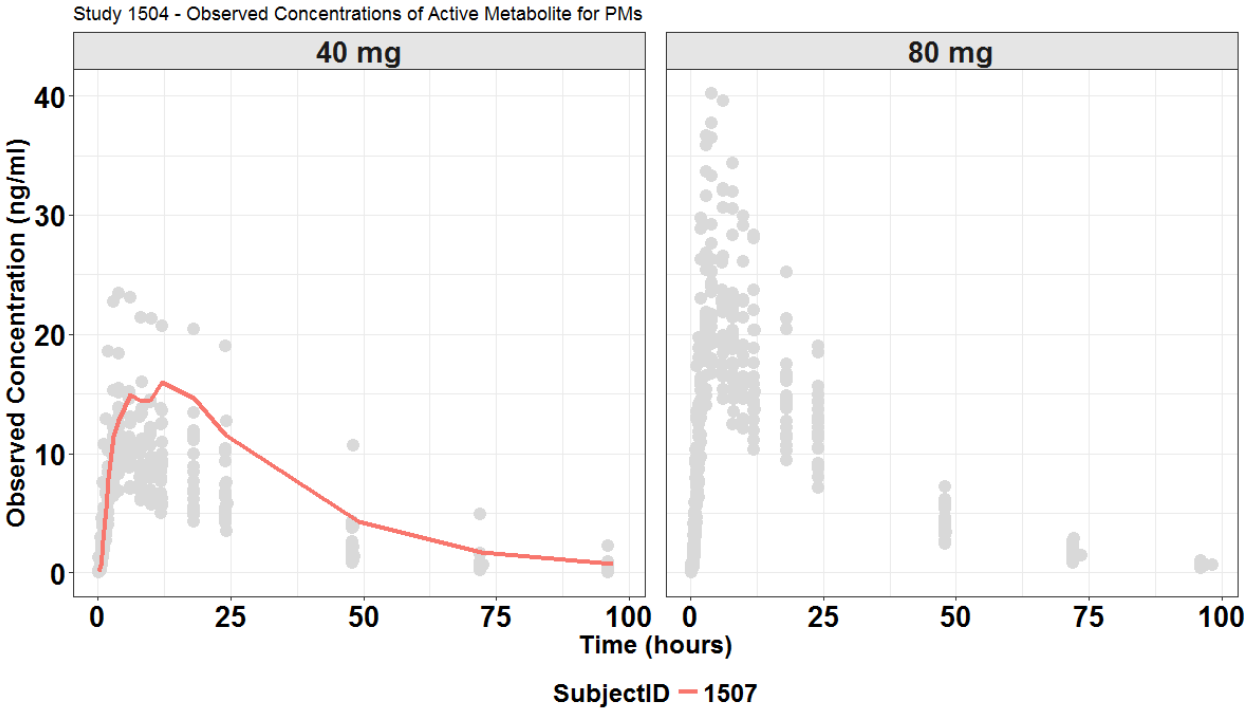


Figure 17: Observed concentrations of NBI-98782 in Study 1202 – Individuals who are PMs (in color) vs. non-PMs (in grey) – Reviewer's analyses

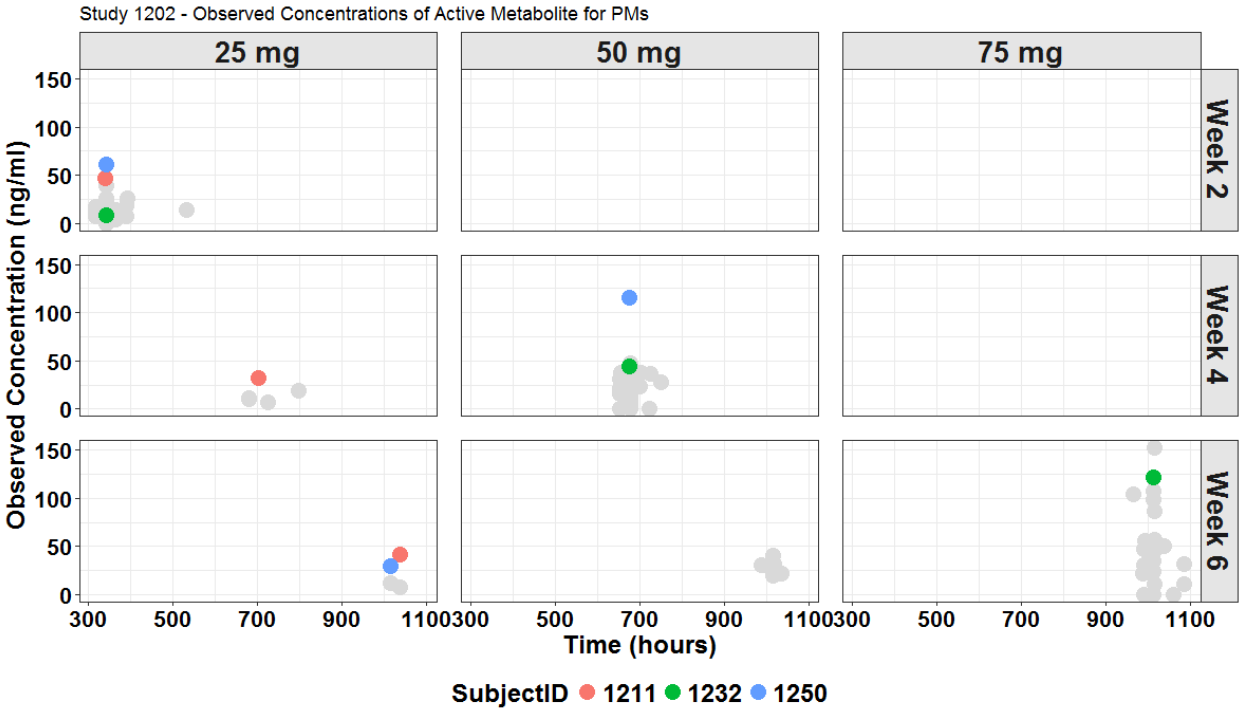


Figure 18: Observed concentrations of NBI-98782 in Study 1304 – Individuals who are PMs (in blue) vs. non-PMs (in red) – Reviewer's analyses

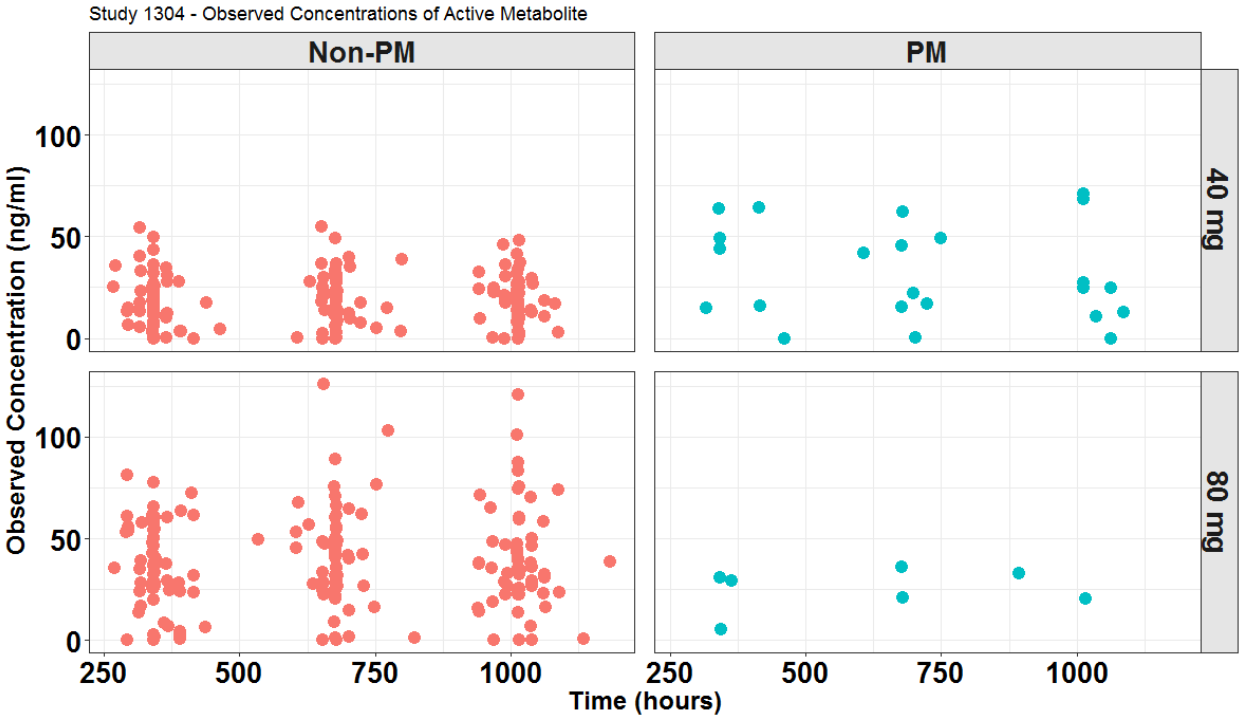


Figure 19: Observed concentrations of NBI-98782 in Study 1304 – Individuals who are on concomitant CYP2D6 inhibitors – Reviewer's analyses

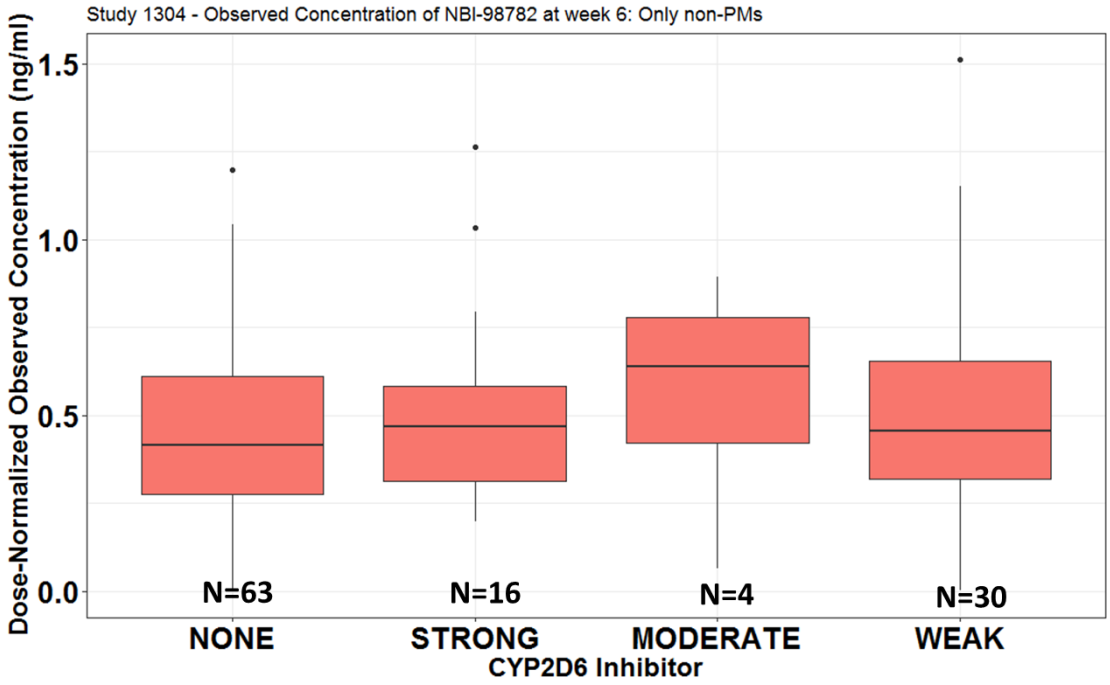


Figure 20: Observed concentrations of NBI-98782 in Study 801 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

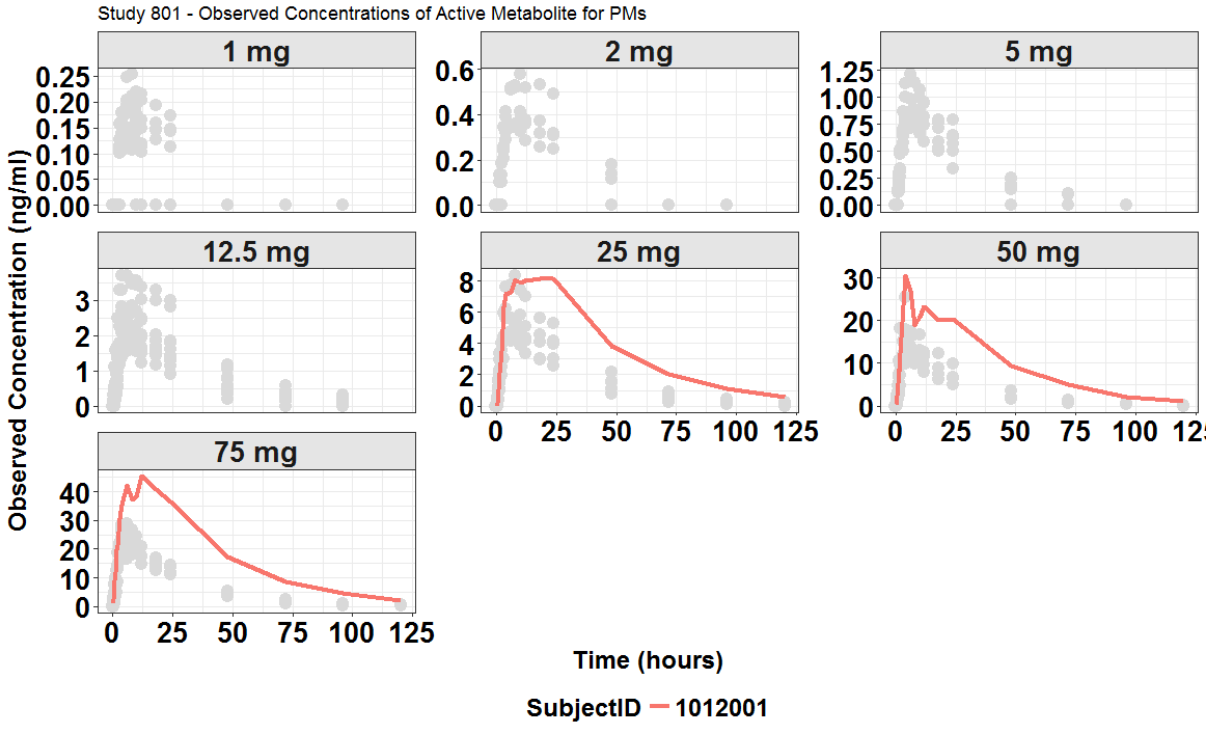


Figure 21: Observed concentrations of NBI-98782 in Study 1102 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

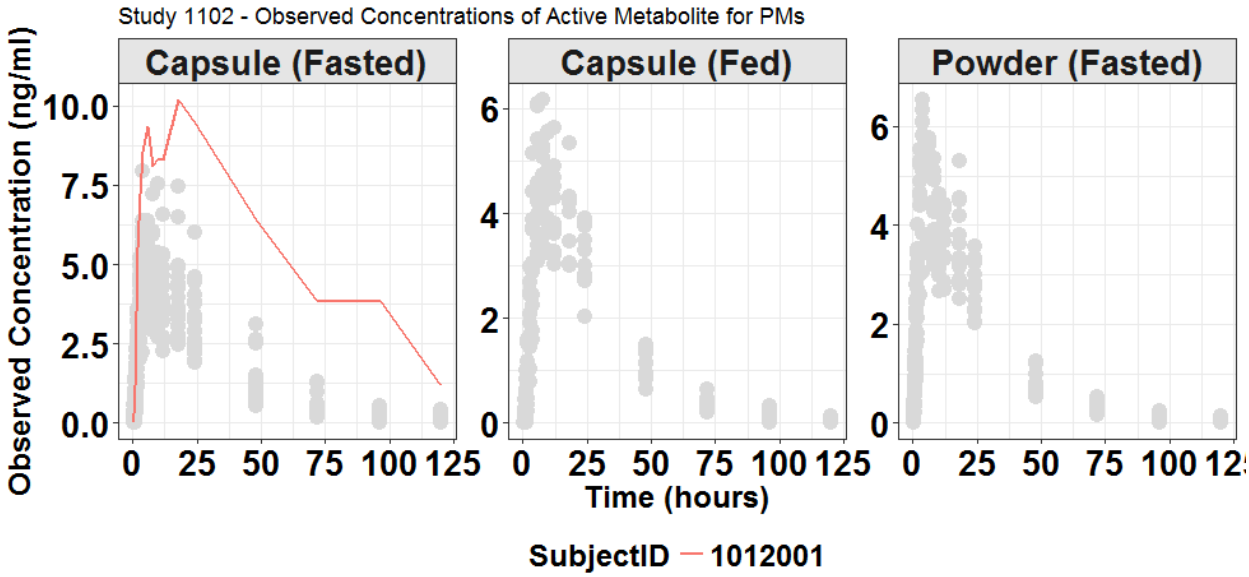


Figure 22: Observed concentrations of NBI-98782 in Study 1203 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

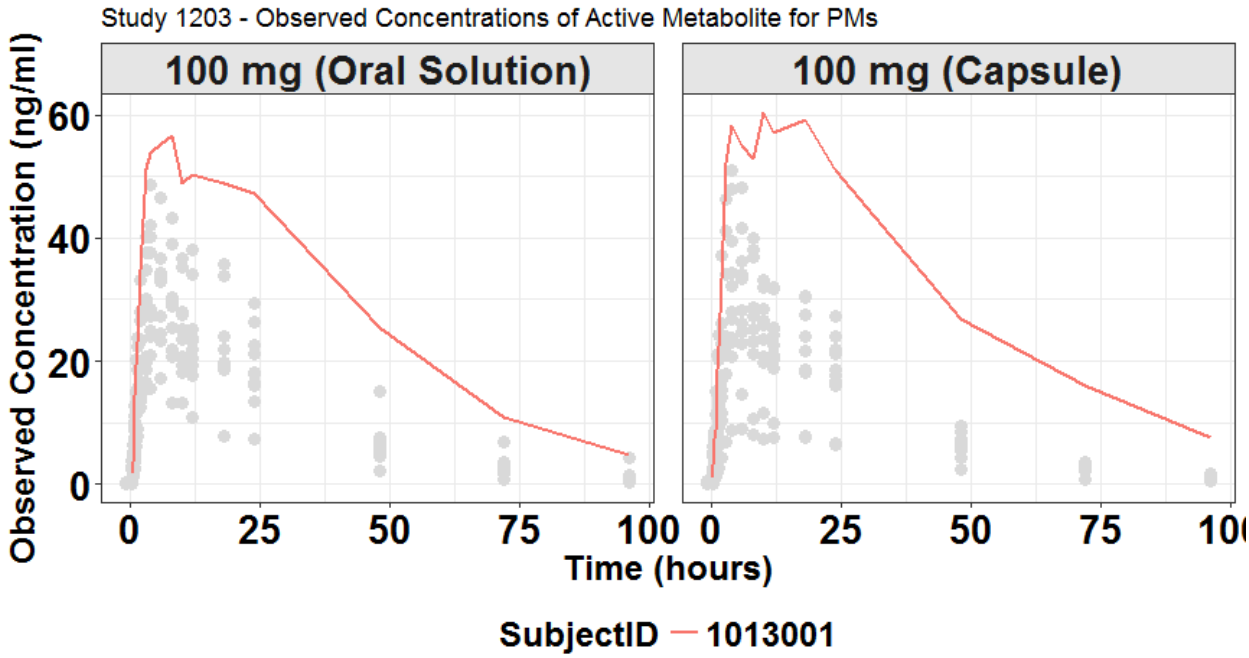


Figure 23: Observed concentrations of NBI-98782 in Study 1204 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

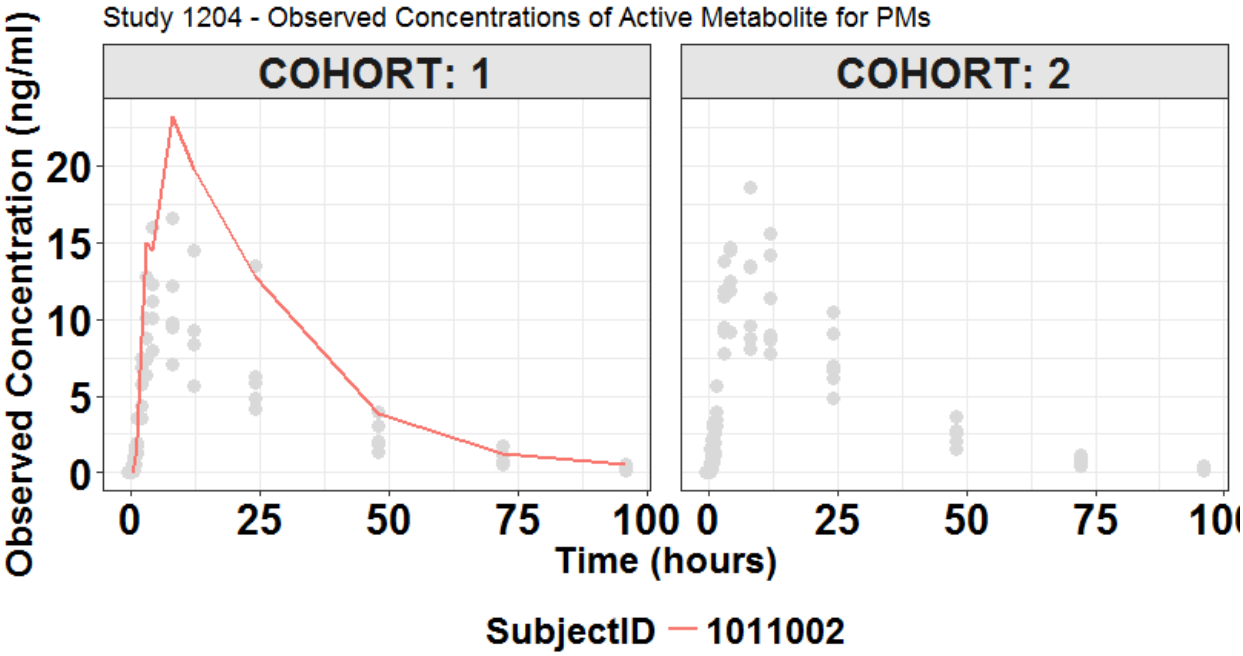


Figure 24: Observed concentrations of NBI-98782 in Study 1302 – Individuals who are PMs (in red line) vs. non-PMs (in grey) – Reviewer's analyses

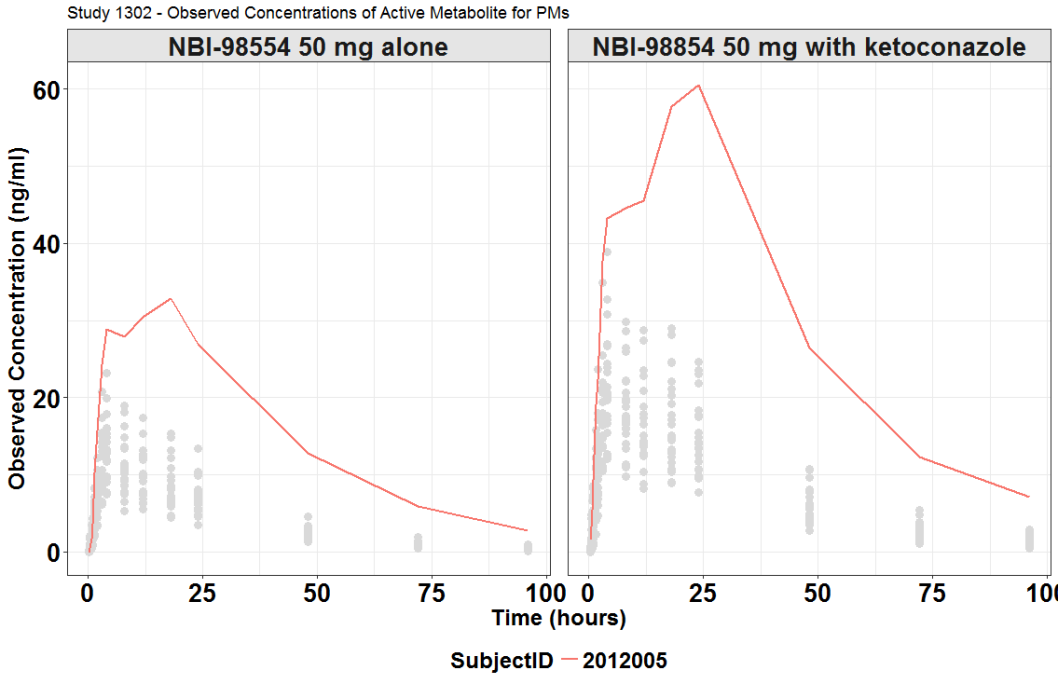
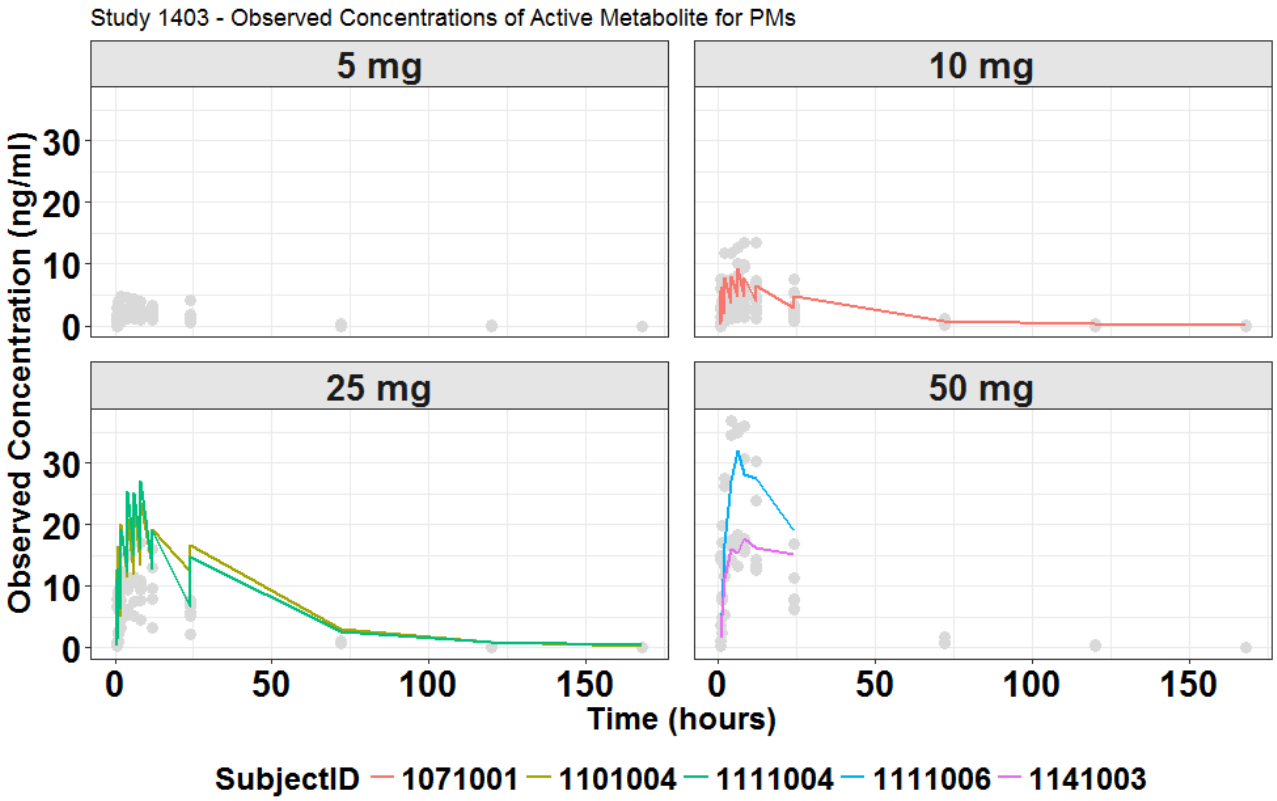


Figure 25: Observed concentrations of NBI-98782 in Study 1403 – Individuals who are PMs (in colored lines) vs. non-PMs (in grey) – Reviewer's analyses



From these figures, it can be observed that while in a few studies at certain doses with available information, the PMs seem to show approximately 2-fold higher exposures than the non-PMs in the respective studies, while in other studies this trend was not evident. On the other hand, no specific trend was not observed for subjects who were on concomitant CYP2D6 inhibitors. Owing to a diversity in the observed trends, varying from 2-fold higher exposures to no specific trends, a consistency was lacking to quantitatively assess the precise magnitude of the impact of CYP2D6 polymorphisms and/or concomitant CYP2D6 inhibitors from the current data. Therefore, the findings from this dataset and analyses appear inconclusive and cannot support the findings from the PopPK model and consequent dosing recommendation to reduce the dose in CYP2D6 PMs or in subjects who are on concomitant strong CYP2D6 inhibitors. Based on the *in-vitro* studies, NBI-98782 is known to be substrate for CYP2D6, and increased exposures in patients who are PMs or on concomitant CYP2D6 inhibitors are expected. Furthermore, NBI-98782 is structurally similar to α-dihydrotetrabenazine, which is one of the active metabolites of tetrabenazine, and is reported to have approximately 3-fold higher exposures in PMs than the non-PMs. Therefore, based on this prior knowledge, a dose reduction may be considered for subjects who are CYP2D6 PMs or who are on concomitant strong CYP2D6 inhibitors.

Overall, owing to the major concerns with the PopPK analyses, it is important to exercise caution when interpreting the simulated exposure metrics and utilizing them for the exposure-response analyses. For instance, relying on the exposure metrics (steady-state Cmax) predicted from the PopPK model that were used to estimate the mean changes in QTcF from baseline at therapeutic doses in PMs vs. non-PMs may lead to inaccurate conclusions in assessing the risks associated with prolongation of QTcF

List of Analysis Codes and Output files

Filename	Description	Link to PM Review Shared Drive
QBR_Plots.R	Exploration of the impact of CYP2D6 metabolizer status and concomitant CYP2D6 inhibitor on the exposures of NBI-98782 in the PopPK analyses dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Valbenazine_NDA209241_GG\FDA_Review\QBR
QBR_Plots_Appendix.R	Exploration of the impact of CYP2D6 metabolizer status on the exposures of NBI-98782 in individuals submitted as response to late-cycle meeting minutes	

4.3. Exposure-Response Analyses

4.3.1 Exposure-Efficacy Analyses

4.3.1.1. Sponsor's Exposure-Efficacy Analyses

Relationships were explored between exposure metrics (Cmax, AUC) of valbenazine and NBI-98782 and the percent change from baseline (%CFB) in Abnormal Involuntary Movement Scale (AIMS) score, the at the end of week 6 in TD patients from studies 1202 and 1304. These analyses were performed separately for each study due to the differences in trial design (titration in 1202 vs.fixed dose in 1304). Based on the parameter estimates from the PopPK model and week 6 doses of valbenazine, rick PK profiles were simulated to obtain the Cmax and AUC of valbenazine and NBI-98782. These exposure metrics were divided into placebo and 4 concentration bins (**Table 14**, and **Table 15** for valbenazeine and NBI-98782 respectively) and the shape of the association with the efficacy endpoint was investigated.

Table 14: Efficacy Endpoint at Week 6 by NBI-98782 Exposure (Cmax, AUC) Quantiles in Study 1304

Quantile No.	Mean Cmax (µg/L)	Mean %CFB in AIMS	N
0	0	7.97	67
1	14.64	0.92	30
2	24.22	-22.9	29
3	36.22	-26.03	29
4	58.87	-45.40	29

Quantile No.	Mean AUC (µg.hr/L)	Mean %CFB in AIMS	N
0	0	7.97	67
1	268.71	-9.09	30
2	478.02	-12.54	29
3	727.68	-28.14	29
4	1251.09	-43.29	29

Source: Population PK report(2016-PK-056) Figure 23 on Page 76

Table 15: Efficacy Endpoint at Week 6 by NBI-98782 Exposure (Cmax, AUC) Quantiles in Study 1202

Quantile No.	Mean C_{max} (µg/L)	Mean %CFB in AIMS	N
0	0	0.03	44
1	20.90	-46.16	9
2	31.92	-59.00	8
3	44.96	-63.85	8
4	77.53	-51.05	8

Quantile No.	Mean AUC (µg.hr/L)	Mean %CFB in AIMS	N
0	0	0.03	44
1	392.61	-39.12	9
2	651.81	-57.99	8
3	975.36	-67.58	8
4	1709.06	-56.25	8

Source: Population PK report(2016-PK-056) Figure 24 on Page 77

Clear trends in the exposure-response are observed for both valbenazine and NBI-98782 exposures. However, owing to the correlation between the exposures of the two, it was difficult

to discern the relative contributions of both the moieties. NBI-98782 exposures were chosen because it showed 7-fold higher potency than valbenazine, and is believed to be the active moiety contributing to efficacy and safety events.

For study 1304, a linear model was able to best describe and quantify the exposure–response relationship both Cmax and AUC of NBI-98782. The parameter estimates for this relationship is shown in **Table 16** and the model prediction was overlaid with the observed relationship shown in **Figure 26**

Table 16: Parameter Estimates for the Linear Model Used to Describe the Exposure-Response Relationship for NBI-98782 in Study 1304

Model	Placebo Effect (%)	Slope Estimate[a]	SD of Residual Variability
	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)
Cmax model	5.92 (102%)	-0.837 (19%) [%/µg/ml] (p-value <0.05)	54.6 (29%)
AUC model	4.47 (132%)	-0.0378 (20%) [%/µg*hr/ml] (p-value <0.05)	54.8 (29%)

[a] For treatment model, the slope estimate is the coefficient of treatment effect
%RSE: percent relative standard error = SE(standard error)*100/Mean;

Source: Population PK report(2016-PK-056) Table 7 on Page 45

For study 1202, an Emax model was used to describe and quantify the exposure-response relationship both for Cmax and AUC of NBI-98782. The parameter estimates for this relationship is shown in **Table 17** and the model prediction was overlaid with the observed relationship shown in **Figure 27.**

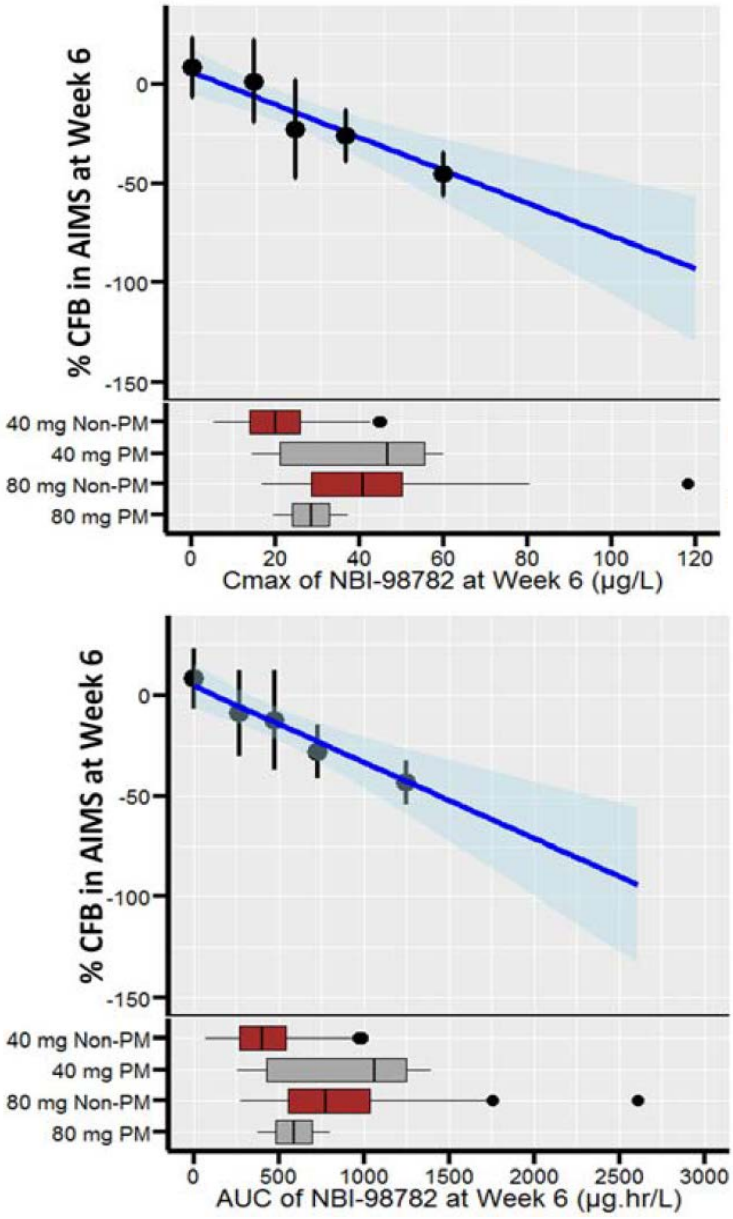
Table 17: Parameter Estimates for the E_{max} Model Used to Describe the Exposure-Response Relationship for NBI-98782 in Study 1202

Model	Placebo Score	E_{max}	EC_{50}	SD of Residual Variability
	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)
Cmax model	0.03 (Fixed)	-62.8 (34%)	4.88 (285%)	57.8 (24%)
AUC model	0.03 (Fixed)	-66.1 (37%)	141 (248%)	57.7 (24%)

E_{max}=maximum effect; EC_{50}=concentration of drug that gives half-maximal response; %RSE: percent relative standard error = SE(standard error)*100/Mean;

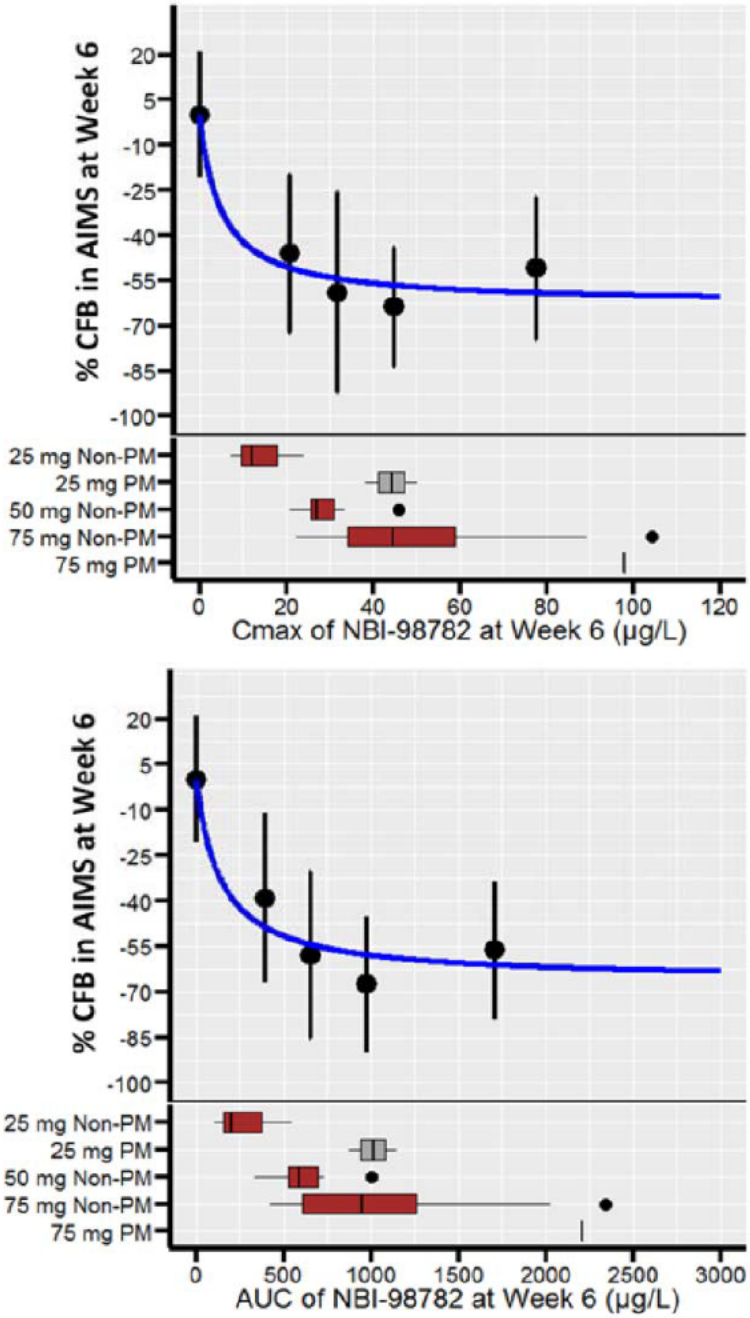
Source: Population PK report (2016-PK-056) Table 12 on Page 47

Figure 26: Exposure (Cmax, AUC) -Response for Efficacy at Week 6 for NBI-98782 – Study 1304



Source: Population PK report(2016-PK-056) Figure 23 on Page 76

Figure 27: Exposure (Cmax, AUC) -Response for Efficacy at Week 6 for NBI-98782 – Study 1202



Source: Population PK report(2016-PK-056) Figure 24 on Page 77

Reviewer's comment:

Clear trends between the exposures (Cmax and AUC) of NBI-98782 and primary efficacy endpoint are observed for both the studies 1202 and 1304. However, owing to the concerns with the PopPK analyses and its model parameter estimates as described in detail above, the results need to be interpreted with caution. Additionally, it should also be noted that valbenazine was dosed in both studies 1304 and 1202 without regard to food, and the sponsor reports decrease in Valbenazine Cmax (by 40%) when administered with food, which presumably results in lower Cmax of NBI-98782. The significance was also noted in the pre-NDA meeting minutes (02-04-2016, in response to question 8), when we expressed concern with accurately estimating the Cmax,ss using the sparse PK sampling scheme, especially when the doses were administered without regard to food.

Though the exposure-response model fits seem to be in reasonable agreement when overlaid with the observed data for both the studies, the parameter estimates in ***Table 16-Table 17*** *show high standard errors (%RSE) for placebo effect in study 1304 and had to be fixed for study 1202, while* EC_{50} *estimates showed high standard errors (%RSE) and the standard deviation for the residual variability is very high. Lastly, it seems plausible for the titration design of study 1202 to show* E_{max} *type exposure-response relationship as the subjects with clinical improvement on sub-maximal dose remained on the lower dose.*

The exposure-efficacy response relationship for NBI-98782 in study 1304 does not seem to plateau within the tested dose range of 80 mg suggesting a potential benefit with higher dose(s).

4.3.1.2. Reviewer's Exposure-Efficacy Analyses

Introduction

There are limitations with the sponsor's exposure-response analyses for the primary efficacy endpoint. It is not advisable to utilize the the exposure metrics (Cmax and AUC) derived from the PopPK analyses and its model parameter estimates owing to the concerns about the identifiability of the PopPK model and reliability of its parameter estimates. The reviewer performed independent exposure-efficacy analyses using the geometric mean of the observed concentrations ("Cmax") of NBI-98782 at weeks 2, 4 and 6 in study 1304 (as it was a pivotal trial and has a fixed dose design, facilitating easy interpretation of the exposure-response relationship) and using it as the exposure metric.

Objective

- To evaluate the exposure efficacy response relationship using the geometric mean of the observed concentrations ("Cmax") of NBI-98782 at 2, 4, 6 weeks in study 1304

Datasets

Datasets used in the analyses are summarized in the **Table 18** below.

Table 18: Analysis Datasets

Study Number	Name	Link to EDR
2016-PK-056	er134m.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\2016-pk-056\analysis\legacy\datasets
2016-PK-056	pkmstrfm.xpt	

Software

The statistical software NONMEM (version 7) and R version (3.3.1) were utilized for dataset compilation, analyses and generation of plots.

Methods

The observed concentrations of NBI-98782 at weeks 2, 4, 6 were explored for variability in study 1304 as a whole and also within each individual. In general, the concentrations at those time points seem to be within ± 30% range for most of the individuals suggesting it was reasonable to explore the geometric mean across the time intervals as an exposure metric for exposure-efficacy response analyses.

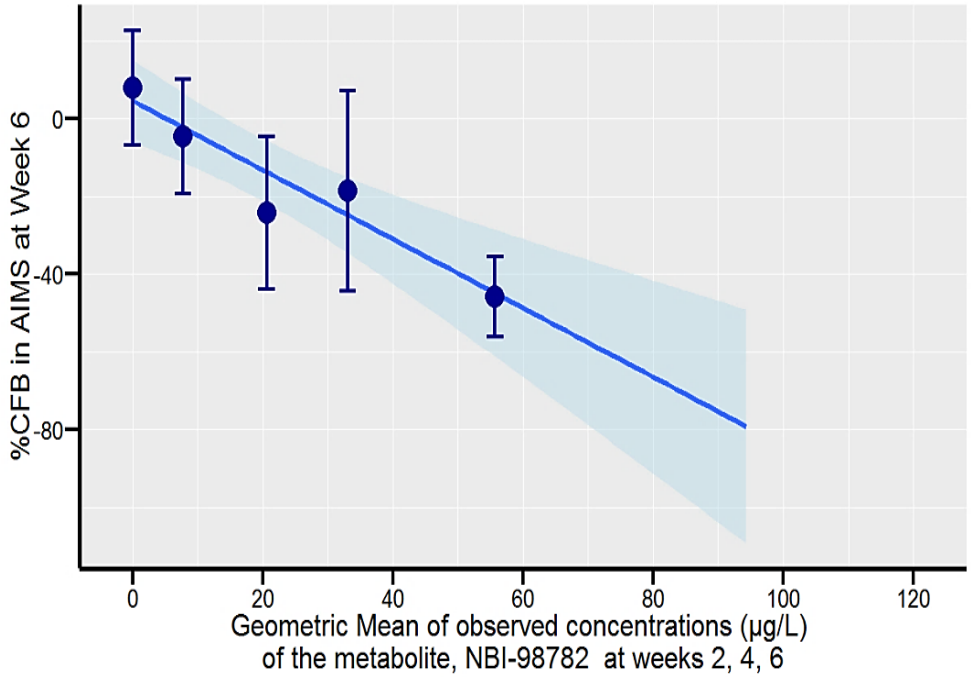
Results

The fit (**Figure 28**)and the parameter estimates (**Table 19**)for the exposure-response model based on the geometric mean of the observed concentrations at weeks 2, 4 and 6 was comparable to the sponsor's analyses. Therefore, the interpretation of the final exposure-efficacy analyses and its final conclusion for study 1304 remain unchanged. The exposure-response response analyses from the pivotal phase 3 study 1304 is consistent with the observed dose-response relationship.

Table 19: Parameter Estimates for the Linear Model Used to Describe the Exposure-Response Relationship of NBI-98792 in Study 1304 – Reviewer's analysis

Model	Placebo Effect (%)	Slope Estimate[a]	SD of Residual Variability
	Estimate (%RSE)	Estimate (%RSE)	Estimate (%RSE)
Reviewer's analysis: Geometric mean of observed conc.	*4.61 (120%)*	*-0.888 (18%) [%/µg/ml] (p-value <0.05)*	*54.5 (15%)*
Sponsor's model: Cmax from PopPK model	5.92 (102%)	-0.837 (19%) [%/µg/ml] (p-value <0.05)	54.6 (29%)

Figure 28: Exposure –Response for Efficacy of NBI-98782 for Study 1304 – Reviewer's analysis



No further analysis was performed for exposure-response analysis of efficacy using AUC as the exposure metric (as there was only single observed concentrations at each time point) for study 1304.

Reviewer's Note:

Based on the reviewer's analyses, the (dose/)exposure-response for efficacy analyses do not seem to plateau within the tested dose range. Hence, subject to the safety/tolerability profiles, there can be substantial merit in testing if dose(s) higher than 80 mg can confer additional therapeutic benefit for patients with tardive dyskinesia.

List of Analysis Codes and Output files

Filename	Description	Link to PM Review Shared Drive
E-R_Valbenazine.R	E-R analyses for efficacy with data from study 1304 – Dataset generation and analysis (in R)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Valbenazine_NDA209241_GG\ER_Analysis\
ER1304MGeommean.csv	Dataset for E-R efficacy analyses for study 1304 – using geometric mean of the observed concentrations as exposure metric	
Run4.mod	E-R model for efficacy for study 1304 – using ER1304MGeommean.csv dataset and in NONMEM	
Run4.lst	Output file for run4.mod	

4.3.2. Exposure-Safety Analyses

4.3.2.1. Sponsor's Exposure-Safety Analyses

Relationships were explored between exposures of valbenazine and NBI-98782 and the various safety endpoints (BARS – Barnes Akathisia Rating Scale; CDSS – Calagary Depression Rating Scale; MADRS – Montgomery-Asberg Depression Rating Scale; SAS – Simpson Angus Scale, Prolactin levels) at the end of week 6 in TD patients from studies 1202 and 1304. These analyses

were also performed separately for each study due to the differences in trial design. The exposure metrics, Cmax and AUC of valbenazine/NBI-98782, were derived from rich PK profiles simulated using the final PopPK model parameter estimates and using week 6 valbenazine doses. The exposure metrics were divided into placebo and 4 concentration bins and the shape of the association was explored with the proportion of subjects who had occurrence of the event for each of the safety.

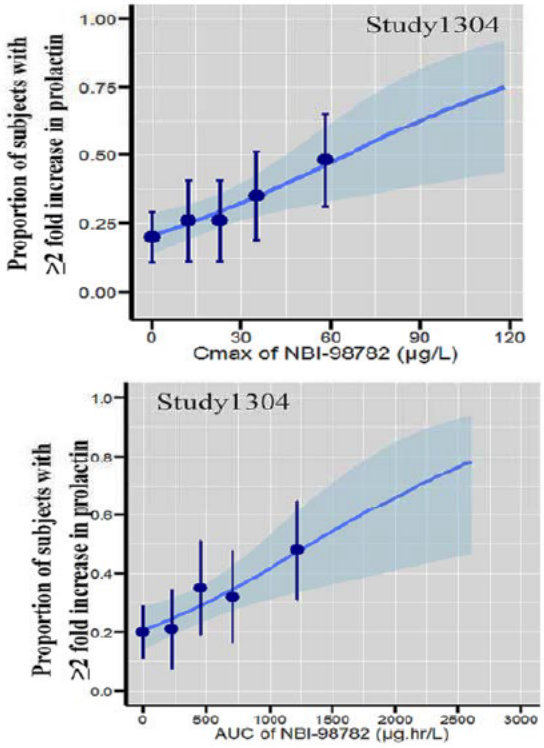
Clear trends were observed for proportions of subjects with ≥2-fold increase in prolactin concentrations and exposures (Cmax, AUC) of the NBI-98782 in study 1304 and the quantiles are shown in **Table 20** and the associations was quantified using logistic regression modeling. The exposure-safety relationship for the proportion of subjects with ≥2-fold increase in prolactin concentrations is shown in **Figure 29** and model parameters are shown in **Table 21**.

Table 20: Proportion of Subjects with ≥2-Fold Increase in Prolactin Concentrations at Week 6 and NBI-98782 Exposure (Cmax, AUC) Quantiles in Study 1304

Quantile No.	Mean Cmax (µg/L)	Proportion ≥2-fold prolactin change 1304	N
0	0	0.20	75
1	12.55	0.26	34
2	22.98	0.26	34
3	34.94	0.35	34
4	58.02	0.48	33

Quantile No.	Mean AUC (µg.hr/L)	Proportion ≥2-fold prolactin change 1304	N
0	0	0.20	75
1	226.87	0.21	34
2	450.51	0.35	34
3	702.65	0.32	34
4	1226.03	0.48	33

Figure 29: Proportion of Subjects with ≥2-Fold Increase in Prolactin Concentrations at Week 6 versus NBI-98782 Exposure (Cmax, AUC) in Study 1304



Source: Population PK report(2016-PK-056) Figure 39 & 40 on Page 92 & 93

Table 21: Logistic Regression Parameter Estimates for Proportion of Subjects with ≥2-Fold Increase in Prolactin Concentrations at Week 6 versus Exposure (Cmax & AUC) of NBI-98782 in Study 1304

Exposure Metric	Parameter	Estimate	95%CI
C_{max} of NBI-98782	Intercept	-1.356	-1.822, -0.922
	Slope	0.0208	0.0071, 0.0351
AUC of NBI-98782	Intercept	-1.353	-1.8092, -0.9284
	Slope	0.001017	0.00037, 0.00169

Source: Population PK report(2016-PK-056) Table 20 on Page 52

Based on the exposure-safety logistic model for proportion of subjects with ≥2-fold increase in prolactin concentrations, 10 µg/ml increase in Cmax of NBI-98782 translates to an increase in the odds of observing an event by 23%; while an increase in 1000 µg.hr/ml increase in AUC of NBI-98782 translates to an increase in odds of observing an event by 50%

Reviewer's comment:

Clear trends between the exposures (Cmax and AUC) of NBI-98782 and proportion of subjects with ≥2-fold in prolactin concentrations at week 6 were observed for study 1304. However, owing to the concerns with the PopPK model and its parameter estimates as described in detail above, utilization of the Cmax and AUC derived from it maybe inappropriate and need to interpreted with caution. Similar to the discussion in exposure-efficacy response analyses, since valbenazine was dosed in study 1304 without regard to food and given the sponsor's finding of lower Cmax of Valbenazine (by 40%) and consequently lower NBI-98782, it is even more important to carefully interpret the results.

4.3.2.2. Reviewer's Exposure-Safety Analyses

Introduction

There are limitations with the sponsor's exposure- safety response analyses. It is not advisable to utilize the the exposure metrics (Cmax and AUC) derived from the PopPK model and its parameter estimates owing to the concerns about the identifiability of the PopPK model and reliability of its parameter estimates. The reviewer performed independent exposure-safety analyses for the proportion of subjects with ≥2-fold increase in prolactin concentrations using the geometric mean of the observed concentrations ("Cmax") of NBI-98782 at weeks 2, 4 and 6 in study 1304 and using it as the exposure metric.

Objective

- To evaluate the exposure safety response relationship using the geometric mean of the observed concentrations ("Cmax") of NBI-98782 at 2, 4, 6 weeks in study 1304

Datasets

Datasets used in the analyses are summarized in the **Table 22** below.

Table 22: Analysis Datasets

Study Number	Name	Link to EDR
2016-PK-056	er134m.xpt	\\cdsesub1\evsprod\NDA209241\0002\m5\datasets\2016-pk-056\analysis\legacy\datasets
2016-PK-056	pkmstrfm.xpt	
2016-PK-056	PRL21304.xpt	

Software

The statistical software R (version 3.3.1) were utilized for dataset compilation, analyses and generation of plots.

Methods

The observed concentrations of NBI-98782 at weeks 2, 4, 6 were explored for variability in study 1304 as a whole and also within each individual. In general, the concentrations at those time points seem to be within ± 30% range for most of the individuals suggesting it was reasonable to explore the geometric mean across the time intervals as an exposure metric for exposure-safety response analyses.

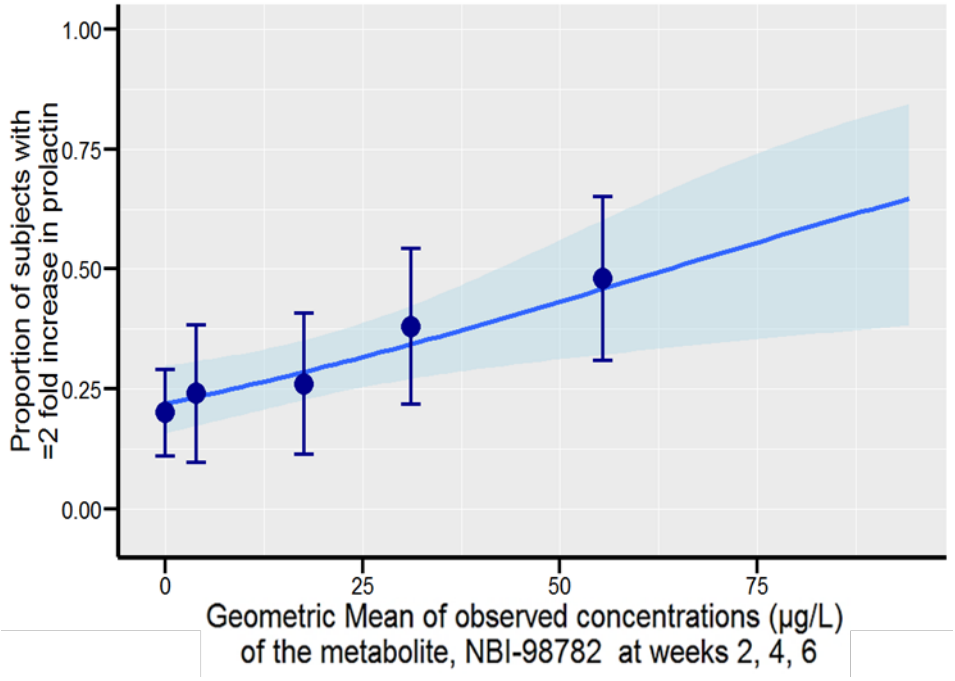
Results

The fit (**Figure 30**)and the parameter estimates (**Table 23**)for the exposure response model based on the geometric mean of the observed concentrations at weeks 2, 4 and 6 was comparable to the sponsor's analyses. Based on the reviewer's exposure-safety logistic model for proportion of subjects with ≥2-fold increase in prolactin concentrations, 10 µg/ml increase in Cmax of NBI-98782 translates to an increase in the odds of observing an event by 26 %, which was comparable to sponsor's odd of observing an event by 23%. Therefore, the interpretation of the sponsor's exposure-safety analyses and its final conclusion for study 1304 remain unchanged.

Table 23: Logistic Regression Results of Exposure (Geometric Mean of NBI-98782 Exposure (Cmax)) – Safety for Proportion of Subjects with ≥2-Fold Increase in Prolactin Concentrations in Study 1304 – Reviewer's Analysis

Exposure Metric	Parameter	Estimate	95%CI
C_{max} of NBI-98782	*Intercept*	*-1.266*	*-1.694, -0.865*
(Reviewer's results)	*Slope*	*0.01988*	*0.0060, 0.0341*
C_{max} of NBI-98782	Intercept	-1.356	-1.822, -0.922
(Sponsor's results)	Slope	0.0208	0.0071, 0.0351

Figure 30: Exposure (Geometric Mean of NBI-98782 Exposure (Cmax)) – Safety for Proportion of Subjects with ≥2-Fold Increase in Prolactin Concentrations in Study 1304 – Reviewer's Analysis



No further analysis was performed for exposure-response analysis of safety using AUC as the exposure metric (as there was only single observed concentrations at each time point) for study 1304.

List of Analysis Codes and Output files

Filename	Description	Link to PM Review Shared Drive
E-R_Valbenazine.R	E-R analyses for safety with data from study 1304 – Dataset generation and analysis (in R)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Valbenazine_NDA209241_GG\ER_Analysis

4.4 Individual Study Summaries

Note: Reviews for 4.1 and 4.4 will be finalized in DARRTS separately.

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

/s/

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03/06/2017

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