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RESEARCH**

APPLICATION NUMBER:

209241Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 209241, Ingrezza (valbenazine) 40mg Capsules

Product Name:

PMR/PMC Description: Conduct an in vitro study to assess the induction potential of NBI-136110 on CYP2B6 enzyme.

PMR/PMC Schedule Milestones: Final Protocol Submission: 12/30/2017
(PMR 3177-1)

Study/Trial Completion: 07/30/2018

Final Report Submission: 12/30/2018

Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

NBI-136110 is not an active metabolite of valbenazine. But it is a major circulation moiety. This in-vitro study will be used to test induction potential of NBI-136110 on CYP2B6 enzyme and so the study can be done post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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. The goal is to assess the *in-vitro* induction potential of NBI-136110 on CYP2B6 enzyme.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In-vitro drug interaction study using human biomaterials

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

In-vitro drug interaction study using human biomaterials

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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 in the current submission. 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.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This will be 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).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Study pharmacokinetics in subjects either in the presence of a strong CYP2D6 inhibitor or in subjects who are CYP2D6 poor metabolizers (PMs)
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This will be a pharmacokinetics trial in subjects with severe renal impairment. The study will be conducted in subjects with severe renal impairment (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

Study pharmacokinetics in subjects with severe renal impairment

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 209241, Ingrezza (valbenazine) 40mg Capsules

Product Name:

PMR/PMC Description:
(PMR# 3177-4)

Evaluate the potential for clinical dependence and withdrawal symptoms associated with valbenazine. Implement the following assessments in a current or future study in which subjects will receive valbenazine treatment (40 and 80 mg/day) for at least four consecutive weeks: Administer withdrawal scales, assess for withdrawal-related AEs, and monitor vital signs on the last day of treatment, day 1 off-treatment, every other day thereafter for the first week, and then 2-3 times weekly for two additional weeks.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/31/2018</u>
	Study/Trial Completion:	<u>01/31/2019</u>
	Final Report Submission:	<u>01/31/2020</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This PMR to evaluate for withdrawal symptoms was driven by the lack of evaluation of short-term (e.g., days to weeks) withdrawal symptoms in clinical trials and the theoretical concern based on animal findings of increased activity at trough drug levels. It is not a pre-approval requirement because the lack of safety findings four weeks post-withdrawal suggests the concerns are not substantial enough to delay market entry for the first treatment for tardive dyskinesia.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Existing human clinical studies do not assess for the existence of short-term withdrawal symptoms following valbenazine discontinuation. Rodent studies found increased activity at trough drug levels. It is important to assess whether there are any short-term withdrawal symptoms in humans so appropriate information could be added to product labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Visits and assessments will be added to the end of existing clinical studies (NBI-98854-1304 and -1402) for patients who have not yet completed study participation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Additional visits and assessments will be included for ongoing clinical studies.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 209241, Ingrezza (valbenazine) 40mg Capsules
Product Name: _____

PMR/PMC Description: (PMC# 3177-5) Perform a randomized controlled trial to assess whether a higher dose would confer additional therapeutic benefit. You may consider a design in which subjects with an inadequate response to valbenazine 80 mg are randomized to continue the 80 mg dose or receive a higher dose. Depending on findings from the clinical pharmacology study evaluating the effect of CYP2D6 inhibition on plasma concentrations, CYP2D6 poor metabolizers may be excluded from this trial to reduce the risk for exposure-related adverse events such as QT prolongation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2019</u>
	Trial Completion:	<u>03/2023</u>
	Final Report Submission:	<u>03/2024</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The Clinical Pharmacology and Clinical reviews both concluded that there may be a potential for an improved benefit/risk ratio with a higher dose of valbenazine in some patients. It would not be reasonable to institute this as a pre-approval requirement, as it would delay market entry for the first treatment for tardive dyskinesia.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Clinical pharmacology dose/exposure/response analyses, a clear dose-response relationship for response to 40 mg vs. 80 mg daily, and the existence of a substantial proportion of patients with residual TD symptoms suggests trial of a higher dose may be warranted for evaluating the benefit/risk ratio.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized controlled trial is being requested. The trial can include a design in which subjects with an inadequate response to valbenazine 80 mg/day are randomized to continue 80 mg/day or receive a higher dose. Depending on findings from the clinical pharmacology study (PMR) evaluating the effect of CYP2D6 inhibition on plasma concentrations, CYP2D6 poor metabolizers may be excluded from this trial to reduce the risk for exposure-related adverse events such as QT prolongation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

The rationale for this PMC was based on the fact that in Study NBI-98854-1304, a subset of subjects did not appear to return to baseline tardive dyskinesia severity following discontinuation of valbenazine for 4 weeks. This raises the possibility that a subset of patients may not require chronic treatment with valbenazine for suppression of tardive dyskinesia symptoms. This could be important for labeling and maximizing the benefit/risk ratio. Exploratory analyses conducted by the Applicant and the review team suggested the absence of continued antipsychotic use might predict whether subjects fully relapsed following valbenazine discontinuation. This proposed randomized withdrawal study, stratified by antipsychotic use, will help address this question.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized withdrawal trial. Subjects who have demonstrated an adequate response to valbenazine treatment for reduction in tardive dyskinesia symptoms will be randomized to continue their current valbenazine dose vs. placebo, and tardive dyskinesia symptoms will be assessed for recurrence. Subjects should be stratified based on continued antipsychotic usage, as exploratory analyses conducted by the Applicant and the clinical review team suggest this might be a predictor of relapse extent.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 209241, Ingrezza (valbenazine) 40mg Capsules

Product Name:

PMR/PMC Description: (PMC# 3177-7) To provide evidence as to whether improvement on the AIMS total dyskinesia scale translates into long-term functional improvements, perform a trial to address this question. Given the functional heterogeneity of patients with TD, it will be important to select an appropriate patient population and outcome measures. As discussed at the late-cycle meeting, one potential measure could assess social isolation.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2018</u>
	Trial Completion:	<u>04/2020</u>
	Final Report Submission:	<u>04/2021</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There was adequate evidence to support initial drug approval at this time based on the primary efficacy endpoint (change in AIMS total dyskinesia score at the end of Week 6). The review issue was deemed not significant enough to delay market entry for the first approved treatment for tardive dyskinesia. At the Late Cycle Meeting, the Applicant reported they are conducting a non-treatment clinical study assessing for common functional problems associated with tardive dyskinesia (i.e., social isolation). Their findings will help design the post-marketing study to best capture functional benefits, considering the heterogeneity of individuals with tardive dyskinesia.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue prompting this PMC was that although valbenazine treatment was associated with a decrease on the Abnormal Involuntary Movement Scale at the end of Week 6, it was not shown whether improvement on this scale translates into desired long-term functional improvements. The goal of this PMC would be for a study to be performed to assess whether patients treated with valbenazine show improvement on a common functional problem associated with tardive dyskinesia (such as social isolation), as compared to placebo. This would further substantiate the presumed clinical meaningfulness of improvements observed in studies submitted with the NDA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized controlled trial. The trial should assess an outcome measure related to a functional problem associated with tardive dyskinesia (i.e., social isolation).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

JASMEET K KALSI
04/10/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 10, 2017

To: Mitchell Mathis, MD
Director
Division of Psychiatry Products (DPP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Lisa Hubbard, Rph, RAC
Deputy Director, Division of Professional Drug Promotion
Office of Prescription Drug Promotion (OPDP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Christine Bradshaw, PharmD, PRS
Regulatory Reviewer Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): INGREZZA (valbenazine)

Dosage Form and Route: Capsules, for oral use

Application Type/Number: NDA 209241

Applicant: Neurocrine Biosciences, Inc.

1 INTRODUCTION

On August 11, 2016, Neurocrine Biosciences, Inc., submitted for the Agency's review part two of a rolling review, to the original New Drug Application (NDA) 209241 for INGREZZA (valbenazine) capsules, for oral use. INGREZZA (valbenazine), a new molecular entity, is a selective, orally active, vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of tardive dyskinesia. INGREZZA (valbenazine) capsules, for oral use, was granted fast track designation by the Division of Psychiatry Products (DPP) in January 2012 and breakthrough therapy designation in October 2014.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry Products (DPP) on September 09, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for INGREZZA (valbenazine) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft INGREZZA (valbenazine) PPI received on August 25, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 06, 2017.
- Draft INGREZZA (valbenazine) Prescribing Information (PI) received on August 11, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 06, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
03/10/2017

CHRISTINE J BRADSHAW
03/10/2017

BARBARA A FULLER
03/10/2017

LASHAWN M GRIFFITHS
03/10/2017

MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 7, 2017
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 209241
Product Name and Strength: Ingrezza (valbenazine) capsules
40 mg
Submission Date: February 28, 2017
Applicant/Sponsor Name: Neurocrine Biosciences, Inc.
OSE RCM #: 2016-2015-1
DMEPA Primary Reviewer: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Psychiatry Products (DPP) requested that we review the revised container labels, blister labels and carton labeling for Ingrezza (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review.^{a,b}

2 CONCLUSION

The revised container labels, blister labels and carton labeling for Ingrezza are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Holmes, L. Label and Labeling Review for Ingrezza (NDA 209241). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Feb 02. 9 p. OSE RCM No.: 2016-2015.

(b) (4)

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/s/

LORETTA HOLMES
03/07/2017

LOLITA G WHITE
03/09/2017



Food and Drug Administration
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date: March 6, 2017

From: Tamara Johnson, MD, MS
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne Yao, MD
Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products (DPP)

Drug: Ingrezza (valbenazine)

NDA: 209241

Applicant: Neurocrine Biosciences, Inc.

Drug Class: vesicular monoamine transporter 2 (VMAT2)

Indication: For treatment of adults with tardive dyskinesia

Subject: Pregnancy and Lactation Labeling Rule (PLLR) compliance

Submission Date: August 11, 2016

Consult Date: September 6, 2016

Consult Request: Assistance with labeling revision consistent with PLLR

PURPOSE

The purpose of the memorandum is to acknowledge the input of the Division of Pediatric and Maternal Health (DPMH) on labeling recommendations in order to bring the Ingrezza labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format and content requirements.

BACKGROUND

The Pregnancy and Lactation Labeling Rule

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect.¹ The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

RECOMMENDATIONS

DPMH revised the highlights and subsections 8.1, 8.2, 8.3, and 17 of the Ingrezza labeling for compliance with the PLLR. DPMH labeling recommendations were conveyed to DPP in January 2017. DPMH agrees with the PLLR labeling for Ingrezza and refers the reader to the final NDA action for the final labeling.

¹ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

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/s/

TAMARA N JOHNSON
03/06/2017

LYNNE P YAO
03/06/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 2, 2017

To: Gioia Guerrieri, MD, Clinical Reviewer
Division of Psychiatry Products (DPP)
Javier Muniz, MD, Clinical Reviewer Team Leader, DPP
Jasmeet (Mona) Kalsi, Regulatory Project Manager, DPP

CC: Kim Updegraff, ADL, DPP

From: Christine Bradshaw, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, Team Leader, OPDP

Subject: **NDA 209241/O-1**
OPDP labeling comments for INGREZZA™ (valbenazine) capsules,
for oral use (Ingrezza)

In response to DPP's consult request dated August 30, 2016, OPDP has reviewed the draft product labeling (PI) for Ingrezza.

OPDP's comments on the draft PI for Ingrezza are based on the version of the PI provided by Mona Kalsi via email on February 10, 2017 and updated by Kim Updegraff on February 28, 2017, and are provided below.

If you have any questions, please feel free to contact me by phone at 301-796-6796 or by email at Christine.Bradshaw@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials.

Thank you!

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/s/

CHRISTINE J BRADSHAW
03/02/2017



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 28, 2017

To: Mitchell Mathis, M.D., Director
Division of Psychiatry Products

Through: Michael Klein, Ph.D., Director
Martin Rusinowitz, M.D., Medical Officer
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D. Medical Officer
Controlled Substance Staff

Subject: **NDA 209241/IND 111591**
Name: Ingrezza (valbenazine tosylate, NBI-98854)
Dosages: 40 or 80 mg, given orally once a day
Indication: Treatment of tardive dyskinesia (TD)
Sponsor: (b) (4) / Neurocrine Biosciences, Inc.
PDUFA Goal Date: April 11, 2017

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA submission, (NDA 209241, August 11, 2016)
Additional materials: CSS filing review, Dr. S. Calderon, dated September 27, 2016
Response to CSS Information Request dated January 17, 2017

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A. SUMMARY

I. BACKGROUND

This memorandum responds to a consult request by the Division of Psychiatry Products (DPP) to review the abuse potential and possible scheduling of valbenazine tosylate (Ingrezza), NDA 209241, which was submitted by [REDACTED] (b) (4) for the treatment of tardive dyskinesia. This product will be administered orally as 40 mg capsules at a dosage of 40 or 80 mg given once a day.

Valbenazine is a new molecular entity (NME) currently being developed for the treatment of tardive dyskinesia (TD) [REDACTED] (b) (4). A rolling review for valbenazine was granted on March 29, 2016. Additionally, valbenazine was granted Fast Track designation on January 24, 2012. Breakthrough Therapy Designation was granted by DPP in October 2014, for the treatment of TD.

Tardive dyskinesia is a neurological disorder characterized by repetitive, involuntary, purposeless movements. It emerges after the long-term use of neuroleptics for psychiatric, gastrointestinal, and neurological disorders. TD may include grimacing, tongue protrusion, lip smacking, puckering, pursing and rapid eye blinking. Rapid movements of the arms, legs, and trunk may also occur. The disorder persists even after discontinuation of the neuroleptic drug.

Valbenazine (also known as NBI-98854 throughout development) is an orally-active selective and reversible vesicular monoamine transporter 2 (VMAT2)¹ inhibitor. VMAT2 plays an important role in presynaptic dopamine release, regulating monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release.

In humans, valbenazine metabolizes primarily to NBI-98782 and NBI-136110. NBI-98782 (*R,R,R*-dihydrotrabenzazine) is considered the most active metabolite of tetrabenazine and is formed by the cleavage of the valinate ester residue of valbenazine. NBI-136110 is formed by oxidative metabolism of valbenazine, to give a monooxidative derivative.

Tetrabenazine (TBZ, also known by code name [REDACTED]^{(b) (4)}) is a VMAT2 inhibitor and was approved by FDA in 2008 for the treatment of chorea associated with Huntington's disease.

NBI- 98782 displayed approximately 45-fold higher affinity than valbenazine for the VMAT 2 transporter. Although pharmacokinetic (PK) studies show that the human maximum plasma concentration (C_{max}) for valbenazine is approximately 10-fold higher than that of NBI 98782, based on the relative potency of in vitro VMAT2 inhibition, this metabolite appears to be the primary contributor to in vivo VMAT2 inhibition .

The clinical development program for the safety evaluation of the TD indication includes 20 studies:

- 14 Phase I studies: 12 in healthy subjects, 1 in hepatically impaired adults, and 1 in children and adolescents with TS
- 4 Phase II studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or GI disorder
- 2 Phase III studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, or mood disorder.

The total population enrolled in all studies included 993 subjects in 20 studies, where 846 subjects were exposed to valbenazine and 292 received placebo. Of the 427 subjects enrolled who have TD, 167 (38%) discontinued treatment with valbenazine.

II. CONCLUSIONS

1. Valbenazine is an NME also known by the code name of NBI-98854. Three metabolites of valbenazine, NBI-98782 , NBI-136110 and NBI-679006 have been identified as circulating metabolites in in vivo radiolabeled mass balance studies conducted in rats, dogs, and humans (Report# 13-98854-001-MT). In human plasma, valbenazine represented 42.4% of the total exposure of drug-related radioactivity, whereas NBI-98782, NBI-136110 and NBI-679006

¹ The vesicular monoamine transporter 2 (VMAT2) is an integral membrane protein that transports monoamines, particularly neurotransmitters such as dopamine, norepinephrine, serotonin, and histamine, from cellular cytosol into synaptic vesicles. In nigrostriatal pathway and mesolimbic pathway dopamine-releasing neurons, VMAT2 function is also necessary for the vesicular release of the neurotransmitter GABA.

represented 9.9%, 12.7 %, and 8.2 %, respectively, of the total exposure of drug-related radioactivity.²

2. In vivo animal studies conducted in male and female rats showed that at oral doses of 15, 25 and 50 mg/kg of drug, valbenazine displayed dose-related depressant effects on the central nervous system (CNS). These studies showed effects consistent with monoamine depletion. Administration of valbenazine resulted in depressed neuromuscular/sensorimotor functions, low arousal, and stimulation of the parasympathetic nervous system (miosis and increased lacrimation) as well as decreased motor activity at the highest dose tested. Decreased motor activity and impaired neuromuscular function were still observed 24 hours after administration.
3. Valbenazine is a psychoactive substance which produces mixed effects of stimulation and sedation in humans.
 - a. In healthy subjects, mixed effects of stimulation (insomnia, anxiety, restlessness, energy increased, nervousness, panic attack) and sedation (somnolence, fatigue) were observed.
 - b. In subjects with schizophrenia, AEs of somnolence, sedation, fatigue, insomnia and panic attacks were more frequent in patients treated with valbenazine than in a placebo group.
4. Drug accountability issues were noted during the clinical trials phase 2/3. Of the 6069 kits dispensed, approximately 157 valbenazine kits and 13 placebo kits were not returned (section 4.4).
5. The Sponsor did not submit data from specifically abuse-related animal or human studies to assess valbenazine's abuse potential, nor did the Sponsor formally assess dependence and withdrawal. Of note:
 - The safety data from phase 2/3 clinical trials is conflicted because of CNS abnormalities related to schizophrenia and the use of other psychoactive drugs (anti-psychotic drugs, antidepressants, benzodiazepines, anticholinergics).
 - The safety data from phase 1 trials is exceedingly sparse, derived mainly from single dose studies which are not particularly informative with regard to abuse potential and dependence.
 - Dependence and withdrawal were not assessed in a systematic manner in clinical trials, and only data for 182 subjects were submitted from 430 (81 patients are still enrolled and 167 discontinued).

² NBI-98782 (*R,R,R*- dihydrotetrabenazine) is considered the most active metabolite of tetrabenazine as a VMAT2 transporter, and is formed by the cleavage of the valinate ester residue. NBI-136110 is formed by oxidative metabolism of valbenazine, to give a monooxidative derivative. NBI-670006 is a hydroxylated analogue of NBI-98782.

- Dependence and withdrawal were not systematically evaluated in Phase 2/3 trials:
 - no specific withdrawal questionnaires were used
 - the visits evaluating patients' status during the discontinuation period were not frequent enough to capture possible withdrawal symptoms of the drug which has a half-life ~20 hours (after 2 weeks in studies # NBI-98854-1201 and NBI-98854-1202 and after 4 weeks post-discontinuation in study #NBI-98854-1304 and #NBI-98854-1402)
 - in an IR from Jan 17 2017, the Sponsor indicated that withdrawal was evaluated with multiple disease-specific scales; however, large numbers of patients discontinued and some scales do not show baseline values; therefore this data cannot represent the evaluation of withdrawal (see Discussion for details):
 - Because valbenazine decreases the levels of dopamine, serotonin and norepinephrine (Erickson et al., 2000) through inhibition of the VMAT2 transporters, and GABA release requires activity of the vesicular monoamine transporter VMAT2 (Tritsch et al., 2012), the sudden reversal of long standing inhibition, which is claimed to be the main action of valbenazine, may cause an acute withdrawal syndrome causing cardiovascular and neurological AEs.

III. RECOMMENDATIONS

1. CSS agrees with the Sponsor that additional animal behavioral studies (drug discrimination or self administration) or a human abuse potential (HAPS) study in recreational drug users are not necessary at this time to characterize the abuse potential of valbenazine, based on the following:
 - a. The chemical structure and pharmacological properties of valbenazine are similar to tetrabenazine, which is not known to be a drug of abuse.
 - b. The selectivity of valbenazine and its metabolites is for the VMAT2 transporter binding site. There is a lack of binding of valbenazine and its metabolites to receptor systems associated with abuse (i.e., benzodiazepine, 5-HT_{2A}, mu opioid receptors, and monoamine transporter systems).
 - c. Findings from in vivo animal studies show no signals of abuse potential.
 - d. The abuse potential assessment of valbenazine is based primarily on the analysis of adverse events observed in clinical trials and on postmarketing data for tetrabenazine, which do not provide a signal of abuse potential.
2. Although no cases of abuse or misuse were reported in clinical trials we recommend continuing post marketing assessment of AEs suggestive of abuse-potential. These assessments should be included in the standard Periodic Adverse Event Reports (PADERS). The Sponsor should provide more details about the basis for the drug accountability discrepancies, i.e., unreturned drug kits.
3. We recommend that a clinical assessment of physical dependence and withdrawal be conducted at the conclusion of any ongoing clinical trial, preferably a trial performed in the patient population for which the drug will be indicated (see Discussion section 5.2, recommended PMR). The on-going phase II studies (Study 1304 and Study 1402 mentioned in ISS, page 24)

might be used to systematically evaluate dependence and withdrawal using appropriate withdrawal scales and time points for these assessments.

4. After consideration of all data available related to the abuse potential and physical dependence of valbenazine, CSS recommends that the label not include a DRUG ABUSE AND DEPENDENCE section. This recommendation may be revised when the clinical assessment of physical dependence is completed.

B. DISCUSSION

1. Chemistry

1.1 Substance Information

Drug Substance

Valbenazine (NBI-98854) is available as a ditosylate salt.

Physical and Chemical Properties

Chemical Name: (2R,3R,11bR)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11bhexahydro-2H-pyrido[2,1-a]isoquinolin-2-yl L-valinate bis(4-methylbenzenesulfonate)

Non-proprietary Name: Valbenazine tosylate

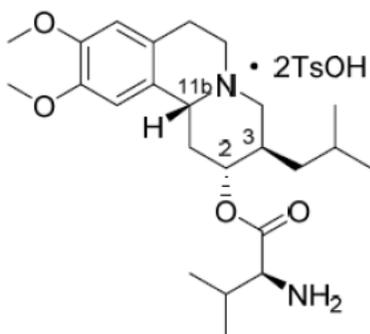
Molecular Formula: $C_{38}H_{54}N_2O_{10}S_2$

Molecular Weight (salt): 762.97

NBI Number: NBI-98854 2Ts

Dissociation Constant: $pK_a =$ (b) (4)

Structural Formula:



Drug Product

The product will be a (b) (4) purple (b) (4) cap/ (b) (4) white opaque body, (b) (4) gelatin capsule with VBZ/40 printed on the cap/body, containing 40 mg (b) (4) valbenazine (free base) in common pharmaceutical excipients, see table showing drug product composition.

Table 1: Quantitative Composition of Valbenazine, 40 mg capsules

Component	Quality Standard	Function	Weight (mg/unit)	% (w/w)
NBI-98854 ditosylate ^a	In-house	Drug Substance	73.0 ^b	(b) (4)
Mannitol (b) (4)	USP			(b) (4)
Partially pregelatinized (b) (4) starch (b) (4)	NF			
Fumed silica (b) (4)	NF			
Magnesium stearate (b) (4)	NF			
Total Fill Weight				
(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 ^{a, f}	Pharmaceutical	Capsule Shell	--	1 capsule

1.2 Potential Drug Isomers

Valbenazine ditosylate, also known under the development code of NBI-98854, is chemically known as (2*R*,3*R*,11*bR*)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11-hexahydro- 2*H*-pyrido[2,1-*a*]isoquinolin-2-yl *L*-valinate bis(4-methylbenzenesulfonate), and can be described as the valinate ester of the most active enantiomer (VMAT2 inhibitor) of the eight dihydrotetrabenazine possible enantiomers. Valbenazine has an *R, R, R* absolute configuration at 2, 3 and 11*b* positions.

2. Nonclinical Pharmacology

Valbenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor. It belongs to the same group of drugs as Tetrabenazine (TBZ, XENAZINE) and Dihydrotetrabenazine (DHTBZ, NDA 208082, AUSTEDO). NBI-98854, after oral administration, is rapidly absorbed and slowly metabolized to NBI-98782, which is much more potent at VMAT2. This metabolite is also a stereoisomer ((+) α -DHTBZ; *R,R,R*-DHTBZ), considered to be the most potent and selective VMAT2 inhibitor of the four stereoisomers of DHTBZ formed upon reduction of TBZ. The potency of NBI-98782 is approximately 45 times higher than the parent drug, see more in section 2.1. Table 2 below shows the contribution of parent and the main metabolites in the plasma of human and other species.

Table 2. Relative Exposures of NBI-98854, NBI-98782, NBI-136110 determined using lc-ms/ms and total plasma radioactivity data (from Table 2, study # 13-98854-001-MT, page 39)

Component	% of Total Plasma Radioactivity Exposure Within the Time Interval Used for Plasma Pooling						
	Human ¹	Dog ²			Rat ³		
		Male	Female	Mean	Male	Female	Mean
NBI-98854	40.3	29.2	36.6	32.9	4.9	10.9	7.9
NBI-98782	7.9	3.8	4.8	4.3	10.3	16.7	13.5
NBI-136110	12.7	8.1	8.1	8.1	5.7	4.0	4.8

Component	% of Total Plasma Radioactivity Exposure (from 0 extrapolated to infinity)						
	Human	Dog			Rat		
		Male	Female	Mean	Male	Female	Mean
NBI-98854	35.0	28.1	34.2	31.2	4.2	8.9	6.5
NBI-98782	7.1	3.6	7.3	5.5	10.1	15.6	12.8
NBI-136110	12.6	8.1	7.8	7.9	5.4	3.7	4.6

1. The time interval used for the human plasma pool was 0-72 hours.
2. The time interval used for the dog plasma pools was 0-48 hours.
3. The time interval used for the rat plasma pools was 0-48 hours.

The clinical pharmacology review (communication) provides a summary of the contribution of the parent drug and its major metabolites in human plasma.

Table 3. Percent contribution of parent drug and major metabolites in human plasma.

Metabolite	Percent of total plasma exposure of [14C]NBI-98854-related Radioactivity
NBI-98854	42.4
NBI-98782	9.9
NBI-136110	12.7
NBI-679006	8.2

Mechanism of Action

Valbenazine tosylate (NBI-98854), is a highly selective, orally active, and reversible vesicular monoamine transporter 2 (VMAT2). The in vivo pharmacological studies established that activity of the drug is largely mediated by the main active metabolite NBI-98782 with a possible minor contribution from valbenazine (NBI-98854). NBI-136110 is another circulating human metabolite of NBI-98854, but is not expected to contribute to the pharmacology of VMAT2 inhibition.

1.1 Receptor Binding and Functional Assays

Study # 08-98854-001-PH: In vitro Pharmacological Characterization of NBI 98782 and NBI 98854 and Study # 11-98854-001-PH In vitro Pharmacology of NBI-136110, a metabolite of NBI-98854

Binding studies demonstrate that valbenazine and its major metabolites are selective VMAT2 inhibitors. They do not interact with other receptor systems associated with abuse (Report 11-98854-001-PH).

The affinity of valbenazine and its major metabolites for the human VMAT2 transporter was evaluated by inhibition of the binding of the selective titrated dihydrotetrabenazine ligand (3H-DHTB) to the VMAT2 transporter in human platelet and rat striatum tissue. Valbenazine and its metabolite, NBI-136110, displayed similar affinity for the VMAT2 transporter with K_i of 150 nM and 220 nM, respectively. Under the same conditions, NBI-98782 displayed approximately a 45-fold higher affinity for the VMAT 2 transporter with a K_i of 3.3 nM, whereas its hydroxylated metabolite, NBI-679006, had a K_i of 74 nM. (Report 11-98854-001-PH).

The affinity of valbenazine, NBI-98782 and NBI-136110 for various receptor systems associated with abuse was determined by binding covering multiple classes of receptor proteins including G-protein-coupled receptors (GPCRs), cell-surface monoamine transporters, and ion channels. Valbenazine at a 10 micromolar concentration and NBI-98782 and NBI-136110 at 1 micromolar concentration, resulted in binding lower than 50 % at the sites tested.

2.2 Safety Pharmacology/Metabolites

See section 2.

2.3 Findings from Safety Pharmacology and Toxicology Studies

Study # 08-98854-002-PH In vivo characterization of NBI 98782 and NBI 98854 with surrogate markers of activity (Effect on Locomotor Activity)

As monoamine depletors are known to decrease locomotor activity, both valbenazine and its main active metabolite NBI-98782 were tested using this paradigm, with tetrabenazine as a positive control. Both tetrabenazine and valbenazine produced a dose-dependent decrease in activity with a minimum effective dose (MED) of 3 mg/kg. NBI-98782 was more potent at decreasing locomotor activity, with an MED of 0.3 mg/kg and a maximal effect at 3 mg/kg.

Study # 08-6656 Central nervous system assessment with functional observational battery of NBI-98854 when administered orally to conscious rats

Design

The study was performed in Sprague-Dawley CD® rats (8/sex/group). Doses were administered orally as a single doses via gavage: 0, 15, 25, or 50 mg/kg in 0.25% methylcellulose.

Results

Valbenazine exhibited a dose-related effect on the CNS at ≥ 15 mg/kg which included: depressed neuromuscular function (abnormal posture/gait, impaired locomotion and decreased hind limb grip strength), sensorimotor function (abnormal pupil response), behavior (low arousal), and stimulation of the parasympathetic nervous system (miosis and increased lacrimation). Less frequent findings included tremors, abnormal proprioception/air righting reflex, and decreased pain response. The CNS effects at doses of 15 and 25 mg/kg, seen at 1.5 hours postdose, returned to normal within 24 hours of dose administration.

However rats administered 50 mg/kg of drug still had impaired neuromuscular function (abnormal posture, hunched/crouched body position, and/or body drags/flattened, abnormal gait, ataxia, hind limbs splayed/dragging, low arousal, and miosis) at the 24-hour post dose, more pronounced in females.

CSS Comment

Valbenazine shows a dose-dependent CNS depressant activity in rodents, drug effects were more pronounced in females.

Selected Toxicology Studies

Study # 2011-TX-040 Report # 11-98854-007-TX: 24-Day Oral Safety Assessment and Toxicokinetics of NBI-98854 in CD-1 Mice

Design

A total of 80 male and female CD-1 mice were administered orally: 30, 100, 300, 600 mg/kg for 24 days.

Results

At Day 1 mice in the groups of 100 and 300 mg/kg showed decreased activity and ptosis, starting within half an hour of dosing and lasting for at least 4 hours. Some animals in the 300 mg/kg group exhibited abnormal posture (hunched or splayed out) which was dose dependent and disappeared by the next morning.

Starting on the Day 12, increased activity was noted before drug administration in the 100 and 300 mg/kg/day animals, with restless pacing, running and jumping around in the cage, and aggression. These continued throughout the dosing period and were also seen during the initial 9-10 days of the drug free recovery period in these dose groups.

At 600 mg/kg, four females and one male were found dead within one hour of dosing on Day 1; an additional male was found dead at approximately 7 hours postdose. Clinical observations preceding death at 600 mg/kg included abnormal gait, hypoactivity, hunched posture, lying on side, unable to right itself, limbs extended, shallow breathing, jittery movements, tremors, and/or convulsions.

Study # Tox-HTBZ-98854-07-02: 12 Day Oral Safety Assessment and Toxicokinetics of Daily HTBZ NBI-98854 Administration in the Male Sprague Dawley Rat

Design

A total of 25 male Sprague Dawley rats (approximately 8 weeks of age) in 7 groups received valbenazine at doses of 0, 15, 30, and 60 mg/kg.

Results

All animals that received valbenazine from day 1 were lethargic with an abnormal posture (hunched or splayed out) and ptosis within an hour of dosing and lasting at least 4 hours. The severity of these observations was dose related. Starting on the 7th day of dosing and lasting throughout the study, prior to dosing, the animals were hyperactive with restless pacing. This hyperactivity included not only running around in the cage, but also strong vocalizations and aggression. Oral administration of drug at 60mg/kg/day lead to a statistically significant decrease (19%) in body weight at the conclusion of the study.

Study # 2011-TX-001: A 91-Day Study of NBI-98854 by Oral Gavage in Rats with a 6-Week Recovery Period

Design

Valbenazine was administered to 6 groups of rats at doses 0, 1, 3, 5, 15 mg/kg. The objectives of this study were to determine the potential toxicity of NBI-98854 when given orally for 91 days to rats, to evaluate the potential reversibility of any findings, and to provide data to support the continued use of NBI-98854 in humans. In addition, the toxicokinetic characteristics of NBI-98854 and NBI-98782 were determined.

Results

Valbenazine oral doses of 1, 3, 10, and 15 mg/kg/day were tolerated in rats. Drug related effects were observed at ≥ 3 mg/kg/day in males and females and included partially closed eyelids and included increased activity (prior to dose administration) and decreased activity following dose administration. In addition to the postdose observations, increased activity prior to dose administration was noted approximately 4 weeks following study initiation, and continued throughout the dosing period and was mainly noted in the 3, 10, and 15 mg/kg/day animals. This clinical sign was also observed during the initial week of the drug-free recovery period in these dose groups for up to 10 days following the cessation of the dosing phase. Valbenazine administration, also resulted in decreases in body weights relative to controls at doses ≥ 10 mg/kg/day for males and at ≥ 3 mg/kg/day for females as a result of decreased body weight gains (especially during Weeks 1 to 3)

Study # No. 2011-TX-002: A 91-Day Study of NBI-98854 by Oral Capsule in Dogs with a 28-Day Recovery Period

Design

Valbenazine was administered for 91 days to 5 groups of dogs (male and female), see design below.

Results

Drug-related clinical signs were observed at ≥ 5 mg/kg/day in males and females and were noted primarily during the 1 to 4 hour postdose observation period and included decreased activity, tremors, and ataxia (i.e., wobbly gait). Drug-related differences in body weights were observed at ≥ 12.5 mg/kg/day resulting in a reduction in body weights from 8% to 15% lower in males and from 5% to 13% lower in female on Day 91, when compared to controls. No other meaningful clinical signs were noted during the recovery phase.

Study # 2012-TX-090: A 9-month Study of NBI-98854 by Oral Capsule Administration in Dogs with a 1-month Recovery Period

Design

Drug was administered to Beagle dogs (5 male, 5 female) at doses of 0, 3, 10 and 15 mg/kg/day for a period of 273 days.

Results

The drug produced, in males and females at ≥ 10 mg/kg/day, tremors, partially closed eyelids, and

decreased activity, there was some reductions in body weight, body weight gain, and food consumption at ≥ 10 mg/kg/day in females primarily early in the dosing period.

CSS comment

In animals the drug caused mixed sedative and stimulant behavioral signs, also, the signs suggesting withdrawal syndrome of restless pacing, running and jumping around in the cage, increased activity, and aggression were also observed.

2.4 Animal Behavioral Studies

There are no animal abuse potential studies.

2.5 Tolerance and Physical Dependence Studies in Animals

There are no animal dependence and tolerance studies.

2. Clinical Pharmacology

Evaluation of PK parameters of valbenazine (NBI-98854) following an intravenous (IV) and/or oral single doses of the drug were conducted in the mouse, rat, dog, monkey and humans and are summarized in Table 3 below (from Mod 2.6.3 Pharmacokinetics written summary, page 13).

Table 3: Pharmacokinetic Parameters of NBI-98854 After Oral and Intravenous dosing

Species (Study No.)	Dose	Oral dosing				Intravenous dosing			
		t _{max} (hr)	C _{max} (ng/mL)	AUC _(0-∞) (ng×hr/mL)	%F	Dose	CL (mL/min/Kg)	V _{ss} (L/Kg)	t _{1/2} (hr)
CD1 Mouse (09-98854-001-PK)	8.5 mg/kg	0.5	1,570	3,680	ND	ND	ND	ND	ND
SD Rat (08-98854-006-PK)	10 mg/kg	0.5-1.0	1,910	4,990	68.5	2.5 mg/kg	23.2	2.04	1.3
Beagle Dog (08-98854-007-PK)	10 mg/kg	0.25-0.5	9,170	27,400	123	2.5 mg/kg	7.72	1.90	5.9
Cynomolgus Monkey (08-98854-008-PK)	10 mg/kg	0.5-2.0	1,790	7,770	91.0	2.5 mg/kg	18.6	3.84	6.8
Human (NBI-98854-1204)	50 mg	0.5-0.73	415	3,450	48.6	0.015 mg	1.71 ^a	1.32 ^a	16

AUC_{0-∞}=area under the plasma concentration versus time curve from 0 hours extrapolated to infinity; CL=systemic plasma clearance; C_{max}=maximum plasma concentration; F=Oral bioavailability; ND=not determined; t_{1/2}= terminal half-life; t_{max}=time to maximum plasma concentration. SD=Sprague-Dawley; V_{ss}=volume of distribution at steady state.

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

Based on Module 2.5 Clinical overview, and Module 2.7.2 Summary of Clinical Pharmacology Studies

Administration

Orally administered valbenazine is rapidly absorbed with T_{max} ~0.5 to 1.0 hours. The absolute oral bioavailability of valbenazine is estimated to be 49%. The active metabolite NBI-98782 has a T_{max} of 4-8 hours. Both valbenazine and NBI-98782 are eliminated with a terminal half-life (t_{1/2}) ~ 20 hours.

Daily administration of the drug results in some accumulation of valbenazine and an approximately 2-fold accumulation of the metabolite NBI-98782. Steady state is reached within 4 to 5 days. Both the C_{max} and AUC of valbenazine and NBI-98782 increase proportionally within the therapeutic dose range of 40 mg to 80 mg. The C_{max} of valbenazine is approximately 10-fold higher than its active metabolites, however the active metabolites appears to be the primary contributors to in vivo VMAT2 inhibition. PK values for valbenazine and its metabolites are presented in the table below (table 1 from the Study # NBI-98854-0801, PK of ascending doses in Healthy Volunteers). A clinical pharmacology (Dr. Di Zhou, communication) assessment of this data found that the T_{max} for valbenazine is similar in the dose range of 5mg to 75 mg and the higher value under 1mg and 2mg is due to the variability. For the metabolites, T_{max} is similar across different doses, there is no significant trend with the increase of the dose. C_{max} and AUC are the key exposure metrics in PK. For NBI-98854, the AUC_{0-inf} and C_{max} increased modestly more than proportionally with increasing dose in the range of 1 to 75 mg. For NBI-98782, this lack of proportionality was only apparent for the C_{max}, but not for AUC of that metabolite. (Table below).

Table 1. Select NBI-98854 and NBI-98782 Plasma Pharmacokinetic Parameters (Mean [SD]) by NBI-98854 Dose

Analyte	PK Parameter	1 mg (N=8)	2 mg (N=4)	5 mg (N=6)	12.5 mg (N=11)	25 mg (N=6)	50 mg (N=5)	75 mg (N=6)
NBI-98854	t _{max} (hr) ⁽¹⁾	1.3 (0.8, 3.0)	1.5 (0.5, 3.0)	0.5 (0.3, 1.3)	0.5 (0.5, 4.0)	0.6 (0.3, 0.8)	0.5 (0.3, 4.0)	0.6 (0.3, 1.3)
	C _{max} (ng/mL)	2.94 (1.33)	6.42 (3.09)	17.4 (7.21)	56.9 (18.9)	156 (68.2)	412 (236)	827 (229)
	AUC _{0-∞} (ng×hr/mL)	<i>40.7 (15.9)</i>	102 (35.2)	207 (82.2)	614 (148)	1610 (304)	4120 (1680)	7290 (1690)
	t _{1/2} (hr)	16 (2.4)	15 (2.7)	17 (3.0)	16 (2.3)	20 (3.7)	19 (2.4)	20 (1.2)
	CL/F (L/hr)	26.9 (7.06)	21.4 (7.22)	26.6 (7.63)	21.6 (5.67)	16.0 (3.42)	14.1 (6.22)	10.9 (3.13)
	V/F (L)	603 (179)	462 (129)	625 (176)	496 (107)	454 (131)	381 (133)	309 (86)
NBI-98782	t _{max} (hr) ⁽¹⁾	7.0 (4.0, 12)	9.0 (6.0, 10)	7.0 (4.0, 12)	6.0 (4.0, 10)	7.0 (3.0, 24)	4.0 (4.0, 6.0)	5.0 (4.0, 12)
	C _{max} (ng/mL)	0.19 (0.04)	0.46 (0.11)	0.98 (0.16)	2.55 (0.67)	6.39 (1.57)	20.4 (7.51)	28.5 (9.11)
	AUC _{0-∞} (ng×hr/mL)	<i>9.22 (4.30)</i>	<i>21.9 (5.92)</i>	<i>29.9 (7.35)</i>	93.0 (36.2)	255 (118)	575 (350)	978 (581)
	t _{1/2} (hr)	32 (17)	31 (22)	16 (3.0)	19 (4.0)	23 (4.2)	20 (2.8)	21 (2.2)
	Molar Ratio (%) ⁽²⁾	32 (18)	32 (18)	21 (7.9)	20 (5.7)	21 (10)	20 (11)	18 (8.1)

Data source: NBI-98854-0801 CSR Tables 14.3.3 and 14.3.6.

AUC_{0-∞}=area under the plasma concentration versus time curve from time 0 to infinity, C_{max}=maximum plasma concentration; t_{1/2}=apparent terminal half-life; t_{max}=time to maximum plasma concentration; CL/F=apparent systemic clearance after oral administration; V/F=apparent volume of distribution during the terminal phase after oral administration; *italic*=AUC_{0-∞} extrapolated >10%.

(1) Median (min, max) is reported for t_{max}.

(2) Molar Ratio of AUC_m/AUC_p calculated using AUC_{0-∞} and corrected for differences in molecular weight.

Metabolism

The primary (rate-limiting) metabolic pathways identified for NBI-98854 in in vitro studies is oxidative metabolism and ester hydrolysis. This includes hydrolysis of NBI-98782 and oxidation of other metabolites (including NBI-136110). Oxidative metabolism of valbenazine is primarily catalyzed by CYP3A4/5. NBI-98782 is metabolized in part by CYP2D6.

Distribution

The systemic clearance and steady state volume of distribution were estimated to be 7.2 L/hr and 92 L, respectively. Based on rodent data, valbenazine and NBI-98782 readily cross the blood brain barrier. At physiologically relevant concentrations, valbenazine is extensively bound to proteins in plasma at >99% whereas for NBI-98782, binding was approximately 64%.

Elimination

Following the administration of a single oral dose, [14C]-valbenazine (Study # NBI-98854-1204: Human ADME/Absolute oral bioavailability) was extensively metabolized. Mean recovery of radioactivity was high (91%) with approximately 60% excreted in urine and 30% excreted in feces. Less than 2% of the administered dose of valbenazine was excreted as unchanged valbenazine or NBI-98782 in urine or feces), indicating minimal renal or biliary excretion of valbenazine or NBI-98782.

3.2 Drug/Product Interactions

- Co-administration of valbenazine with strong CYP3A4/5 inhibitors causes an approximately 2-fold increase in systemic exposures of both valbenazine and NBI-98782.
- **Food Effect:**
Administration of valbenazine capsules with a high-fat, high-calorie meal showed a longer time to maximum concentration (Tmax) and attenuated maximum plasma concentration (Cmax) but a negligible effect on total systemic exposure of valbenazine, compared with the fasted condition. The Tmax was also longer for the metabolite NBI-98782, however the total and peak systemic exposures were similar under the fed versus fasted conditions.

4. Clinical Studies

The clinical development program for the safety evaluation for the tardive dyskinesia indication includes 20 studies:

- 14 Phase I studies: 12 in healthy subjects, 1 in hepatically impaired adults, and 1 in children and adolescents with Tourette syndrome
- 4 Phase II studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or GI disorder
- 2 Phase III studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, or mood disorder.

The total population enrolled in all studies included 993 subjects in 20 studies, where 846 subjects were exposed to valbenazine and 292 have received placebo (table 3, ISS, p 24).

Table 3: Number of Exposures by Study Phase

Study Phase	No. Subjects Exposed to NBI-98854	No. Subjects Exposed to Placebo	No. Subjects Enrolled
Phase 1	321	78	337
Phase 2	195	138	254
Phase 3 ^a	381	76	402
Total	846^b	292	993

^a Studies are ongoing, but number of subjects exposed will not change.

^b Unique NBI-98854 exposures in the Safety Population.

The sponsor presented the safety data in the ISS using various pooling strategies, therefore there was a need to present selected abuse potential data from not pooled studies.

Table 1: List of Studies Included in this review

Study ID (Period)	Phase	Design	Drug dose range	Population	Single or multiple dose	Age/Sex
NBI-98854-1301	Phase 1	DB, PL	150, 300	HV	Single	male, female
NBI-98854-0901	Phase 1	DB, PL	50, 100, 125, 150	HV	single, multiple	male
NBI-98854-1503	Phase 1	OL	80	HV	multiple	male, female
NBI-98854-1403	Phase 1b	OL	5,10, 25, 50	PT--TS	multiple	

4.1 Human Abuse Potential Studies

No human abuse potential studies were conducted.

4.2 Adverse Event Profile Through all Phases of Development

4.2.1 Abuse-Related Adverse Events in Phase 1 Studies

SINGLE DOSE Studies in Healthy Volunteers

In order to assess valbenazine’s abuse potential the Sponsor pooled safety data from 6 completed Phase 1 studies in healthy subjects which were either single-dose studies or studies with a single-dose cohort (NBI- 98854-0801, -0901, -1102, -1203, -1204, and -1301). In the 6 Phase 1 single-dose studies, 72 subjects (40.9%) who were administered valbenazine and 12 subjects (17.6%) receiving placebo reported a treatment-emergent AE (TEAE). The most common AEs which were defined as occurring $\geq 5\%$ were headache, anxiety, fatigue, nausea, and somnolence; however headache, nausea, and somnolence were also reported by subjects receiving placebo. In general, AEs for valbenazine were more frequent than in the placebo group, see table 2.

Table 2. Abuse-related Adverse Events Reported in >1% Subject in Phase 1 Single-Dose Studies based on Abuse Liability Report Table 2 and ISS Table 1.2.2.1 p 417.

Adverse Event PT	Placebo (N=68) n (%)	Valbenazine Doses >100 mg (N=78) n (%)	Valbenazine All Doses (N=176) n (%)
Any adverse event	12(17.6)	36(46.2)	72(40.9)
Neurological Disorders			
Somnolence	2 (2.9)	7 (9.0)	9 (5.1)
Dizziness	0	3 (3.8)	4 (2.3)
Dizziness postural	0	1 (1.3)	3 (1.7)
Disturbance in attention	0	1 (1.3)	1 (0.6)
Psychiatric Disorders			

Anxiety	0	14 (17.9)	15 (8.5)
Insomnia	0	5 (6.4)	8 (4.5)
Restlessness	0	3 (3.8)	3 (1.7)
Depressed mood	0	2 (2.6)	2 (1.1)
Confusional state	0	1 (1.3)	1 (0.6)
General Disorders			
Fatigue	0	9 (11.5)	10 (5.7)
Energy increased	0	2 (2.6)	2 (1.1)

Comment

Although there are numerous AEs which reflect valbenazine’s CNS activity, there are none which show a signal for abuse potential. The data from other relevant studies, such as maximal dose in healthy volunteers and multiple doses studies, and children population are presented below.

1. Maximal dose Study # NBI-98854-1301 A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NBI-98854

In this study single maximal doses of 150 and 300 mg in healthy volunteers (men and women) there was a higher frequency of CNS related AEs vs placebo. However, the total number of subjects was very low.

Table 3. Abuse related adverse events based on the table 14.8.1, p 181, in the study report.

Adverse Event PT	Placebo Dose (N=3) n (%), (AEs)	Valbenazine Dose 150 mg (N=6) n (%), (AEs)	Valbenazine Dose 300 mg (N=6) n (%), (AEs)
Neurological Disorders			
Somnolence	0	0	1 (16.7), 1
Psychiatric Disorders			
Anxiety	0	1 (16.7), 1	1 (16.7), 1
Insomnia	0	1 (16.7), 1	0
Depressed mood	0	1 (16.7), 1	0
Nervousness	0	1 (16.7), 1	0

MULTIPLE DOSE S Studies in Healthy Volunteers

There were 3 very short multiple dose studies lasting 7 and 8 days in healthy volunteers and one 14 day study in a pediatric population with Tourette syndrome. The AE profiles were similar.

2. Study # NBI-98854-0901: A Phase I, Double-Blind, Randomized, Placebo-Controlled, Single-and Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NBI-98854 in Healthy Men

Design:

Population: 40 male healthy subjects

Doses:

For the single-dose part:

Doses: 50, 100, 125, 150 mg and placebo

For the multiple-dose part:

Population: 32 male healthy subjects

Doses: 50, 100 mg and placebo

Duration: 8 days

Table 4. Adverse events in the multiple dose study in healthy volunteers based on the Table 14.25.1, p 588, from the study report titled Summary of Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term (Safety Analysis Set, Multiple-Dose Cohort).

Adverse Event PT	Placebo (N=10) n (%), AEs	Valbenazine Dose 50 mg (N=14) n (%), (AEs)	Valbenazine Dose 100 mg (N=8) n (%), AEs
n-subjects, events-AEs			
Overall	6 (60), 14	8 (57.1), 24	6 (75), 21
Neurological Disorders			
Disturbance in attention	0	0	2 (25), 2
Somnolence	0	1 (7.1), 1	0
Dizziness postural	1 (10), 1	1 (7.1), 1	1 (12.5), 1
Psychiatric Disorders			
Anxiety	0	0	1 (12.5), 1
Insomnia	0	0	3 (37.5), 3
Nervousness	0	0	2 (25), 2
General Disorders			
Fatigue	0	1 (7.1), 1	2 (25), 2

Comment

Stimulant-type AEs, such as insomnia, nervousness, anxiety, predominated, but sedative AEs of somnolence and fatigue were also present.

3. Study # NBI-98854-1503: A Phase 1, Open-Label, One-Sequence Crossover Study to Assess the Effect of NBI-98854 on the Pharmacokinetics of Digoxin in Healthy Subjects

Design

Population: 24 healthy adult subjects (12 males and 12 females)

Doses: single dose of valbenazine 80 mg (administered as two 40 mg capsules) for 7 days (days 10-16) and digoxin 0.5 mg (administered as two 0.25 mg IR tablets) once daily on Days 1 and 14 at
Duration: 7 days

Table 5. Abuse related adverse events in healthy subjects taking digoxin based on Table 14.3.1.1, p 307, there is no placebo group.

Adverse Event PT	Valbenazine Dose 50 mg (N=23) n (%), (AEs)
Neurological Disorders	
Somnolence	9 (39.1), 9
Dizziness postural	1 (7.1), 1
Psychiatric Disorders	
Anxiety	4 (17.4), 4
Insomnia	2 (8.7), 2
Panic attack	1 (4.3), 1
Restlessness	1 (4.3), 1
General Disorders	
Fatigue	1 (7.1), 1

Comment

Sedative-type AEs, such as somnolence, predominated and occurred at high frequency of 39%, but stimulant-type AEs such as anxiety, insomnia, panic attacks, and restlessness were also present.

4. Multidose Study # NBI-98854-1403: A Phase 1b, Open-Label, Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of NBI-98854 in Children and Adolescents with Tourette Syndrome

Design:

Doses: children (5, 10 mg qd) and adolescents (10, 25, 50 mg qd) for 14 days.
Population: 28 subjects: 11 children and 17 adolescents

Table 6. Adverse events in pediatric patients with Tourette syndrome based on tables Table 14.3.1.2 and Table 14.3.1.4 in the study report.

Adverse Event PT	Children Valbenazine Dose 5, 10 mg (N=11) n (%), (AEs)	Adolescents Valbenazine Dose 10, 25, 50 mg (N=11) n (%), (AEs)
n-subjects, events-AEs		
Overall	5 (45.5), 15	14 (82.4), 34
Neurological Disorders		

Lethargy		1 (5.9), 1
Somnolence		3 (17.6), 3
Dizziness postural		
Psychiatric Disorders		
Suicidal ideation	1 (9.1), 1	
Insomnia		1 (5.9), 1
Anxiety		1 (5.9), 1
Agitation		1 (5.9), 1
Depressed mood		1 (5.9), 1
Restlessness		1 (5.9), 1
General Disorders		
Fatigue	1 (9.1), 1	8 (47.1), 8
Irritability		1 (5.9), 1

Comment

Both stimulant and sedative type AEs were seen in this pediatric population.

4.2.2 Clinical Studies Phase 2/3 in Patients with Schizophrenia or Schizoaffective disorder

A phase 2/3 controlled studies pool consists of 3 studies (Studies 1201, 1202, and 1304) that included placebo-controlled periods of up to 6 weeks in subjects with tardive dyskinesia. There were 254 subjects who received NBI-98854 and 178 subjects received placebo. The most frequent TEAEs (assessed by the sponsor as possibly or definitely related to study drug) occurred in 55 subjects (22%) treated with valbenazine and 27 subjects (15%) who received placebo. The only events assessed by the Sponsor as related to valbenazine, that occurred in $\geq 2\%$ of subjects, included somnolence (6% drug vs 2% placebo), fatigue (4% drug and 1% of placebo), dry mouth (3% NBI-98854 vs 2% placebo), akathisia (2% of drug vs 0% placebo), and headache (2% of drug vs 0% placebo).

Table 7. Treatment-emergent adverse events by in patients schizophrenia or schizoaffective disorder system organ class and preferred term: Phase 2/3 controlled studies based on ISS, Table 1.2.2.2, p 421.

Adverse Event PT	Placebo (N=178) n (%) [#]	Valbenazine Doses 100 mg (N=27) n (%)	Valbenazine All Doses (N=254) n (%)
Any adverse event – All SOC	71 (39.9)	8 (29.6)	111 (43.7)
Neurological Disorders			
Somnolence	4 (2.2)	1 (3.7)	14 (5.5)
Sedation	1 (0.6)	0	3 (1.2)
Disturbance in attention	0	0	1 (0.4)

Psychiatric Disorders			
Suicide attempt	0	1 (0.9)	1 (0.4)
Anxiety	0	0	3 (1.2)
Insomnia	1 (0.6)	0	4 (1.6)
Restlessness	0	0	1 (0.4)
Depressed mood	0	0	1 (0.4)
Panic attack	0	0	2 (0.8)
Hypomania	0	1 (0.9)	1 (0.4)
Hostility	0	0	1 (0.4)
Paranoia	0	1 (0.9)	1 (0.4)
General Disorders			
Fatigue	3 (1.7)	2 (7.4)	10 (3.9)

Comment

The population treated with valbenazine shows, especially at higher doses, an increase of AEs such as somnolence, sedation, anxiety, insomnia, restlessness, suicide attempt, panic attacks, and fatigue.

4.4 Evidence of Abuse, Misuse Diversion and Overdose in Clinical Trials

Overdose accidental and intentional

In an IR from Jan 11 2017 requested by CSS, the Sponsor provided information on overdoses. During the Phase 2 and 3 studies, approximately 26 subjects took one or more extra doses of valbenazine. Apparently, subjects often mistakenly took an extra dose for 1 or 2 days. However, 2 subjects took extra doses for longer than a week.

- Subject 1402-472-4001 misunderstood the dosing instructions and took two capsules (total of 80 mg/day) instead of 1 capsule as instructed, for approximately 2 weeks. The subject experienced an AE of somnolence that resolved after she took the study drug as instructed.
- Subject 1201-153-1001 was accidentally given the study drug by her caregiver, 100 mg twice a day (total of 200 mg/day), instead of once a day, for 8 days. On Day 8 the subject experienced syncope at work. The subject was taken to an emergency room where a diagnosis of syncope (moderate, not related, resolved on that day) and urinary tract infection (mild, not related, resolved on Day 18). Study drug was discontinued due to these events.

Diversion

Patients received study drug kits for administration at home during the four Phase 2 and 3 studies (Studies NBI-98854-1201, 1202, 1304, 1402). A total of 6069 kits were dispensed and approximately 157 valbenazine kits and 13 placebo kits were not returned to the site, see table below. The sponsor speculates “*that the lower number of unreturned placebo kits likely reflects that fewer placebo kits were dispensed overall.*” Another possibility is drug diversion.

Table 8. Reasons for not returned kits (from IR from Dec 27 2016, page 1).

Table 1: Reasons Study Drug Kits Were Not Returned to Sites

Reason Reported by Site	Number of Study Drug Kits Not Returned	
	Valbenazine Kits	Placebo Kits
Kit was lost	84	2
Subject was lost to follow up	36	0
Kit was discarded by subject	11	2
Kit was discarded by assisted living facility or caregiver	9	0
Kit was stolen	7	1
Unknown	6	6
Subject did not return for Early Termination Visit/Final Study Visit	4	1
Kit was destroyed ^a	0	1
Total	157	13

^a Study drug kit was destroyed in a house fire.

4.5 Evaluation of Dependence, Tolerance and Rebound in Clinical Studies

Dependence and Withdrawal

Dependence was evaluated in Phase 2/3 studies at 2 weeks after drug discontinuation in studies # NBI-98854-1201, NBI-98854-1202 and after 4 weeks in study # NBI-98854-1304. Additionally, part of the study population from study # NBI-98854-1402 is included, where the withdrawal was evaluated at 4 weeks after drug discontinuation. The AEs observed during the discontinuation period are shown in Table 8.

Table 8. Adverse events that occurred during the discontinuation period in the Phase 2/3 studies as provided in IR from Jan 17 2017.

Adverse Event PT	Valbenazine Dose 40 and 80 mg (N=182) n (%), AEs
n-subjects, events-AEs	
Cardiac disorders	
Sinus tachycardia	1 (0.5), 1
Vascular disorders	
Hypertension	1 (0.5), 1
Neurological Disorders	
Ataxia	1 (0.5), 1
Cerebrovascular accident	1 (0.5), 1
Convulsions	1 (0.5), 1
Headache	1 (0.5), 1

Psychiatric Disorders	
Anxiety	2 (1.1), 2
Insomnia	1 (0.5), 1
Agitation	1 (0.5), 1
Schizophrenia	2 (1.1), 2
Delirium	1 (0.5), 1
Nightmare	1 (0.5), 1
General Disorders	
Fatigue	1 (0.5), 1
Irritability	1 (0.5), 1
Pain	1 (0.5), 1
Gastrointestinal disorders	
Constipation	1 (0.5), 1
Dry mouth	1 (0.5), 1
Nausea	1 (0.5), 1
Injuries	
Fall	1 (0.5), 1
Head injury	1 (0.5), 1
Foot fracture	1 (0.5), 1
Metabolism disorders	
Anorexia	1 (0.5), 1

Although infrequent, there were some AEs suggestive of withdrawal, including anxiety, insomnia, agitation, hypertension, fatigue, and irritability.

Conclusions

Dependence and withdrawal were not systematically evaluated in Phase 2/3 trials:

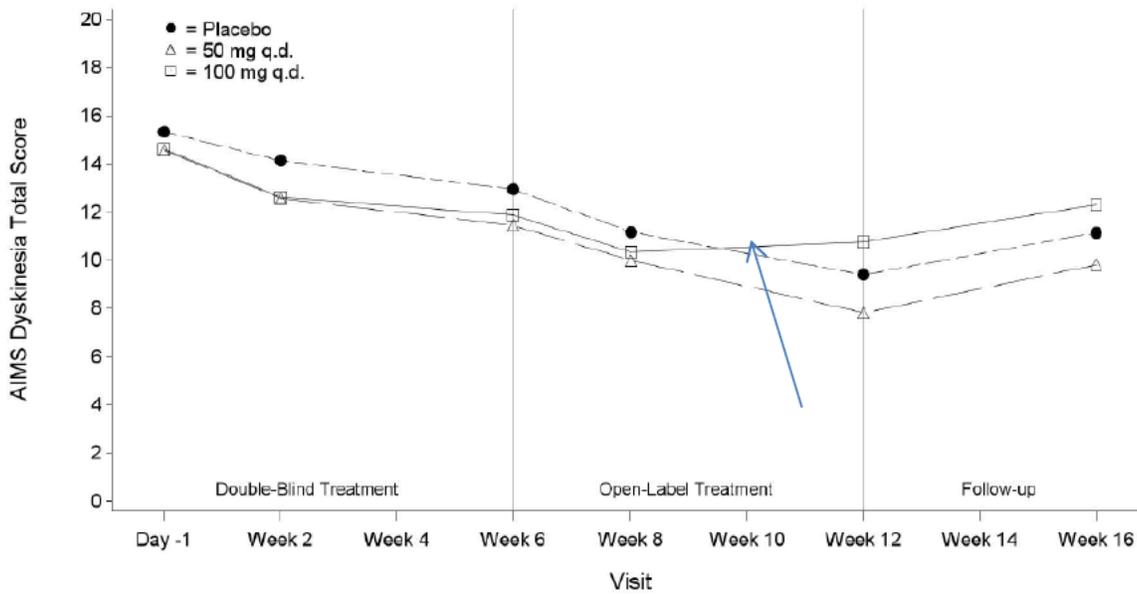
- no specific withdrawal questionnaires were used
- the visits evaluating patient's status during the discontinuation period were not frequent enough to capture possible withdrawal symptoms of the drug which has a half-life ~15-20 hours (after 2 weeks in study # NBI-98854-1201, and NBI-98854-1202 and after 4 weeks post-discontinuation in in study #NBI-98854-1304)
- in an IR response dated Jan 17 2017 the Sponsor indicated that withdrawal was evaluated with multiple disease-specific scales, however large number of patients discontinued and some scales do not show baseline values, therefore this data cannot be representative of an evaluation of withdrawal:
 - Regarding these scales presented in the ISS, it is unclear what they really represent. For example the MADRS scale starts with 121 patients treated with valbenazine at baseline, this number then decreases over subsequent weeks and by week 52 there are only 18 patients; this makes withdrawal data uninterpretable.
 - In the individual studies, the Calgary Depression Scale for Schizophrenia (CDSS) was administered only after 4 weeks of drug discontinuation (study # NBI-98854-1201) and at

- the baseline there were 55 subjects and at the week 16 only 38; again it is difficult to draw any conclusions.
- In the study # NBI-98854-1202, CDSS, Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS) scales don't have baseline values for individual doses and were administered only after 2 weeks of drug discontinuation. MADRS shows some score increase during the withdrawal period for all doses and YMRS only for the highest dose.
 - Study # NBI-98854-1304 MADRS started with 73 patients and at week 52 there were only 18 patients, also MADRS scores increased for all doses for week 52 compared to week 48..
 - Of the AE withdrawal data available for 182 out of 427 subjects who entered the Phase 2/3 studies; apparently 81 patients are still enrolled and 167 discontinued the study
 - Analysis of the selected largest Phase 2/3 studies demonstrates some rebound in study # NBI-98854-1304 at 40 mg (week 6 re-randomized) and some development of tolerance for the studies # NBI-98854-1201 (dose 100 mg) and # NBI-98854-1304 (dose 80 mg). Both tolerance and rebound are indicative of the development of dependence. Additionally, in the studies where functional measures were assessed after 4 weeks (study # NBI-98854-1201 and # NBI-98854-1304) it is possible that the peak of rebound was missed as it usually starts in the first week after drug discontinuation.
 - In some preclinical toxicology studies, a withdrawal syndrome was observed during the initial 9-10 days of the drug free recovery: in the study# 2011-TX-040 increased activity with restless pacing, running and jumping in the cage, along with aggression was observed; in the study # 2011-TX-001 increased activity during the withdrawal period was noted.
 - Because valbenazine's mechanism of action is through VMAT2 dopaminergic, serotonergic and adrenergic systems (Erickson et al., 2000) and GABA release by dopaminergic neurons (Tritsch et al., 2012), the effects of a sudden reversal of long standing inhibition (claimed to be the main action of valbenazine), may cause an acute withdrawal syndrome. Of particular concern are cardiovascular and neurological AEs. Some toxicological studies already showed a withdrawal syndrome, therefore evaluation of clinical dependence and withdrawal is necessary.

Tolerance

The analysis of selected studies suggests development of some tolerance, in particular for the highest dose 100 mg, after week 8 (arrow) in the study # NBI-98854-1201, figure 14.7.5 from the study report, page 382.

Figure 14.7.5
AIMS Dyskinesia Total Score Arithmetic Means by Visit and Randomized Treatment [1]
(ITT Analysis Set)

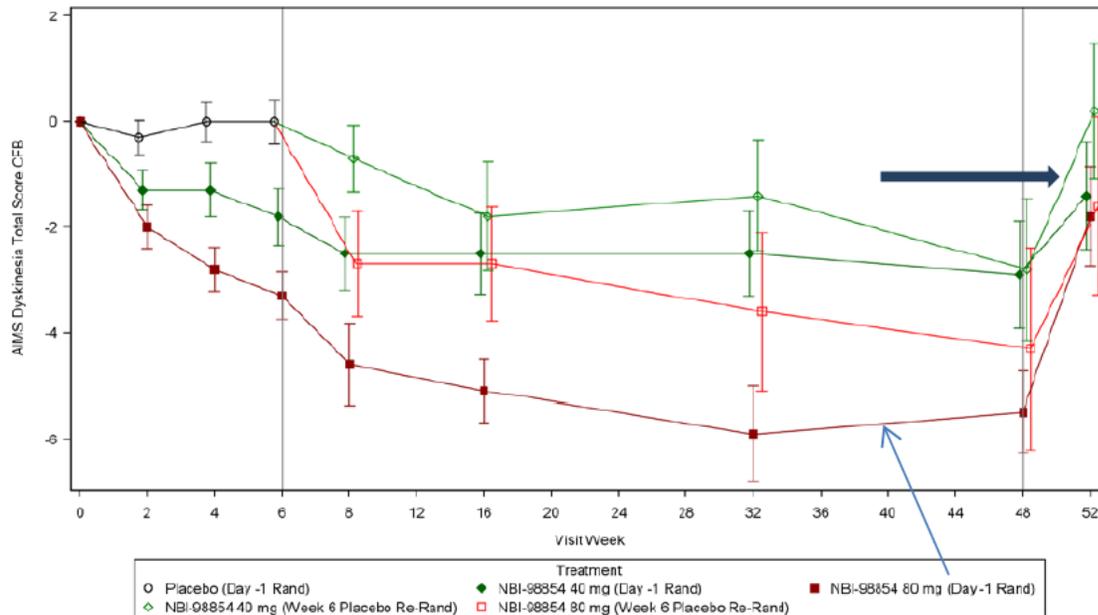


[1] Randomized treatment at Study Day -1.
Source Data Table: 14.13.1

(b) (4)

Also, some mild tolerance was seen developing in the study # NBI-98854-1304, after week 32 for the dose 80 mg, thin arrow, figure below, from the study report, page 111.

Figure 9: Abnormal Involuntary Movement Scale Mean Score Change from Baseline during the Study (Mean ± SEM, ITT Analysis Set)

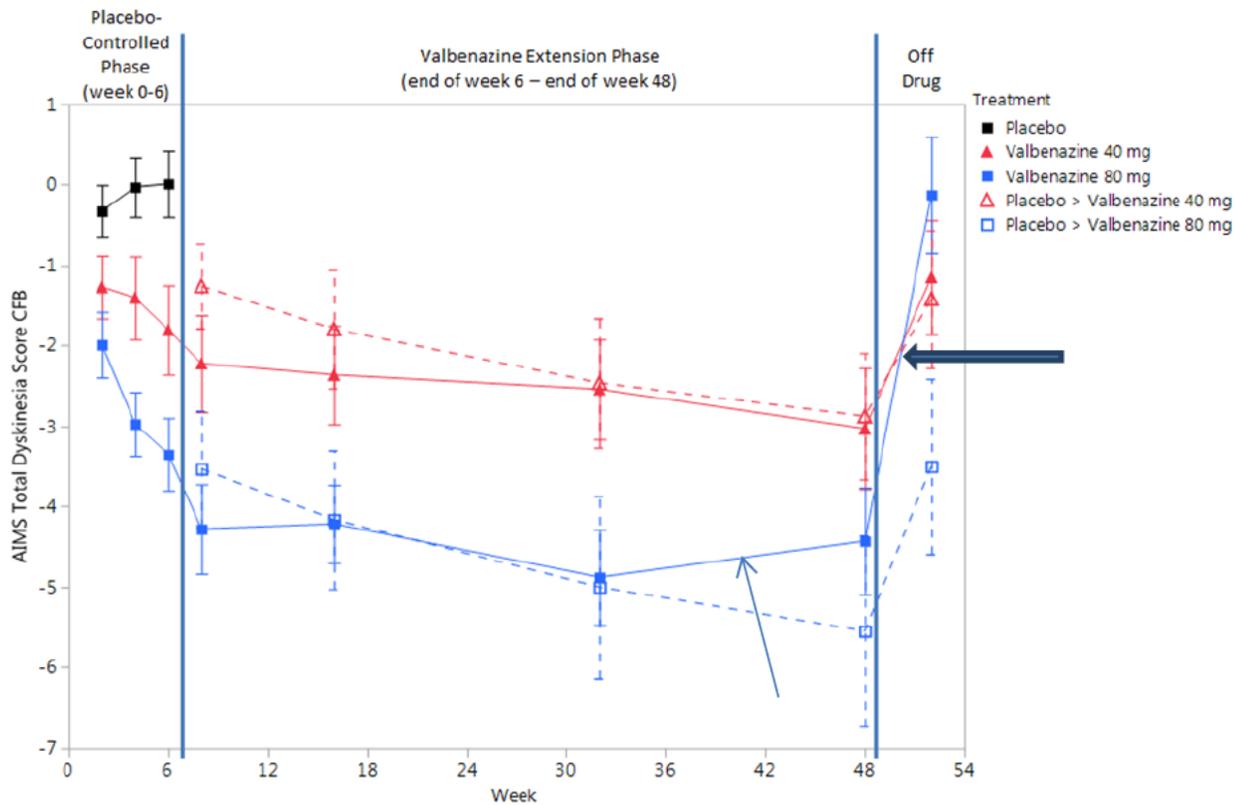


Data Source: [Figure 14.2.1.2](#).

Rebound

The analysis of the selected largest Phase 2/3 studies show some rebound in study # NBI-98854-1304 for the dose 40 mg (week 6 re-randomized) indicated in the figure above with the bold arrow. Both tolerance and rebound are indicative of the development of dependence, also in the studies where functional measure were assessed first after 4 weeks (study # NBI-98854-1201 and # NBI-98854-1304) it remains possible that the peak of rebound was missed as it usually starts in the first week of drug discontinuation.

The Division’s medical officer, Dr. Michael Davis, during a wrap-up meeting, provided efficacy calculations for study # 1304. It shows significant rebound, a worsening of symptoms in comparison with baseline (thick arrow) for the dose of 80 mg, and less for the dose 40 mg, and also development of tolerance with ~14% loss of therapeutic effect which is seen at week 32 for the dose 80 mg, (thin arrow), see below.



Treatment Group (n=)	Subjects/Visit Week								
	0	2	4	6	8	16	32	48	52
Placebo	76	74	73	69	0	0	0	0	0
40 mg	70	67	62	61	59	47	37	34	34
80 mg	79	75	72	69	65	56	49	42	41
Placebo/40mg	0	0	0	0	31	29	26	24	24
Placebo/80mg	0	0	0	0	32	31	25	22	22

5. Regulatory Issues and Assessment

Much of the AE data is confounded as it was collected in schizophrenic patients taking multiple other medications. The data derived from healthy volunteers for multiple doses studies is very small and only for very short time periods. At this point the drug appears to be psychoactive and the data from healthy volunteers fails to clearly show AEs indicative of abuse-potential., Stimulant-type AEs of insomnia, anxiety, restlessness, energy increased, nervousness, panic attack and sedative AEs such as somnolence, fatigue were more common in normal subjects exposed to valbenazine. Very similar AEs were seen in patients with schizophrenia, including somnolence, sedation, fatigue, insomnia panic attacks, all of which were more frequent in patients treated with valbenazine than in the placebo group. Lastly, preclinical studies suggest the presence of a withdrawal syndrome.

5.1. Adverse Event Reporting Post-Approval

Post-approval, we recommend continuing post-marketing assessment of those AEs suggestive of abuse-potential, see Guidance ³. These should be included in the standard Periodic Adverse Event Reports (PADERS).

5.2 Recommended Studies or Trials as Postmarketing Requirements (PMRs)

PMR - Dependence and Withdrawal-

The data provided in this NDA suggests a withdrawal syndrome in preclinical toxicological studies along with evidence of a rebound effect following withdrawal of valbenazine in some clinical studies. Therefore, the Sponsor needs to conduct a dedicated systematic evaluation of clinical dependence and withdrawal. We recommend that you evaluate clinical dependence and withdrawal in the patient population at the completion of on-going Studies # 1304 and # 1402 reviewed in the ISS. We further recommend evaluation of patients for signs and symptoms of clinical dependence and withdrawal for 3 weeks after the abrupt discontinuation of valbenazine.

(b) (4)

(D) (4)

We recommend the Sponsor submit, for FDA review, your planned analyses for the evaluation of potential dependence, withdrawal and rebound.

³ Guidance for Industry for Assessment of Abuse Potential of Drugs Jan 2017
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

V. REFERENCES

1. Erickson JD, Varoqui H. Molecular analysis of vesicular amine transporter function and targeting to secretory organelles. *FASEB J.* 2000 Dec;14(15):2450-8.
2. Tritsch NX, Ding JB, Sabatini BL. Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature.* 2012 Oct 11;490(7419):262-6. doi: 10.1038/nature11466. Epub 2012 Oct 3.

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/s/

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02/28/2017

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02/28/2017

MARTIN S RUSINOWITZ
02/28/2017

MICHAEL KLEIN
02/28/2017

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 22, 2017

TO: Mitchell Mathis, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Office of New Drugs

FROM: Li-Hong Yeh, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Melkamu Getie-Kehtie, R.Ph., Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection of in vivo bioequivalence **Study NBI-98854-1504 (NDA 209241)** conducted by [REDACTED] (b) (4). At the conclusion of the inspection, no significant issues were observed and Form FDA 483 was not issued. The final inspection classification for this inspection is No Action Indicated (NAI). Upon review of inspectional findings, we found the data from the bioanalytical portion of **Study NBI-98854-1504** to be reliable and recommend that the Agency accepts the data for further review.

Audited in vivo bioequivalence study:

NDA 209241

Study Number: NBI-98854-1504

Study Title: "A Phase 1, Randomized, Open-Label, Two-Cohort, Two-Period Crossover Study to Evaluate the Bioequivalence of Two NBI-98854 Capsule Formulations and the Effect of Food on NBI-98854 Pharmacokinetics in Healthy Adult Subjects."

Dates of

Study Conduct: 10/18/2015 - 12/11/2015

Dates of

Sample Analysis: 10/20/2015 - 12/17/2015

OSIS scientists, [REDACTED] (b) (4)
[REDACTED] audited the bioanalytical portion of Study NBI-98854-1504 at [REDACTED] (b) (4)

We thoroughly audited the facility, equipment, records for method validation and study sample analysis, correspondence, SOPs, biological sample management and storage, instrument audit trails, as well as interviews and discussions with management and staff. At the conclusion of the inspection, we did not observe any significant issues and did not issue Form FDA 483.

Conclusion:

After reviewing the EIR and the inspectional findings, we conclude that the bioanalytical portion of **Study NBI-98854-1504** is reliable and recommend that the Agency accepts the data for further review.

(b) (4)

Final Classification:

Bioanalytical site

NAI- [REDACTED] (b) (4)

(b) (4)

CC:

OTS/OSIS/Kassim/Taylor/Choe/Haidar/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah/Miller/Johnson

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Yeh

OTS/OSIS/DGDBE/Cho/Murphy/Skelly/Choi/Au/[REDACTED] (b) (4)

Draft: PY 02/21/2017; MG 2/21/2017

Edits: RCA 2/21/2017 AD 2/22/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/
Analytical Sites [REDACTED] (b) (4)

BE File #: [REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

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/s/

LI-HONG P YEH
02/22/2017

RUBEN C AYALA
02/22/2017

ARINDAM DASGUPTA
02/22/2017

Clinical Inspection Summary

Date	02/14/2017
From	Cara Alfaro, Pharm.D., Clinical Analyst Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Mona Kalsi, Pharm.D., Regulatory Project Manager Michael Davis, M.D., Medical Officer Division of Psychiatry Products
NDA #	209241
Applicant	Neurocrine Biosciences, Inc.
Drug	valbenazine
NME	Yes
Therapeutic Classification	Monoamine transporter 2 inhibitor
Proposed Indication(s)	Treatment of tardive dyskinesia
Consultation Request Date	9/23/2016
Summary Goal Date	2/17/2017
Action Goal Date	4/11/2017
PDUFA Date	4/11/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 209241, five clinical investigator sites and the sponsor (Neurocrine Biosciences, Inc.) were inspected. Based on the results of these inspections, the data submitted by the sponsor in support of the pending application for these sites are acceptable and the studies were conducted adequately.

Four of the clinical investigator inspections have been classified as No Action Indicated (NAI) based upon review of the Establishment Inspection Report (EIR). A Form FDA 483 was issued to one clinical investigator (Castro), and upon review of the EIR, the inspection was classified as Voluntary Action Indicated (VAI). The primary inspectional observation was that there was a change in clinical investigator for Protocol NBI-99854-1202 and Dr. Castro, who had not been previously associated with this study, did not receive IRB approval as the new clinical investigator prior to her participation in the study. The sponsor inspection has been preliminarily classified as NAI, and the EIR for this inspection is pending. An addendum to this Clinical Inspection Summary (CIS) will be generated if conclusions change upon receipt and review of this EIR.

II. BACKGROUND

Valbenazine (NDA 209241) is being developed for the treatment of tardive dyskinesia (TD). Valbenazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor. This transporter protein plays an important role in presynaptic dopamine release. It is hypothesized that modulation of dopaminergic tone through inhibition of VMAT2 may be an effective mode of treatment of TD. Currently there are no medications approved for the treatment of TD.

The sponsor has submitted two double-blind, placebo-controlled clinical studies to support the efficacy and safety of valbenazine in the treatment of TD, NBI-99854-1202 (Phase 2) and NBI-99854-1304 (Phase 3).

Protocol NBI-99854-1202

Title: A Phase 2, randomized, double-blind, placebo-controlled, dose titration study to assess the safety, tolerability, and efficacy of NBI-98854 [valbenazine] for the treatment of tardive dyskinesia

Subjects/Sites: 102 randomized subjects in 27 sites in the United States and 2 sites in Puerto Rico

Study Initiation and Completion Dates: 2/19/2013 – 12/19/2013

This was a Phase 2, randomized, double-blind, placebo-controlled, dose-titration study comparing valbenazine (25 to 75 mg) to placebo administered once daily for 6 weeks. Included were subjects with a diagnosis of schizophrenia, schizoaffective disorder, or a mood disorder with antipsychotic-induced TD or a gastrointestinal disorder with metoclopramide-induced TD. Subjects had to have TD for at least three months prior to screening and moderate to severe TD at screening.

The primary efficacy endpoint was the mean change from baseline to Week 6 in the AIMS total score (items 1 to 7) [also called the AIMS dyskinesia total score] comparing valbenazine to placebo. The sponsor reported a mean change from baseline to Week 6 on the AIMS total score of -3.6 for the valbenazine group and -1.1 for the placebo group; the least squares (LS) mean difference favored valbenazine compared to placebo (-2.4, $p = 0.0005$). The key secondary efficacy endpoint was the Clinical Global Impression of Change - Tardive Dyskinesia (CGI-TD) mean score at week 6 comparing valbenazine to placebo. The sponsor reported CGI-TD mean scores at week 6 of 2.3 for the valbenazine group and 3.1 for the placebo group; LS mean differences favored valbenazine compared to placebo (-0.8, $p < 0.0001$).

Protocol NBI-99854-1304

Title: A Phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study to assess the efficacy, safety, and tolerability of NBI-98854 [valbenazine] for the treatment of tardive dyskinesia

Subjects/Sites: 234 randomized subjects in 59 sites in the United States, 2 sites in Puerto Rico, and 2 sites in Canada

Study Initiation and Data Cutoff Dates: 11/5/2014 – 3/30/2016

This is an ongoing Phase 3, randomized, double-blind, placebo-controlled, parallel, fixed-dose study comparing valbenazine (40 mg and 80 mg) to placebo administered once daily. The inclusion criteria were similar to Protocol NBI-99854-1202, except that only subjects with psychiatric diagnoses were included. The study included a double-blind, placebo-controlled period of six weeks followed by a double-blind valbenazine treatment period of 42 weeks (“extension period”) and a posttreatment period of four weeks.

The primary efficacy endpoint was the mean change from baseline to Week 6 in the AIMS total score (items 1 to 7) comparing each valbenazine dose group to placebo. The sponsor reported a mean change from baseline to Week 6 on the AIMS total score of -1.8 for the valbenazine 40 mg group, -3.3 for the valbenazine 80 mg group, and 0.0 for the placebo group. The least squares (LS) mean difference favored valbenazine 40 mg compared to placebo (-1.8, $p = 0.0021$) and the valbenazine 80 mg group compared to placebo (-3.1, $p < 0.0001$). The key secondary endpoint was the CGI-TD mean score at Week 6 comparing each valbenazine dose group to placebo.

Inspections of clinical sites were considered essential to verify the data submitted for this application. Clinical sites for inspection were chosen primarily based on the numbers of subjects enrolled at the site (including a clustering of high enrolling sites in Hialeah, Florida), and site-specific efficacy effect size. The focus of the clinical site inspections was adherence to protocols (e.g. inclusion/exclusion criteria), protocol deviations, documentation of informed consent prior to subject participation, reporting of adverse events, maintenance of the study blind, and verification of the primary and key secondary efficacy endpoints. Additionally, for the clustering of sites in Hialeah, Florida, to determine if any subjects participated in this study at multiple clinical sites (duplication of subjects).

III. RESULTS (by site)

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Dates	Classification
Site #215 and #312 Kenia Castro, M.D. Reliable Clinical Research, LLC 4160 West 16 Avenue Hialeah, FL 33012	NBI-99854-1202 Subjects: 17 NBI-99854-1304 Subjects: 12	10/26/2016 to 11/03/2016	VAI

Site #, Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Dates	Classification
Site #224 and Site #313 Julio Castro-Gayol, M.D. Research in Miami, Inc. 777 East 25 Street Hialeah, FL 33013	NBI-99854-1202 Subjects: 18 NBI-99854-1304 Subjects: 12	11/14/2016 to 11/18/2016	NAI
Site #355 Dolores Sanchez-Cazau, M.D. Sanchez Cazau Medical Group 777 East 25 Street, Suite 501 Hialeah, FL 33013	NBI-99854-1304 Subjects: 14	11/14/2016 to 11/18/2016	NAI
Site #204 and Site #345 Daniel Mandri, M.D. Biscayne Bay Institute 3408 West 84 St., Suite 209 Hialeah, FL 33018	NBI-99854-1202 Subjects: 11 NBI-99854-1304 Subjects: 11	11/03/2016 to 11/09/2016	NAI
Site #361 Cherian Verghese, M.D. Keystone Clinical Studies, LLC 2460 General Armistead Ave Suite 300 Norristown, PA 19403	NBI-99854-1304 Subjects: 10	10/24/2016 to 10/28/2016	NAI
Neurocrine Biosciences, Inc. 12780 El Camino Real San Diego, CA 92130	NBI-99854-1202 NBI-99854-1304	11/30/2016 to 12/02/2016	NAI*

Compliance Classifications

NAI = NoAction Indicated; no deviation from regulations.

VAI = Voluntary Action Indicated; deviation(s) from regulations.

OAI = Official Action Indicated; significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Clinical Investigator: Kenia Castro, M.D.; Hialeah, FL; Sites #215 and #312

For Protocol NBI-99854-1202, Dr. Hamlet R. Hassan was the clinical investigator from study initiation until 9/30/2013. Dr. Kenia Castro was the clinical investigator from 9/30/2013 until study closure on 12/31/2013. Dr. Kenia Castro was the clinical investigator for Protocol NBI-99854-1304.

For Protocol NBI-99854-1202, twenty-two subjects were screened, seventeen subjects were enrolled, and fifteen subjects completed the study. Two subjects discontinued the study due to adverse events. Per data listings, the adverse events were urinary retention (Subject #215-2009/placebo) and convulsion and myocardial infarction resulting in death (Subject #215-2020/placebo).

For Protocol NBI-99854-1304, twenty-one subjects were screened, twelve subjects were enrolled, and eight subjects completed the study. Three subjects discontinued due to adverse events and one subject was lost to follow-up. Per data listings, the adverse events were mental status changes (Subject #312-3005/placebo), diabetes mellitus, (Subject #312-3006/valbenazine), and blood urea/blood creatinine increased (Subject #312-3016/valbenazine).

Signed informed consent forms were present for all subjects who were screened to participate in the studies prior to participation. An audit of the study records for nine subjects in study NBI-99854-1202 and five subjects in study NBI-99854-1304 (total of 14 subjects) was conducted. Records reviewed included but were not limited to source documents, inclusion/exclusion criteria, adverse event reports, adverse event reporting, concomitant medications, IRB/sponsor communications, financial disclosure, test article accountability, and protocol deviations. Primary efficacy data (AIMS) could not be verified since these ratings were performed via a central video rater (b) (4)

A Form FDA 483 was issued at the conclusion of the inspection. A number of inspectional findings were cited, all of which were noted in monitoring reports available at the site, reported to the sponsor, and are included in sponsor data listings for this application. After review of these findings, the inspection was classified as VAI.

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LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: February 2, 2017
Requesting Office or Division: Division of Psychiatry Products (DPP)
Application Type and Number: NDA 209241
Product Name and Strength: Ingrezza (valbenazine) capsules
40 mg
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Neurocrine Biosciences, Inc.
Submission Date: August 11, 2016
OSE RCM #: 2016-2015
DMEPA Primary Reviewer: Loretta Holmes, BSN, PharmD
DMEPA Team Leader: Lolita White, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels, professional sample blister label, professional sample carton labeling and the prescribing information for new NDA 209241 for Ingrezza (valbenazine) capsules, submitted on August 11, 2016. The Division of Psychiatry Products (DPP) requested that we review the proposed labels and labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed container labels, professional sample blister label, professional sample carton labeling and prescribing information for Ingrezza (valbenazine) to determine if there are any areas of concern or needed improvement from a medication safety perspective. We identified the following:

1. On the container labels, the proprietary name and established name lack prominence relative to the large size of the statement of strength.
2. The Medication Guide (MG) statement lacks sufficient prominence. Additionally, the MG statement does not state how the MG is supplied.
3. The design of the professional sample packaging can be improved upon. Specifically, the instructions for how to open the package are on the back side of the package. This location does not readily provide a visible cue to the patient on how the package should be opened. Additionally, as presented, the placement of the MG/Prescribing Information leaflet(s) that is glued to the back of the package may obstruct the

instructions for opening the package. Furthermore, the back side of the pull-out blister lacks the product identifier information and it faces the principal display panel when the package is opened which is not optimal for the patient's viewing of the information contained on the blister label (see Appendix G).

4 CONCLUSION & RECOMMENDATIONS

We identified areas of needed improvement in the language, size, and/or positioning of certain statements on the container label and professional sample blister and carton labeling.

Additionally, we identified areas where the design of the professional sample blister pack can be improved to help facilitate patient handling and viewing of product identifying information. We provide recommendations in Section 4.1, below.

4.1 RECOMMENDATIONS FOR NEUROCRINE BIOSCIENCES, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. The proprietary name and established name lack prominence relative to the large size of the statement of strength. Increase the relative size of the proprietary and established names. Decrease the size of the statement of strength so that it is not more prominent than the proprietary and established names.
2. The Medication Guide (MG) statement lacks sufficient prominence due to its location below the "Keep out of reach..." statement. Reverse the positions of these two statements in order to increase the prominence of the MG statement.
3. The MG statement does not state how the MG is supplied. We recommend the following language (or similar verbiage) dependent upon how the Medication Guide is supplied [see 21 CFR 208.24(d)].
 - a. "Attention Pharmacist: Dispense the enclosed Medication Guide to each patient." or
 - b. "Attention Pharmacist: Dispense the accompanying Medication Guide to each patient."

B. Professional Sample Blister Pack Labeling and Packaging

1. Blister Label
 - a. The statement of strength on the blister label lacks clarity. The blister pack contains five 40 mg capsules but the individual capsule compartments are not labeled with the capsule strength. We are concerned this may lead to overdose if the user misinterprets the entire package of 5 capsules as being equal to one 40 mg dose. In order to help clarify that each capsule contains 40 mg (and not the entire blister pack of 5 capsules), please revise the

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ingrezza that Neurocrine Biosciences, Inc. submitted on August 11, 2016.

Table 2. Relevant Product Information for Ingrezza	
Initial Approval Date	N/A
Active Ingredient	valbenazine
Indication	Treatment of tardive dyskinesia
Route of Administration	Oral
Dosage Form	Capsule
Strength	40 mg
Dose and Frequency	The initial dose is 40 mg, taken orally as one 40 mg strength capsule, once daily. The dose should be increased to the recommended dose of 80 mg, taken orally as two 40 mg strength capsules once daily, based on therapeutic response and tolerability.
How Supplied	30-count and 90-count bottles
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
Container Closure	High density polyethylene (HDPE) [REDACTED] (b) (4) [REDACTED]

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Ingrezza labels and labeling submitted by Neurocrine Biosciences, Inc. on August 11, 2016 and a physical sample of the professional sample blister pack.

- Container label
- Professional Sample Blister Label
- Professional Sample Carton Labeling
- Physical sample of the Professional Sample Blister Pack

G.2 Labels and Labeling Images (not to scale)

Container Labels



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LORETTA HOLMES
02/02/2017

LOLITA G WHITE
02/02/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: January 5, 2017

Reviewer: Ofir Noah Nevo, PharmD, BCPP, Safety Evaluator
Division of Pharmacovigilance I

(Acting) Team Leader: Vicky Chan, PharmD, BCPS, Safety Evaluator Team Leader
Division of Pharmacovigilance I

Deputy Division Director: Cindy Kortepeter, PharmD
Division of Pharmacovigilance I

Product Name(s): Xenazine (tetrabenazine) and Ingrezza (valbenazine)

Subject: Safety profile in patients with tardive dyskinesia

Application Type/Number: NDAs 21894 and 209241

Applicant/Sponsor: Valeant Pharmaceuticals North America LLC (Xenazine)
Neurocrine Biosciences Inc (Ingrezza)

OSE RCM #: 2016-2741

Special thanks to Dr. David Croteau and Dr. Robert Levin for their assistance with this review.

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EXECUTIVE SUMMARY

This review provides a high-level FDA Adverse Event Reporting System (FAERS) overview of tetrabenazine, and evaluates cases identified in the FAERS database and the published medical literature for an association between tetrabenazine and any serious adverse events (AEs) in the context of off-label use for tardive dyskinesia (TD). The Division of Psychiatry Products (DPP) requested this review in preparation for the valbenazine Advisory Committee meeting scheduled for February 2017.

DPV did not identify any new safety signals for tetrabenazine used in patients with TD. The majority of FAERS reports associated with tetrabenazine are of limited quality, and the role of tetrabenazine cannot be determined in most cases. The FAERS overview did not reveal any unexpected AEs for tetrabenazine. Hyperthermia, (b) (4) has been described in the medical literature in a patient using tetrabenazine for treating TD, and may be worth discussing in relation to risk of hyperthermia and neuroleptic malignant syndrome (NMS) with valbenazine.

DPV does not have any recommendations for regulatory action for tetrabenazine or valbenazine at this time.

1 INTRODUCTION

This review provides a high-level FDA Adverse Event Reporting System (FAERS) overview of tetrabenazine, and evaluates cases identified in the FAERS database and the published medical literature for an association between tetrabenazine and any serious adverse events (AEs) in the context of off-label use for tardive dyskinesia (TD). The Division of Psychiatry Products (DPP) requested this review in preparation for the valbenazine Advisory Committee meeting scheduled for February 2017.

1.1 BACKGROUND

On August 11, 2016, Neurocrine Biosciences Inc. submitted an original new drug application (NDA) for valbenazine (Ingrezza) with the proposed indication for the treatment of TD. Valbenazine is chemically related to tetrabenazine (Xenazine), which was approved in 2008 for the treatment of chorea associated with Huntington's Disease (HD). Valbenazine is the parent drug (prodrug) of the (+)- α -isomer of tetrabenazine (α -dihydro-tetrabenazine [α -DHTBZ]).¹ Tetrabenazine is known for its off-label use for the treatment of TD.^{2,3} During the valbenazine Post Mid-Cycle Communication meeting on November 28, 2016, the utility of evaluating the postmarketing data for tetrabenazine was discussed. Because of the chemical similarities between the two drugs, evaluating cases in the FAERS database for AEs involving tetrabenazine and off-label use for the treatment of TD may provide additional insight on the safety profile of valbenazine. Subsequently, DPP submitted a consult to the Division of Pharmacovigilance I (DPV I) on December 2, 2016 to conduct a review of postmarketing cases of AEs involving tetrabenazine use not related to HD for the time period January, 2010 – December, 2016, which led to this review.

1.2 REGULATORY HISTORY

Tetrabenazine

Tetrabenazine was approved by FDA on August 15, 2008 for the treatment of chorea associated with HD, under the trade name Xenazine.⁴ It is a vesicular monoamine transporter type 2 (VMAT2) inhibitor, and although the exact mechanism of its anti-chorea effects is unknown, it is believed to be related to its reversible depletion of monoamines (dopamine, serotonin, norepinephrine, and histamine).⁴ Although not indicated for the treatment of TD, there are reports in the medical literature of using tetrabenazine for this purpose; in addition, tetrabenazine is approved for use in TD in other countries.^{2,3}

In September 2014, a Tracked Safety Issue (TSI #1362) was opened regarding tetrabenazine, as a result of FDA receiving 14 postmarketing reports of death in pediatric patients. A DPV review of all tetrabenazine death reports and all serious pediatric reports revealed limited availability of clinical information in the majority of cases, and that the cause of death or role of tetrabenazine could not be determined due to the limited quality of the data.⁵ The review of death cases suggested potential discrepancies with postmarketing requirements specified in 21 CFR 314.80, including late 15-day reports and possible serious cases with inadequate follow-up. A previous DPV review of tetrabenazine also noted the poor quality of information in postmarketing reports

associated with tetrabenazine.⁶

(b) (4)

(b) (4)

Although there are seemingly some improvements in compliance with postmarketing requirements in recent years (e.g. better documentation of follow-up), the majority of reports submitted to FAERS by Valeant for tetrabenazine are still of limited quality and contain a paucity of clinical information. The reports are often unassessable – both in terms of characterizing the AE, and in terms of assessing the relationship of the AE with tetrabenazine. Another contributing factor to the ongoing poor quality of the reports may be the distribution of tetrabenazine exclusively through a specialty pharmacy, which results in solicited reporting (current regulatory requirements for solicited AE reports by a specialty distribution program are not well established, leading to inconsistency in the quality of reporting).

Valbenazine

Valbenazine is currently pending approval, with a Prescription Drug User Fee Act (PDUFA) goal date of April 11, 2017. It is a new molecular entity characterized as a selective, orally active VMAT2 inhibitor indicated for the treatment of TD. There are currently no FDA approved drugs for the treatment of TD. A rolling review for valbenazine was granted on March 29, 2016. Valbenazine was also granted fast track designation (January 2012) and breakthrough therapy designation (October 2014). The proposed trade name for valbenazine is Ingrezza.

Valbenazine is chemically similar to tetrabenazine. One of its main active metabolites, α -DHTBZ, is also one of tetrabenazine's main metabolites.⁸

As of the time of this review, valbenazine is not marketed in any foreign country; therefore, no foreign postmarketing data for valbenazine is available to include in this review.

1.3 PRODUCT LABELING

In the United States, the tetrabenazine labeling has a Boxed Warning for “Depression and Suicidality”:⁴

XENAZINE can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of XENAZINE must balance the risks of depression and suicidality with the clinical need for control of chorea. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy. Patients, their caregivers, and families should be informed of the risk of depression and

suicidality and should be instructed to report behaviors of concern promptly to the treating physician.

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.

In addition to depression and suicidality (Section 5.2), tetrabenazine is labeled with the following 12 WARNINGS AND PRECAUTIONS (brief summary provided along with title):⁴

- 5.1 Clinical Worsening and Adverse Effects: Periodically reevaluate the benefit and potential for adverse effects such as worsening mood, cognition, rigidity, and functional capacity
- 5.3 Laboratory tests: Before prescribing a daily dose greater than 50 mg/day, patients should be genotyped to determine their CYP2D6 metabolizer status
- 5.4 Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs
- 5.5 Akathisia, Restlessness, and Agitation: Reduce dose or discontinue if occurs
- 5.6 Parkinsonism: Reduce dose or discontinue if occurs
- 5.7 Dysphagia: Cases of dysphagia associated with aspiration pneumonia have occurred, monitor for dysphagia
- 5.8 Sedation and Somnolence: May impair patient's ability to drive or operate complex machinery
- 5.9 QTc prolongation: Not recommended in combination with other drugs that prolong QTc
- 5.10 Hypotension and Orthostatic Hypotension: Monitor vital signs on standing should be considered in patients who are vulnerable to hypotension
- 5.11 Hyperprolactinemia: Consider lab testing and discontinuation if symptoms occur
- 5.12 Tardive Dyskinesia: Discontinue if symptoms occur
- 5.13 Binding to Melanin-Containing Tissues: clinical relevance unknown, prescribers should be aware of possibility of long-term ophthalmologic effects

The warning regarding TD in tetrabenazine labeling is based on a theoretical risk. Section 5.12 Tardive Dyskinesia reads as follows (emphasis added in **bold**):⁴

*A potentially irreversible syndrome of involuntary, dyskinetic movements may develop in patients treated with neuroleptic drugs. In an animal model of orofacial dyskinesias, acute administration of reserpine, a monoamine depletor, has been shown to produce vacuous chewing in rats. Although the pathophysiology of tardive dyskinesia remains incompletely understood, the most commonly accepted hypothesis of the mechanism is that prolonged post-synaptic dopamine receptor blockade leads to supersensitivity to dopamine. **Neither reserpine nor XENAZINE, which are dopamine depletors, have been reported to cause clear tardive dyskinesia in humans**, but as pre-synaptic dopamine depletion could **theoretically** lead to supersensitivity to dopamine, and XENAZINE can cause the extrapyramidal symptoms also known to be associated with neuroleptics (e.g., parkinsonism and akathisia), physicians should be aware of the*

possible risk of tardive dyskinesia. If signs and symptoms of TD appear in a patient treated with XENAZINE, drug discontinuation should be considered.

Other countries in which tetrabenazine is approved for treating TD include, but are not limited to, Canada, the United Kingdom (UK), Australia, and New Zealand. The labeling language regarding warnings for tetrabenazine in these four countries is similar to labeling language in the United States, with the following notable exceptions:

- Labeling in Canada and Australia does not have a warning for TD associated with tetrabenazine.^{2,9}
- The New Zealand labeling has a warning regarding TD, which is mostly a reiteration of its specific indication, and reads as follows:¹⁰

Tardive Dyskinesia: The condition should be persistent despite withdrawal of antipsychotic therapy, or in cases where withdrawal of antipsychotic medication is not a realistic option; also where the condition persists despite reduction in dosage of antipsychotic medication or switching to atypical antipsychotic medication.
- The British labeling contains a warning for TD associated with tetrabenazine similar to the American labeling, but in addition to noting the theoretical nature of an association between tetrabenazine and TD, the warning also states, "...there have been cases of [TD] with tetrabenazine reported in the literature and in post-marketing; therefore, physicians should be aware of the possible risk."¹¹

The United States labeling for valbenazine is not yet finalized, but the proposed labeling as of December 23, 2016 includes the following five WARNINGS AND PRECAUTIONS (brief summary provided along with title):

- 5.1 Somnolence: Patients should not operate a motor vehicle or hazardous machinery until they know how they will be affected
- 5.2 QTc Prolongation: Avoid in patients with congenital long QT syndrome and history of cardiac arrhythmias

[REDACTED] (b) (4)

- 5.5 MAOIs: Should not be used in combination with an MAOI, or [REDACTED] (b) (4)

Of note, there was not a strong signal for depression and suicidality during clinical trials for valbenazine. [REDACTED] (b) (4)

2 METHODS AND MATERIALS

In this review, DPV conducted both a high-level overview of FAERS data regarding non-HD use of tetrabenazine, as well as a focused analysis of all AEs reported with tetrabenazine used to treat TD in patients who do not have HD. The same FAERS search strategy (Section 2.3) was used for

both the high-level overview and analysis of AEs in patients with TD. Sections 2.1 and 2.2 describe the case definition and causality assessment for the analysis of AEs in patients with TD.

2.1 CASE DEFINITION

The FAERS database was searched to identify all cases of AEs reported with tetrabenazine use in the TD population. In order to be included in this analysis, the following criteria were required:

- Case coded with a serious outcome, defined as one of the following: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events
- Tetrabenazine was reportedly used to treat TD (reported as one of the following: tardive dyskinesia or subacute dyskinesia)
- Tetrabenazine had a probable or possible causal relationship with the AE reported

The following cases were excluded from the case series:

- AE happened before tetrabenazine was initiated (i.e. no temporal relationship between tetrabenazine and the AE)
- A causal relationship between tetrabenazine and the AE was unlikely or unassessable
- Tetrabenazine reported reason for use was not TD or reason for use was unassessable
- Patients diagnosed with HD

2.2 CAUSALITY ASSESSMENT

DPV used the World Health Organization Uppsala Monitoring Centre (WHO-UMC) Causality Scale¹² in Table 1 to assess the relationship of the AE to tetrabenazine use.

Causality term	Assessment Criteria
Probable	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • A time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	December 8, 2016
Time period of search	January 01, 2010 [†] – December 8, 2016
Search type	FBIS Quick Query
Product Terms	Product Active Ingredient: tetrabenazine
Outcome Serious?	Serious
* See Appendix A for a description of the FAERS database.	
[†] Time period requested in the DPP consult was from the year 2010.	

2.4 LITERATURE SEARCH

DPV searched the medical literature with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Date of search	December 15, 2016
Database	PubMed@FDA
Search Terms	("Tetrabenazine"[Mesh]) AND Tardive Dyskinesia
Years included in search	All through time
Article types	Case reports

2.5 OTHER DATA SOURCES

DARRTS and Enterprise Search were searched for previous DPV reviews of tetrabenazine.

3 RESULTS

3.1 FAERS OVERVIEW

For the FAERS overview, please note that these are total counts of FAERS reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, and nurse), miscoded reports, or unrelated reports. Reported serious outcomes for this section are the coded outcomes submitted to FDA; causality and the role of the product in the coded outcome have not been determined for this evaluation.

Table 4 provides descriptive characteristics for all FAERS reports with serious outcomes for tetrabenazine, and includes all indications – HD and non-HD.

Table 4. Descriptive Characteristics of FAERS Reports with serious outcomes* for tetrabenazine, including all indications, received by FDA from January 1, 2010 to December 8, 2016		
(N=3152)†		
Sex	Female	1851
	Male	1242
	Unknown	59
Age, y (n = 2325)†	Mean = 58.69	
	Median = 61	
	Range = 1 – 98.87	
Country	Domestic = 2936	
	Foreign = 214	
	Unknown = 2	
Report type	Expedited	2925
	Direct	17
	Periodic	210
Serious Outcomes*	Death	1397
	Hospitalized	1097
	Other serious	1074
	Life-threatening	87
	Disability	79
	Congenital anomaly	2
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.		
† May include duplicates.		

Table 5 summarizes the coded reasons for use for all FAERS reports with serious outcomes for tetrabenazine.

Table 5. Reported reasons for use with N ≥ 5 for tetrabenazine FAERS reports with serious outcomes*, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per reason for use		
(N=3014)†		
Row	Reported Reasons for Use	Number of FAERS Reports†
1	Huntington's disease	1368
2	Not Reported / Product used for unknown indication	595
3	Huntington's Chorea	411
4	Dyskinesia	281
5	Chorea	202
6	Tardive dyskinesia	154 [§]

Table 5. Reported reasons for use with N ≥ 5 for tetrabenazine FAERS reports with serious outcomes*, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per reason for use		
(N=3014)†		
Row	Reported Reasons for Use	Number of FAERS Reports‡
7	Dystonia	82
8	Tourette's disorder / Tourette's syndrome	55
9	Orofacial dyskinesia	33
10	Meige's syndrome	24
11	Tic	21
12	Tremor	19
13	Off label use	18
14	Movement disorder	17
15	Torticollis	13
16	Hemichorea	12
17	Extrapyramidal disorder	10
18	Parkinson's disease	6
19	Ballismus	6
20	Cerebral palsy	5
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious. † May include duplicates. ‡ A report may have one or more reasons for use. § Included in hands-on analysis in Section 3.2.		

Tables 6 through 8 summarize counts of Preferred Terms (PTs) for reports coded with non-HD indications with a serious outcome (total number of reports = 1023). This excludes all reports coded with the following reasons for use:

- Huntington's Disease
- Huntington's Chorea
- Not reported / product used for unknown indication

Although reports that were not coded for HD as reason for use were excluded from Tables 6 through 8, some reports that were coded with non-HD indications for use may include patients with a medical history of HD.

Table 6. MedDRA PTs with N ≥ 10 FAERS reports with serious outcomes* for tetrabenazine used for non-HD indications, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per PT

(N=881)[†]

Row	MedDRA PT	Number of FAERS Reports
1	Off label use	255
2	Death	248
3	Hospitalisation	106
4	Depression	81
5	Suicidal ideation	64
6	Intentional product use issue	52
7	Fall	50
8	Somnolence	42
9	Pneumonia	37
10	Parkinsonism	33
11	Condition aggravated	32
12	Gait disturbance	30
13	Insomnia	30
14	Dyskinesia	28
15	Fatigue	28
16	Tremor	28
17	Dyspnoea	27
18	Dizziness	26
19	Drug ineffective	26
20	Dysphagia	26
21	Anxiety	25
22	Seizure	25
23	Cerebrovascular accident	24
24	Drug administration error	23
25	Nausea	20
26	Agitation	19
27	Drug dose omission	19
28	Musculoskeletal stiffness	19
29	Prescribed overdose	19
30	Confusional state	17
31	Vomiting	17
32	Dystonia	16
33	Movement disorder	16
34	Restlessness	16
35	Weight decreased	16
36	Urinary tract infection	15
37	Balance disorder	14
38	Crying	14

Table 6. MedDRA PTs with N ≥ 10 FAERS reports with serious outcomes* for tetrabenazine used for non-HD indications, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per PT

(N=881)[†]

Row	MedDRA PT	Number of FAERS Reports
39	Malaise	14
40	Tardive dyskinesia	14
41	Aggression	13
42	Asthenia	13
43	Feeling abnormal	13
44	Pain	13
45	Speech disorder	13
46	Muscle spasms	12
47	Activities of daily living impaired	11
48	Dehydration	11
49	Headache	11
50	Loss of consciousness	11
51	Abnormal behaviour	10
52	Decreased appetite	10
53	Dysarthria	10
54	Feeding disorder	10
55	Hallucination	10
56	Hyperhidrosis	10
57	Muscular weakness	10
58	Product use issue	10

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious.

† A report may contain more than one PT.

The PTs in Table 6 are mostly consistent with current labeling for tetrabenazine. Several PTs also potentially reflect the underlying disease, such as *Dyskinesia*, *Dystonia*, *Movement disorder*, and *Speech disorder*.

Following is a summary of a hands-on analysis of the 14 reports coded with *Tardive dyskinesia*: TD was the reason for tetrabenazine use in ten cases (all were included in the hands-on analysis in Section 3.2, of which two are part of the case series presented in Table 10). All ten cases were uninformative. In six cases, TD was unrelated to tetrabenazine and was either part of the patient's past medical history and miscoded as an AE (n=4), or was an AE attributed to metoclopramide or neuroleptic exposure (n=2). Three cases reported worsening of TD after the patient's tetrabenazine dose was decreased: in one case dose was decreased due to akathisia, a labeled event, and in another case dose was decreased due to dizziness, discomfort in lower legs, difficulty breathing, tension in neck and upper back, jawbone pain, pain behind eye, and bruising. The case is confounded by concurrent pyelonephritis and is largely unassessable due to

limited clinical information. In the third case, the patient ran out of tetrabenazine. None of these three cases reported whether TD was worse than baseline. The remaining case involving a patient with TD was unassessable due to limited clinical information.

In the remaining four cases coded with *Tardive dyskinesia*, tetrabenazine was reportedly used for the following reasons: chorea NEC (Not Elsewhere Classified), orofacial dyskinesia, Tourette’s syndrome, and dystonia. All four cases were unassessable due to limited clinical information.

Table 7. MedDRA PTs with N ≥ 3 FAERS reports with fatal outcomes for tetrabenazine used for non-HD indications, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per PT		
(N=292)*		
Row	MedDRA PT	Number of FAERS Reports
1	Death	248
2	Off label use	84
3	Intentional product use issue	20
4	Fall	9
5	Hospitalisation	8
6	Prescribed overdose	8
7	Pneumonia	7
8	Drug administration error	6
9	Cerebrovascular accident	5
10	Pneumonia aspiration	5
11	Decreased appetite	4
12	Dysphagia	4
13	Dyspnoea	4
14	Gait disturbance	4
15	Hip fracture	4
16	Myocardial infarction	4
17	Cardiac arrest	3
18	Coma	3
19	Dizziness	3
20	Dyskinesia	3
21	Huntington's disease	3
22	Respiratory failure	3
23	Restlessness	3
24	Tardive dyskinesia	3
25	Urinary tract infection	3
* A report may contain more than one PT.		

Regarding the number of reports coded with *Death*, a previous DPV review from 2015 notes, “In over 70% of cases with an outcome of death, “Death” was the only AE reported. Only 22.6% of cases reporting an outcome of death had follow-up information. It is unclear in the majority of

case narratives without follow-up if an attempt at obtaining additional information was unsuccessful.”⁵

The three fatal reports coded with *Tardive dyskinesia* were included in the hands-on analysis on pages 11-12 of this review. Two of the three cases involved patients with TD: in the first case, involving a 68-year-old male, cause of death was not reported. In the second case cause of death was cardiopulmonary arrest secondary to aspiration in a 75-year-old female with several comorbidities, including dysphagia, end-stage renal disease (dialysis-dependent), depression with history of psychosis, anemia of chronic kidney disease, secondary hyperparathyroidism, coronary artery disease, hypotension, transient ischemic attack, and type 2 diabetes mellitus; the case noted that tetrabenazine was unlikely related to the event. Aspiration and dysphagia are labeled events for tetrabenazine, but the case is confounded by the patient’s medical history of dysphagia. In the third case, involving an 83-year-old female prescribed tetrabenazine for “Chorea NEC,” cause of death was reported as, “natural causes and the death was not attributed to therapy with tetrabenazine.”

Table 8 below summarizes the number of FAERS reports coded with a Designated Medical Event (DME). DMEs are AEs that are considered rare, serious, and associated with a high drug-attributable risk and which constitute an alarm with as few as one to three reports. The Office of Surveillance and Epidemiology (OSE) created the DME list for working purposes; it has no regulatory significance. See Appendix B for a list of OSE’s current DMEs.

Table 8. Designated Medical Event (DME)-related MedDRA PTs from FAERS reports for tetrabenazine used for non-HD indications, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per PT		
(N=59)*		
Row	MedDRA PT	Number of FAERS Reports
1	Seizure	27
2	Pancreatitis	5
3	Neuroleptic malignant syndrome	3
4	Renal failure	3
5	Respiratory failure	3
6	Rhabdomyolysis	3
7	Acute kidney injury	2
8	Anaphylactic reaction	2
9	Epilepsy	2
10	Renal impairment	2
11	Acute respiratory distress syndrome	1
12	Blindness unilateral	1
13	Completed suicide	1
14	Deafness neurosensory	1
15	Epilepsy	1
16	Erythema multiforme	1
17	Generalised tonic-clonic seizure	1

Table 8. Designated Medical Event (DME)-related MedDRA PTs from FAERS reports for tetrabenazine used for non-HD indications, received by FDA from January 1, 2010 to December 8, 2016, sorted by decreasing number of FAERS reports per PT

(N=59)*		
18	Hepatitis acute	1
19	Pulmonary fibrosis	1
20	Septic shock	1
21	Serotonin syndrome	1
22	Sudden death	1
23	Sudden visual loss	1
* A report may contain more than one PT.		

A hands-on analysis of the 59 DME-related reports was performed:

- **Seizure:** of the 27 cases coded with *Seizure*, TD was the indicated reason for use in five cases. None of the 27 seizure cases provided compelling evidence of a causal relationship between seizures and tetrabenazine, as most of the cases provided limited clinical information and were unassessable (n=21), were confounded by a pre-existing seizure disorder (n=5), or the AE was actually severe akathisia, rather than a true seizure, in a healthy subject enrolled in a study (n=1).
- **Pancreatitis:** of the five cases coded with *Pancreatitis*, TD was the indicated reason for use in two cases, including one patient who also had a concurrent diagnosis of Huntington’s chorea. All cases were unassessable due to limited clinical information.
- **Neuroleptic malignant syndrome (NMS):** None of the three cases coded with *Neuroleptic malignant syndrome* involved patients with TD. Of the three cases, NMS was clearly diagnosed in one case only, involving a seven-year-old male with “extrapyramidal disorder.” The case reported a positive dechallenge with tetrabenazine, but did not specify the temporal relationship with tetrabenazine, and recent changes to tetrabenazine and baclofen therapy may have contributed to the AE (the case noted the placement of an intrathecal baclofen pump along with a dose decrease of tetrabenazine some unspecified time prior to the development of NMS). In the second case, involving a 28-year-old male, the physician was not certain that the patient met all criteria for NMS, but either way had a “severe reaction” that resolved “as soon as Xenazine was stopped.” The last case, involving a 12-year-old female with congenital encephalopathy and dystonia, was confounded by suspected septic shock; the outcome was fatal. NMS is already a labeled event for tetrabenazine under Section 5 WARNINGS AND PRECAUTIONS.
- **Renal failure:** None of the three cases coded with *Renal failure* involved patients with TD. Two of the cases were unassessable due to limited clinical information and the third case was confounded by rhabdomyolysis secondary to status

dystonicus in a 19-year-old male with a history of “upper limbs dystonic movements” since the age of 18 months secondary to epileptic encephalopathy.

- **Respiratory failure:** of the three cases coded with *Respiratory failure*, TD was the reported reason for use in two cases. One case, involving an 89-year-old female, was confounded by pneumonia (aspiration pneumonia is also a labeled event for tetrabenazine, although the type of pneumonia was not specified in this case). The second case, involving a 68-year-old female, was unassessable due to limited clinical information. The remaining case, involving a 38-year-old male with severe primary generalized dystonia, was confounded due to underlying disease.
- **Rhabdomyolysis:** None of the three cases coded with *Rhabdomyolysis* involved patients with TD. In one case, rhabdomyolysis was secondary to NMS and already discussed under *Neuroleptic malignant syndrome* (7-year-old male with “extrapyramidal syndrome”). Another case was also coded with *Renal failure* and already discussed as well (19-year-old male with epileptic encephalopathy). The third case involved a 9-year-old female with a medical history of “cerebral palsy on kernicterus with pharmacoresistant dystonias.” Rhabdomyolysis was secondary to “major hyperthermia.” NMS could not be ruled out, and was confounded by the underlying disease. The patient’s condition improved with supportive measures and discontinuation of tetrabenazine.
- Of the remaining DME-related reports (n=15), TD was the reported reason for use in two cases, one case coded with *Anaphylactic reaction* and another coded with *Epilepsy*; both were unassessable due to limited clinical information. There was one duplicate report (the *Sudden death* case was a duplicate of the *Pulmonary fibrosis* case). All cases were either unassessable or tetrabenazine was unlikely related to the AE.
- Overall, none of the DME-related cases provided sufficient evidence of a potential safety signal between the reported AEs and tetrabenazine used in patients with TD.

3.2 FAERS CASE SELECTION

The FAERS search retrieved 3152 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 16 cases were included in the case series of serious AEs reported with tetrabenazine use to treat TD (see Figure 1). Of note, the search included a total of 235 cases with reported use of tetrabenazine for treatment of TD (without concurrent HD).

Figure 1. FAERS Case Selection

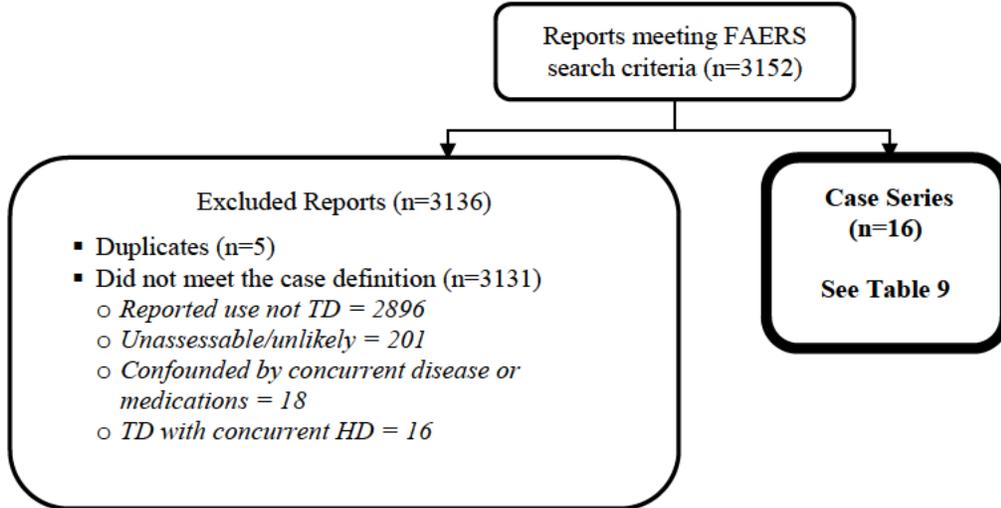


Table 9 summarizes the 16 FAERS cases of AEs reported with tetrabenazine used to treat TD for this case series.

Appendix C lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 16 cases in this case series.

Table 9. Descriptive characteristics of FAERS cases reporting serious AEs with tetrabenazine used to treat TD, received by FDA from January 1, 2010 to December 8, 2016	
(N=16)	
Sex	Female = 13 Male = 3
Age (years)	Mean = 65.59 Median = 64.22 Range = 40 – 88.09
Report type	Expedited = 14 Periodic = 1 Direct = 1
Serious outcome*	Death = 1 Life-threatening = 1 Hospitalization = 2 Other = 12
Year received by FDA	2010 = 5 2011 = 3 2012 = 3 2013 = 3 2014 = 1 2016 = 1

Table 9. Descriptive characteristics of FAERS cases reporting serious AEs with tetrabenazine used to treat TD, received by FDA from January 1, 2010 to December 8, 2016

(N=16)

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.

Table 10 describes the causality assessment for the 16 cases in the case series. The comments in the table note the temporal relationship (the timeframe between initiation of tetrabenazine and onset of the AE), whether a dechallenge was reported (and timeframe between discontinuation of tetrabenazine and resolution of the AE, if applicable and reported), as well as whether the AE was diagnosed by a healthcare provider, if any confounders were reported, and other miscellaneous details pertinent to the case.

Table 10. Causality assessment of cases reporting serious AEs with tetrabenazine used to treat TD in FAERS, received by FDA January 1, 2010 to December 8, 2016

(N=16)

FAERS#	Age (y)	Sex	Adverse event*	Causality assessment	Comments
7396606	88	F	Parkinsonism (bradykinesia)	Probable	+ temporal (1 day) + dechallenge (8 days) HCP diagnosed AE
10669025	76	F	Hallucination and panic attacks	Possible	+ temporal (2 days) + dechallenge (2 days) Confounded by PMH of panic attacks and hallucinations
12282186	66	F	Product substitution issue (generic drug ineffective)	Possible	+ temporal (2 days) + dechallenge (3 days)
7475966	65	F	Akathisia	Possible	+ temporal (within a month) + dechallenge with dose decrease (within a month) HCP diagnosed AE
7689963	84	F	Amnesia (memory loss NOS)	Possible	+ temporal relationship (within a month) No dechallenge reported (treatment ongoing) Confounded by patient's age
7711383	77	F	Therapy non-responder	Possible	TBZ 25 mg tid for 1.5 yrs with no improvement Confounded by treatment with olanzapine Confounded by off-label use in patient with PMH of Alzheimer's dementia, TD, schizophrenia

Table 10. Causality assessment of cases reporting serious AEs with tetrabenazine used to treat TD in FAERS, received by FDA January 1, 2010 to December 8, 2016

(N=16)

FAERS#	Age (y)	Sex	Adverse event*	Causality assessment	Comments
7756851	59	F	Depression, suicidal ideation	Possible	+ temporal (within 3 months) + dechallenge (time NS) Confounded by PMH of bipolar disorder
7975925	63	F	Worsening anxiety and depression	Possible	+ temporal (1 week) Confounded by PMH of bipolar disorder
8087514	57	F	Anger (rage), homicidal and suicidal thoughts	Possible	+ temporal (3 days) + dechallenge (1 day) HCP diagnosed AE Confounded by PMH of schizophrenia
8155045	58	M	Amnesia (memory loss NOS) and disturbance in attention (“hard time concentrating”)	Possible	+ temporal (1 month) Confounded by PMH of depression
8354222	78	F	Bradykinesia, gait disturbance, muscle rigidity	Possible	+ temporal (within 5 months) + dechallenge (within 3 weeks) HCP diagnosed AE Dechallenge confounded by concurrent physical therapy
8784924	68	F	Depression and suicidal ideation	Possible	+ temporal (within 3 months) + dechallenge (time NS) HCP diagnosed AE Confounded by PMH of bipolar disorder, depression, anxiety, panic attacks
8791489	66	M	Depression	Possible	+ temporal (within 2 months) + dechallenge (time NS) HCP diagnosed AE PMH not reported
9396442	61	F	Vision blurred and “feeling like she was losing her vision”	Possible	+ temporal (0 days) + dechallenge (3-4 days) Confounded by PMH of cataracts
9457758	40	F	Dysphagia, nausea, throat tightness	Possible	+ temporal (1 hour) + dechallenge (1 day) Confounded by TD (dysphagia)
9725670	41	M	Incomplete effect	Possible	TBZ 25 mg / day provided “minor benefit” in pt with TD; treated with TBZ for over 3 years Confounded by low dose

* Adverse events listed in this table incorporate pertinent coded preferred terms (PTs) and narrative description, but may not be inclusive of all coded PTs per case, e.g. some cases had coded PTs that were not relevant to tetrabenazine use specifically.

Definitions: HCP = health care provider; AE = adverse event; PMH = past medical history; NS = not specified; TBZ = tetrabenazine

Of the 16 cases, one was assessed as probable, with the remaining 15 cases assessed as possible. The one probable case (FAERS #7396606) reported a patient who developed bradykinesia one day after starting tetrabenazine 12.5 mg once daily for TD. The caregiver for the 88-year-old patient initially reported, "...the patient became 'almost paralyzed', as it was very hard to move and function." A follow-up report from the physician clarified that the AE was bradykinesia, and the patient recovered 8 days after discontinuing tetrabenazine. The physician diagnosed the AE as, "Parkinsonism from tetrabenazine." One other case in the case series reported the development of bradykinesia and "mild Parkinsonism with parkinsonian gait" (FAERS #8354222) in a 78-year-old. The exact onset of symptoms was unknown, but was first noted by a neurologist during an office visit five months after initiating tetrabenazine 12.5 mg daily for TD (the case mentioned a plan to titrate to 12.5 mg three times daily, but does not specify if the dose was ever titrated up). Tetrabenazine was discontinued, and at a three-week follow-up visit, the neurologist reported that the patient's TD had worsened, but "the patient's abnormality of gait had improved with physical therapy."

Reviewer's comments: the events Balance disorder, Extrapyramidal disorder, Parkinsonism, and Muscle rigidity were observed in valbenazine clinical trials, and are currently included in proposed labeling for valbenazine under Section 6 ADVERSE REACTIONS.

The most commonly reported AEs in the case series were related to depression (n=4) and suicidal behaviors (n=3). Four cases specifically reported that the patient became depressed or experienced a worsening in depression, and two of these cases also reported the development of suicidal behaviors. Cases of suicidal behaviors provided limited clinical information, with one case (FAERS #7756851), reported by the consumer, describing the AE as, "...the patient experienced suicidal thoughts, extreme depression, and facial grimacing and movements." The second case (FAERS #8784924), reported by a physician, described the AE as, "The patient reportedly 'lost control' and 'almost committed suicide.' She became very depressed." A third case (FAERS #8087514) reported suicidal behavior without mentioning depression, which was reported by a neurologist as, "[The patient] became 'increasingly enraged' and was almost homicidal and suicidal." Suicidal thoughts "resolved" in all three patients after discontinuation of tetrabenazine. All three cases were confounded by a past medical history of psychiatric illness, and none of the cases provided baseline information on how well-controlled the patient's mental condition was prior to initiating tetrabenazine.

Reviewer's comments: the events Suicidal ideation and Depression were observed in valbenazine clinical trials, (b) (4)

3.3 LITERATURE SEARCH

The literature search as described in Section 2.4 retrieved one case report regarding a patient treated with tetrabenazine for TD. The case is summarized below.

Stevens et al. reported a case of a 45-year-old male who experienced hyperthermia during treatment with tetrabenazine for TD.¹³ The patient had a past medical history of mild psychosis with depression and TD that developed after receiving "various neuroleptic drugs." Huntington's

chorea was excluded by gene testing. After 6 months of therapy with tetrabenazine 25 mg three times daily, the patient was found by neighbors lying on the floor, after carrying heavy shopping bags up the stairs on a hot day (“high ambient temperature”). “Altered consciousness, profuse sweating, urine loss, and agitation with bizarre dyskinetic movements” were noted by the emergency physician upon arrival to the patient’s home. The patient’s concurrent medications included clomipramine 100 mg/day, mianserin 30 mg/day, and lorazepam 2.5 mg/day. Blood pressure was 110/60 mm Hg and heart rate was 150/min. Rectal temperature was 41.3 °C. Plasma concentrations of clomipramine, desclomipramine, and mianserin were considered within therapeutic ranges. Tetrabenazine and its hydroxyl metabolite were detected in urine upon admission. After a thorough workup and failure of external cooling and antipyretic drug therapy, “drug-induced hyperthermia similar to neuroleptic malignant syndrome [NMS] was suspected,” and the patient was started on dantrolene (1 mg/kg i.v. every six hours) and bromocriptine (5 mg orally every eight hours). Patient improved over the course of three days with one recurrent episode of hyperthermia above 40 °C on the fourth day of admission. Acute liver cytolysis and rhabdomyolysis were observed on the third and fourth day, respectively, of admission, but completely resolved. Patient was discharged after 10 days with complete resolution of hyperthermia. Tetrabenazine and clomipramine were permanently discontinued. The patient did not display classic features of NMS, such as muscle rigidity, cardiac and autonomic instability, or abrupt response to treatment with sodium dantrolene and bromocriptine. The authors postulate that the serotonergic activity of clomipramine and mianserin may have played a role, and the patient may have had “a more complex pathogenesis of hyperthermia...than simple dopamine depletion and blockade by tetrabenazine alone.” The authors also suggest that “high ambient temperature and physical exercise probably worsened our patient’s hyperthermia.”

Reviewer’s comment: this case report provides a very well-documented account of hyperthermia during treatment with tetrabenazine in a patient with TD. The case provides evidence of a temporal relationship between tetrabenazine and development of hyperthermia, although with a lag time of six months. The case also provides evidence of a positive dechallenge. Major confounders are clomipramine and mianserin, which may have contributed to overlapping serotonin syndrome along with what the authors describe as “neuroleptic malignant syndrome-like hyperthermia.” The warm weather and patient’s physical activity likely contributed as well. Tetrabenazine is currently labeled for NMS under Section 5 WARNINGS AND PRECAUTIONS. Proposed labeling for valbenazine does not currently include language regarding hyperthermia or NMS.

Of note, during the literature search for cases of tetrabenazine associated-AEs in patients with TD, DPV found one case report of TD caused by tetrabenazine.¹⁴ LeWitt describes a case of a 55-year-old man with cervical dystonia who was prescribed tetrabenazine 12.5 mg two times a day. After 10 months of treatment, he “experienced a gradual onset of generalized and near-continuous involuntary movements” which included slow and repetitive lip puckering, tongue movements, lateral jaw shifting, increased blinking, slow “choreic” hand movements, and athetoid movements of the legs and trunk. Short trials of gabapentin and clonazepam did not affect the involuntary movements. Tetrabenazine was discontinued, and the involuntary movements gradually remitted over two months (only baseline cervical dystonia symptoms persisted). No other medication changes were made besides discontinuation of tetrabenazine, and other causes for involuntary movements (brain abnormalities as evidenced by magnetic

resonance imaging, infection, hepatic dysfunction, genetic disorders, and so on) were ruled out. Concurrent medications included desvenlafaxine. Patient had no history of dopamine-blocking drug use.

Reviewer's comments: this is a compelling case of tardive dyskinesia associated with tetrabenazine use, in which there was a temporal relationship, a positive dechallenge, and lack of obvious confounders. Although not entirely relevant to the subject of this review (i.e. the case involved a patient with cervical dystonia and not a patient with pre-existing TD), this literature case report provides further evidence of an association between new onset tardive dyskinesia and tetrabenazine use, beyond the theoretical risk stated in tetrabenazine labeling.

3.4 OTHER DATA SOURCES

Since tetrabenazine's approval on August 15, 2008, DPV has conducted two postmarketing safety reviews and one pharmacovigilance memo regarding tetrabenazine:

- September 8, 2011: Dr. Andrew Fine completed a FDA Amendments Act (FDAAA) Section 915 Safety Summary for <10,000 patients Exposed (also known as a "915c" review) for tetrabenazine. At the time of Dr. Fine's review, there were 801 reports in AERS for tetrabenazine. *Product quality issue* and *Drug administration error* were the only PTs identified for further review to determine the need for consultation with the Office of Compliance and/or the Division of Medication Error Prevention and Analysis (DMEPA). No other safety signals were identified in the review.⁶
- October 31, 2011: Dr. Kelley Simms completed a Documentation of Pharmacovigilance Activity memo regarding tetrabenazine and product quality issues and drug administration errors, as follow-up for the "915c" review completed by Dr. Fine in 2011. DPV found 23 FAERS reports coded with the PTs *Product quality issue* and 17 reports coded with *Drug administration error*. The majority of administration error reports described patients who were cutting their tablets in half. DMEPA was made aware of these reports. Besides continued routine PV activities, DPV did not recommend any further action based on the findings of this memo.¹⁵
- February 25, 2015: Dr. Monica Muñoz and Dr. Kusum Mistry completed a Pharmacovigilance and Drug Utilization Review regarding tetrabenazine and deaths and pediatric AEs. The review characterized all cases in FAERS with an outcome of death reported with tetrabenazine. Because of the limited quality of the data, the cause of death or role of tetrabenazine could not be determined in the majority of cases. Office of Compliance was notified of potential discrepancies with postmarketing requirements. The review recommended the sponsor follow-up on all death cases and all pediatric cases with a serious outcome.⁵

None of the previous DPV postmarketing safety reviews for tetrabenazine made recommendations for regulatory action.

4 DISCUSSION

DPV did not identify any new safety signals for tetrabenazine in patients with TD. The majority of FAERS cases analyzed provided limited clinical information, which may have contributed to

the lack of positive findings. The poor quality of information in FAERS reports associated with tetrabenazine has been noted in previous DPV reviews.^{5,6} The Office of Compliance's PADE team is aware of the issue and has noted several deficiencies in a 2015 inspection of Valeant's previous PV service provider, (b) (4) Valeant has changed their PV service provider in recent years, in part to remedy discrepancies with postmarketing requirements.

Of the 16 cases in which a causality assessment of "possible" or "probable" could be made with tetrabenazine used in patients with TD, depression and suicidal behavior was the most commonly reported AE. No completed suicides in patients with TD using tetrabenazine were identified in FAERS or the medical literature. All of the cases reporting depression or suicidal behavior were confounded by a medical history of psychiatric illness, when medical history was reported. Depression and suicidal behavior is an expected AE for tetrabenazine, and is labeled with a Boxed Warning. Other AEs identified in FAERS that had a probable or possible causal relationship with tetrabenazine did not provide compelling evidence of an unexpected AE.

Several of the AEs reported with tetrabenazine used in patients with TD in FAERS, such as depression, suicidal ideation, bradykinesia, anxiety, gait disturbance, and akathisia, are currently included in proposed labeling for valbenazine. AEs included in the case series that are not currently included in proposed labeling for valbenazine include: memory loss/amnesia, anger, homicidal thoughts, hallucinations, panic attacks, nausea, dysphagia, and throat tightness. Although these AEs can be serious, definitive conclusions on the relationship with tetrabenazine, and even more so with valbenazine, cannot be made due to the small number and limited quality of the cases.

The one case that may be worth considering in discussions of valbenazine's safety is the literature case report regarding hyperthermia. Despite the case being confounded by the use of multiple serotonergic agents, and the atypical presentation of NMS, the case provides evidence of tetrabenazine contributing to "NMS-like" hyperthermia. Tetrabenazine's labeling has a Warning and Precaution regarding NMS. Proposed labeling for valbenazine does not currently contain language regarding NMS, hyperpyrexia, or hyperthermia. Due to the potential role of dopamine depletion and blockade in NMS,¹⁶ even with limited evidence, it may be prudent to monitor for NMS in valbenazine.

5 CONCLUSION

DPV did not identify any new safety signals for tetrabenazine used in patients with TD. The majority of FAERS reports associated with tetrabenazine are of limited quality, and the role of tetrabenazine cannot be determined in most cases. The FAERS overview did not reveal any unexpected AEs for tetrabenazine. Hyperthermia, (b) (4) has been described in the medical literature in a patient using tetrabenazine for treating TD, and may be worth discussing in relation to risk of hyperthermia and NMS with valbenazine.

6 RECOMMENDATIONS

DPV does not have any recommendations for regulatory action for tetrabenazine or valbenazine at this time.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. LIST OF OSE DESIGNATED MEDICAL EVENTS AND ASSOCIATED MEDDRA PREFERRED TERMS

Designated Medical Event	MedDRA Preferred Terms (Version 19.1)
Acute pancreatitis	Pancreatic necrosis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis, Haemorrhagic necrotic pancreatitis
Acute respiratory failure	Acute respiratory distress syndrome, Acute respiratory failure, Respiratory failure
Agranulocytosis	Agranulocytosis, Febrile neutropenia, Neutropenia
Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Anaphylactic transfusion reaction
Aplastic anemia	Aplasia pure red cell, Aplastic anemia, Bone marrow failure
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
Congenital anomalies	Congenital anomaly
Deaf	Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Deafness, Sudden hearing loss
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Haemolysis	Haemoglobinaemia, Haemoglobinuria, Haemolysis, Haptoglobin decreased, Intravascular haemolysis
Hemolytic anemia	Coombs negative haemolytic anaemia, Coombs positive haemolytic anaemia, Haemolytic anaemia
Liver failure	Acute hepatic failure, Hepatic encephalopathy, Hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatitis acute, Hepatitis fulminant, Hepatic necrosis
Liver transplant	Liver transplant
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
Pancytopenia	Pancytopenia
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Suspected transmission of an infectious agent via product, Transmission of an infectious agent via product, Product contamination microbial
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Cor pulmonale, Pulmonary hypertension
Renal failure	Renal failure, Acute kidney injury, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Seizure, Epilepsy, Generalised tonic-clonic seizure
Serotonin syndrome	Serotonin syndrome
Stevens-Johnson syndrome	Erythema multiforme, Stevens-Johnson syndrome
Sudden death	Sudden cardiac death, Sudden death
Suicide	Completed suicide
Torsade de Pointes	Torsade de pointes
Toxic epidermal necrolysis	Dermatitis exfoliative, Toxic epidermal necrolysis
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

FAERS Case #	Version	Manufacturer Control #
10669025	2	(b) (4)
12282186	1	(b) (4)
7396606	2	(b) (4)
7475966	2	(b) (4)
7689963	2	(b) (4)
7711383	2	(b) (4)
7756851	1	(b) (4)
7975925	1	(b) (4)
8087514	2	(b) (4)
8155045	1	(b) (4)
8354222	2	(b) (4)
8784924	2	(b) (4)
8791489	3	(b) (4)
9396442	1	(b) (4)
9457758	1	(b) (4)
9725670	2	(b) (4)

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

/s/

OFIR N NEVO
01/06/2017

VICKY C CHAN
01/06/2017

CINDY M KORTEPETER
01/06/2017

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 209241
Brand Name	INGREZZA™
Generic Name	Valbenazine tosylate
Sponsor	Neurocrine Biosciences Inc.
Indication	Tardive dyskinesia
Dosage Form	Capsule: 40 mg
Drug Class	Selective vesicular monoamine transporter 2 inhibitor
Therapeutic Dosing Regimen	<ul style="list-style-type: none"> • The initial dose is 40 mg once daily. The dose should be increased to the recommended dose of 80 mg based on therapeutic response and tolerability. • Can be taken with or without food. • The recommended dose for patients with moderate or severe hepatic impairment is 40 mg once daily.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Single dose: 300 mg Multiple dose: 100 mg QD for 8 days in healthy volunteers; 100 mg QD for 14 days in subjects with schizophrenia or schizoaffective disorder
Submission Number and Date	0002, 0003, 0007, 0009, 0012
Review Division	CDER/ODEI/DPP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

QTc prolongation effect of INGREZZA™ (valbenazine tosylate capsule, 40 and 80 mg) was detected in the TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between INGREZZA (160 mg) and placebo ($\Delta\Delta\text{QTcF}$) were above 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established. Overall summary of findings is presented in Table 1.

Table 1: The point estimates and the 90% CIs corresponding to the largest upper bounds for INGREZZA (160 mg) and the largest lower bound for moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
INGREZZA 160 mg	8	8.9	(6.1, 11.7)
Moxifloxacin 400 mg*	2	11.8	(9.8, 13.9)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.0 ms.

The 160 mg dose included in the TQT study does not provide adequate exposure to cover the accumulation of the main metabolite (NBI-98782) that inhibits the hERG potassium channel. Therefore, pooled concentration-QTc analysis of data from studies 1301 (SAD study) and 1401 (TQT study) was performed. The analysis suggested that NBI-98782 causes concentration-dependent increases in the QTc interval. The estimated mean changes from baseline in QTcF at the mean C_{max} at steady state following administration at the highest therapeutic dose (80 mg) in patients without and with impaired metabolism are provided in Table 2.

Table 2: The point estimates and the 90% CIs for INGREZZA 80 mg for healthy volunteers and poor metabolizers (FDA Analysis)

	NBI-98782 Mean $C_{\text{max,ss}}$ (ng/mL)	$\Delta\Delta\text{QTcF}$ (90% CI) (ms)
INGREZZA 80 mg	39.0 ng/mL	6.7 (5.1 to 8.4)
(b) (4) 80 mg in CYP2D6 poor metabolizers	70.4 ng/mL	11.7 (8.8 to 14.7)

The selected dose in the TQT study does not represent a suprathreshold dose of valbenazine. This is due to ~2.2 fold accumulation of an active metabolite, NBI-98782, and as a result a single dose of 160 mg of valbenazine yields NBI-98782 exposures comparable to steady-state exposures in patients receiving the maximum therapeutic dose (80 mg daily). Moreover, NBI-98782 appears to be the moiety causing the observed QTc prolongation, which is further supported by *in vitro* experiments. The predicted suprathreshold exposure (for hepatic impairment or CYP2D6 poor metabolizers) of NBI-98782 is expected to be ~1.8 times higher than what was observed in the TQT study. Therefore, the primary assessment of QTc prolongation for valbenazine is based on a pooled concentration-QTc, combining data from the TQT study with data from a SAD study which evaluated 150 and 300 mg doses.

2 PROPOSED LABEL

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

Sponsor's Submission	Review Team's Proposal	Reviewer's comment
<p>5.2 QTc Prolongation</p> <p>(b) (4)</p>	<p>5.2 QTc Prolongation</p> <p>(b) (4) INGREZZA (b) (4) causes an increase in the corrected QT interval. INGREZZA should be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (b) (4).</p> <p>[see Clinical Pharmacology (12.2)].</p>	<p>QTc prolongation was observed in the TQT study and pooled analysis.</p> <p>Similar to the comments provided for section 12.2, we suggest deleting results pertaining to the subgroup analysis.</p>
<p>12.2 Cardiac Electrophysiology</p> <p>(b) (4)</p>	<p>12.2 Cardiac Electrophysiology</p> <p>(b) (4) INGREZZA (b) (4) causes an increase in the corrected QT interval. An exposure-response analysis of clinical data from two (b) (4) healthy volunteer studies revealed a positive correlation in QTc interval with the plasma concentration of the active metabolite. Based on (b) (4) modeling, patients taking an INGREZZA 80 mg dose may have a mean (b) (4) % upper bound) QT prolongation of (b) (4) 6.7 (8.4) msec. Patients taking an INGREZZA 80 mg dose with increased exposure (eg, taking a concomitant strong CYP3A4 or CYP2D6 inhibitor) may have a mean QT prolongation of (b) (4) 1.7 (14.7) msec.</p>	<p>We do not agree with pooling of data from all three studies and not accounting for placebo in the prediction of QTc prolongation. Therefore, we are proposing to replace the sponsor's estimates with the results of the FDA analysis, which are based on pooling of studies 1301 and 1401.</p>
<p>(b) (4)</p>		

3 BACKGROUND

3.1 PRODUCT INFORMATION¹

Valbenazine tosylate (also referred to as NBI-98854) is indicated for the treatment of tardive dyskinesia (TD). It is an orally active selective and reversible vesicular monoamine transporter 2 (VMAT2) inhibitor. The exact mode of action of valbenazine in the treatment of TD is unknown; it is believed that valbenazine causes reversible reduction of dopamine release at the presynaptic nerve terminal by selectively inhibiting the presynaptic VMAT2.

INGREZZA is presented as (b) (4) gelatin capsules for oral administration.

3.2 MARKET APPROVAL STATUS

Valbenazine tosylate is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Appendix 6.1 summarizes preclinical cardiac safety information.

Reviewer's Comment: Results from in vitro patch clamp experiments suggests that the active metabolite is more likely to cause clinical QTc prolongation.

3.4 PREVIOUS CLINICAL EXPERIENCE

Appendix 6.1 summarizes clinical cardiac safety information.

3.5 CLINICAL PHARMACOLOGY^{1,2}

Appendix 6.1 summarizes the key features of valbenazine tosylate clinical pharmacology.

NBI-98782 is a major active metabolite formed by enzymatic or non-enzymatic hydrolysis. It is a potent stereoisomer of dihydrotetrabenazine, a metabolite of tetrabenazine. Tetrabenazine is currently approved by the FDA for the treatment of Huntington's chorea. A marginal QT effect of 8 ms with the tetrabenazine 50 mg was reported in the XENAZINETM Prescribing Information. Demethylation by CYP2D6 is the major elimination route for NBI-98782. Substantial increase in NBI-98782 exposure is expected in patients with moderate or severe hepatic impairment, patients taking ketoconazole, and patients with poor CYP2D6 metabolizer genotype.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting the TQT study (NBI-98854-1401) under IND 111591. It was concluded in the review of the protocol that the proposed suprathreshold dose was not adequate,³ and at a later meeting the sponsor claimed that the concentration-QT relationship was well understood and that a TQT study would not be necessary. The QT-IRT reviewer noted in the review that if the sponsor believed that

¹ EDR: NDA 209241\0002\m2\27-clin-sum\summary-clin-pharm.pdf

² DARRTS: IND 111591: CONSULT REV-QTIRT-01(QT-IRT Review).pdf, 02/17/2016, by Dr. Jiang Liu

³ DARRTS: IND 111591: CONSULT REV-QTIRT-01(QT-IRT Review).pdf, 09/28/2015, by Dr. Jiang Liu

the drug prolonged the QT interval that a TQT study would not be needed and that intensive ECG monitoring should be implemented in clinical trials to ensure patients' safety.²

The sponsor submitted concentration and QTc data from two additional Phase 1 studies to evaluate the concentration-QTc relationship for NBI-98854 and NBI-98782 in healthy subjects.⁴ A summary of the three studies is provided in Table 3.

Table 3: Summary of studies that are included in this QT-IRT review.

	Study Design	Dose: No. Subject	PK/ECG Sampling Schedule
NBI-98854-1401	TQT: SD, DB, 3-way XO, double-dummy, placebo- and moxifloxacin- controlled	160 mg SD: 48 PM not eligible	PK/Continuous 12-lead Holter monitoring: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12,24, 36, 48 hrs postdose
NBI-98854-1301	DB, placebo-controlled, SD, parallel	Placebo: 3 150 mg SD: 6 300 mg SD: 6 PM not eligible	PK: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 96, and 168 hrs postdose Standard 12-lead ECG: screening, Day-2, and final study visit Continuous 12-lead Holter monitoring: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hrs postdose
NBI-98854-0901	DB, placebo-controlled, cross-over/parallel, SD/MD	Placebo: 10 50 mg QD: 1 PM 6 IM 7 EM 100 mg QD: 4 EM 4 IM	PK: 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24 hrs after Day 1 and Day 8 dose Standard 12-lead ECG: screening; Day -1; Day 3-5 predose; 24 hrs after Day 8 dose; final visit Holter monitoring: 0, 2, 4, 8, 10, 24 hrs after Day 8 dose and 5 matching time points on Day -1

DB: double-blind

EM: CYP2D6 extensive metabolizer

F: female

IM: CYP2D6 intermediate metabolizer

M: male

MD: multiple-dose

PM: CYP2D6 poor metabolizer

SD: single-dose

XO: crossover

Reviewer's Comment: Study NBI-98854-1301 contributes to $\Delta QTcF$ data in a wider dose range (up to 300 mg single dose).

4.2 TQT STUDY

4.2.1 Title

A Phase 1, randomized, single-dose, double-blind, crossover, placebo- and moxifloxacin-controlled study to evaluate the effect of NBI-98854 on cardiac repolarization in healthy adult subjects.

4.2.2 Protocol Number

NBI-98854-1401

⁴ EDR: nda209241\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\tardive-dyskinesia\5353-rep-analys-data-more-one-stud\concentration-qt; EDR: nda209241\0002\m5\datasets\concentration-qt\analysis\legacy

4.2.3 Study Dates

First subject enrolled (Day -1):	28 January 2016
Last subject completed:	28 February 2016

4.2.4 Objectives

The primary objective of this clinical study was to assess whether a single oral dose of NBI-98854 160 mg affects QTc in healthy volunteers.

The secondary objectives in this clinical study were:

- To assess the effect of a single oral dose of NBI-98854 160 mg on heart rate, PR interval, QRS duration, and QT interval.
- To assess the relationship between plasma concentrations of NBI-98854 and its metabolites NBI-98782 and NBI-136110 and the effects, if any, on QTc.
- To assess the effect of a positive control (moxifloxacin) on QTc in healthy volunteers.
- To evaluate the pharmacokinetic (PK), safety, and tolerability of a single dose of NBI-98854 (160 mg).

4.2.5 Study Description

4.2.5.1 Design

This was a single-dose, double-blind, double-dummy, 3-way crossover, placebo- and moxifloxacin-controlled study. A total of 48 healthy subjects (24 males and 24 females) were enrolled in the study, and 46 subjects completed the study. The expected duration of study participation for each subject was approximately 8 weeks, including up to 28 days of screening, 3 days of study drug dosing with a 10-day washout between each dose, and a final study visit 10 days after the last dose of the study drug.

4.2.5.2 Controls

The Sponsor used both placebo and positive (400 mg moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Treatment A: 4 x 40 mg NBI-98854 capsules + 1 moxifloxacin placebo tablet

Treatment B: 4 NBI-98854 placebo capsules + 1 x 400 mg moxifloxacin tablet

Treatment C: 4 NBI-98854 placebo capsules + 1 moxifloxacin placebo tablet

The following study drugs were administered during the course of the study:

1. Avelox® (moxifloxacin hydrochloride) Equivalent to 400 mg moxifloxacin Tablets
Manufactured by Bayer HealthCare Pharmaceuticals, Inc.
Lot No.: BXH1P61; Expiration date: September 2017

2. Moxifloxacin 400 mg Placebo film-coated tablets
Manufactured by allphamed PHARBIL Arzneimittel GmbH
Lot No.: K15372; Expiration date: January 2017
3. NBI-98854 40 mg capsules
Manufactured by [REDACTED] (b) (4)
Lot No.: 1570.001
4. NBI-98854 placebo capsules
Manufactured by [REDACTED] (b) (4)
Lot No.: 1571.003

4.2.6.2 Sponsor's Justification for Doses

A single dose of NBI-98854 160 mg was chosen as the dose because the highest exposure scenario for NBI-98854 was a 1.65-fold increase in C_{max} in severely hepatic impaired subjects. Since NBI-98854 does not appear to accumulate significantly after repeat once daily administration (C_{max} accumulation ratio at steady state is 1.16), a 160 mg single dose (2 times the highest proposed therapeutic dose) of NBI-98854 was a suitable dose for this study. The projected single dose NBI-98854 C_{max} at 160 mg is almost identical to the projected steady-state C_{max} of NBI-98854 in severely hepatic impaired subjects and higher than the projected steady-state C_{max} of NBI-98854 in moderately hepatic impaired subjects at the highest proposed therapeutic dose of 80 mg. The changes in NBI-98854 C_{max} for the other factors assessed (food, gender, age, CYP2D6 status, and co-administration of a strong CYP3A4 inhibitor) were less than 1.65-fold.

The 160 mg NBI-98854 single dose would also result in exposure to the active metabolite NBI-98782 at a concentration that would approximate its steady state peak plasma concentration following an 80 mg daily dose in CYP2D6 extensive metabolizers. The time to peak plasma concentrations of NBI-98854 and NBI-98782 are sufficiently separated (0.5 - 1 hours and 4 - 6 hours, respectively) that it may be possible to determine the NBI-98854-QTc relationship without the confounding effects of NBI-98782 on QTc.

Reviewer's Comment: The proposed dose is lower than the supratherapeutic dose.³ Therefore, a pooled analysis was conducted by the sponsor and the reviewer to predict the QTcF effects at supratherapeutic exposures.

4.2.6.3 Instructions with Regard to Meals

Subjects fasted overnight before receiving study drug. Subjects were given 240 mL of water to use as a bolus for ingesting the study drugs. Study drugs, including the bolus of water, were to be ingested within 2 minutes. Subjects remained fasted for a minimum of 2 hours postdose. Subjects received similar meals and snacks during each of the 3 inpatient stays. The percentage of food consumed at each meal was recorded.

Reviewer's Comment: Acceptable. Food appears to decrease NBI-98854 and NBI-98872 exposure.

4.2.6.4 ECG and PK Assessments

Continuous 12-lead Holter monitoring was conducted during each treatment period from approximately 1.5 hours predose until 48 hours postdose on Days 1 to 3, Days 11 to 13, and Days 21 to 23. Standard 12-Lead ECGs for PD assessments were extracted in

triplicate from the 12-Lead Holter recordings. Triplicate 12-lead ECGs were assessed at approximately 45, 30, and 15 minutes predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hours postdose.

Blood samples to evaluate plasma concentrations of NBI-98854 and its metabolites, NBI-98782 and NBI-136110, were collected at approximately 1 hour predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hours postdose during each treatment period. The exact time of sampling was recorded to the nearest minute. Plasma concentrations of NBI-98854, NBI-98782, and NBI-136110 were determined using a validated high performance liquid chromatography-tandem mass spectrometry method at (b) (4). The analytical lower limits of quantitation for NBI-98854, NBI-98782, and NBI-136110 were 1.00 ng/mL, 0.100 ng/mL, and 0.200 ng/mL respectively.

Reviewer's Comment: The timing of ECGs is acceptable. The timing of ECG and PK sampling should be able to capture potential effects at Tmax of NBI-98854 (<1hr) and NBI-98782 (4 hr) under fasted condition.

4.2.6.5 Baseline

The baseline value was the average of the 3 sets of triplet predose measurements (for a total of 9 measurements).

4.2.7 ECG Collection

Continuous 12-lead Holter monitoring was conducted during each treatment period from 1.5 hours predose until 48 hours postdose. Triplicate 12-lead ECGs (extracted from the Holter recordings) were assessed at approximately 45, 30, and 15 minutes predose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hours postdose. Subjects were supine and resting beginning approximately 10 minutes prior to the start of each ECG assessment.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

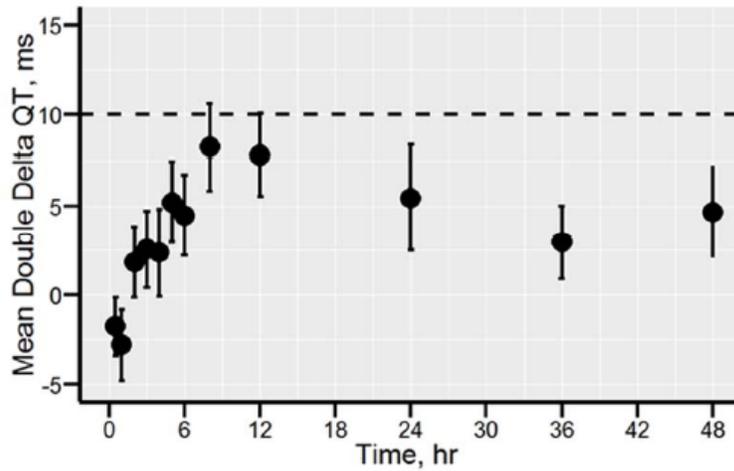
A total of 48 (24 males and 24 females) healthy subjects were enrolled in the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-averaged baseline-adjusted mean difference between NBI-98854 160 mg and placebo in Δ QTcF. The sponsor concluded that NBI-98854 160 mg, the largest mean of Δ QTcF occurred at approximately 8 hour where the upper confidence limit crosses the 10 ms threshold (see Figure below).

Figure 3: Mean Baseline and Placebo Corrected Change in QTcF (ddQTcF) after a Single 160 mg Dose (Study 1401) (The One-Sided 95% Confidence Intervals and a Reference Line [Dash Line] at 10 ms are Also Shown)



Source: Neurocrine Biosciences Study Report No. 2016-PK-057, Page 13/30

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar as those reported by the sponsor.

4.2.8.2.2 Assay Sensitivity

The sponsor's concluded that the lower bounds of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo were greater than 5 ms, therefore establishing assay sensitivity.

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar as those reported by the sponsor.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject QTcF $>$ 500 ms. One subject Δ QTcF $>$ 60 ms.

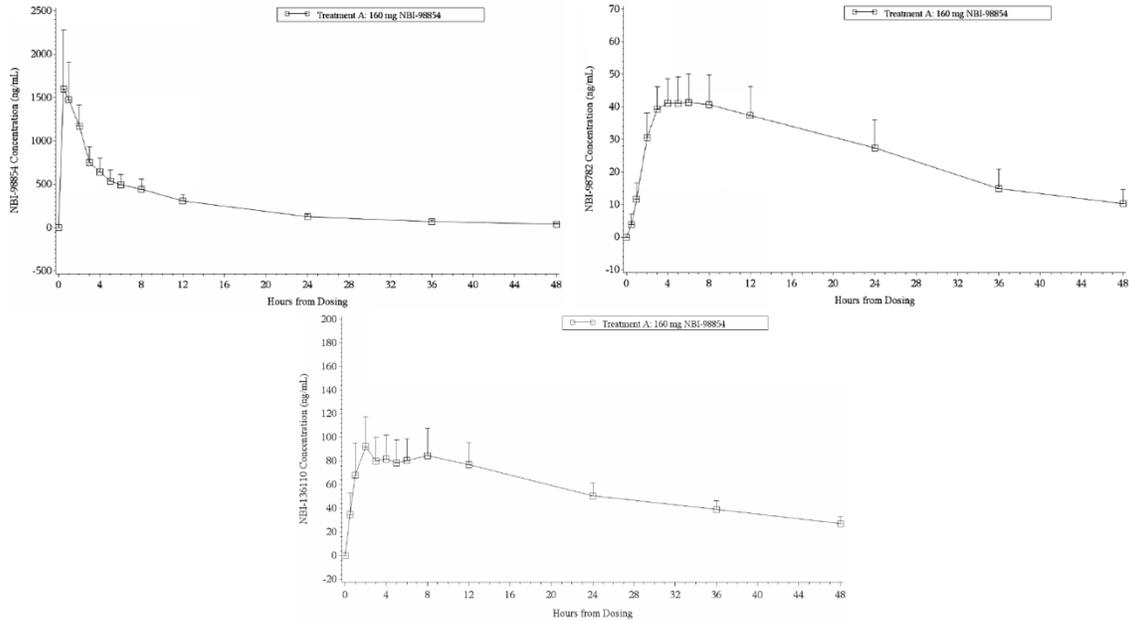
Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results show no subject's Δ QTcF $>$ 60 ms.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

The PK results of NBI-98854 are presented in Figure 1 and Table 4, Table 5, and Table 6. The sponsor did not collect PK of moxifloxacin.

Figure 1: Arithmetic mean (+SD) plasma concentration-time profiles of NBI-98854 (Upper Left), NBI-98782 (Upper Right), and NBI-136110 (Lower panel) following administration of 160 mg NBI-98854.



Source: EDR: nda209241\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\nbi-98854-1401\report-body.pdf, Figure 11-1, Figure 11-3, and Figure 11-5.

Table 4: Summary of the pharmacokinetic parameters of plasma NBI-98854.

Pharmacokinetic Parameters	Treatment A	
	Geometric Mean (CV%)	n
AUC ₀₋₂₄ (ng*hr/mL)	10150 (21.4)	46
AUC _{0-tlast} (ng*hr/mL)	11970 (21.6)	46
C _{max} (ng/mL)	1727 (29.5)	46
t _{max} (hr)	0.5500 (0.550, 3.05)	46
T _{lag} (hr)	0.00 (0.00, 0.00)	46
Treatment A: Administration of 160 mg NBI-98854 (4 x 40 mg NBI-98854 capsules) + 1 moxifloxacin placebo tablet t _{max} and T _{lag} are presented as Median (Minimum, Maximum)		

Source: EDR: nda209241\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\nbi-98854-1401\report-body.pdf, Table 11-2

Table 5: Summary of the pharmacokinetic parameters of plasma NBI-98782.

Pharmacokinetic Parameters	Treatment A	
	Geometric Mean (CV%)	n
AUC ₀₋₂₄ (ng*hr/mL)	789.3 (21.4)	46
AUC _{0-tlast} (ng*hr/mL)	1179 (25.4)	46
C _{max} (ng/mL)	43.93 (17.3)	46
t _{max} (hr)	5.050 (3.05, 12.1)	46
T _{lag} (hr)	0.00 (0.00, 0.550)	46
Treatment A: Administration of 160 mg NBI-98854 (4 x 40 mg NBI-98854 capsules) + 1 moxifloxacin placebo tablet t _{max} and T _{lag} are presented as Median (Minimum, Maximum)		

Source: EDR: nda209241\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\nbi-98854-1401\report-body.pdf, Table 11-3

Table 6: Summary of the pharmacokinetic parameters of plasma NBI-136110.

Pharmacokinetic Parameters	Treatment A	
	Geometric Mean (CV%)	n
AUC ₀₋₂₄ (ng*hr/mL)	1667 (20.5)	46
AUC _{0-last} (ng*hr/mL)	2600 (19.8)	46
C _{max} (ng/mL)	96.91 (22.5)	46
t _{max} (hr)	3.050 (1.05, 12.1)	46
T _{1/2} (hr)	0.00 (0.00, 0.00)	46

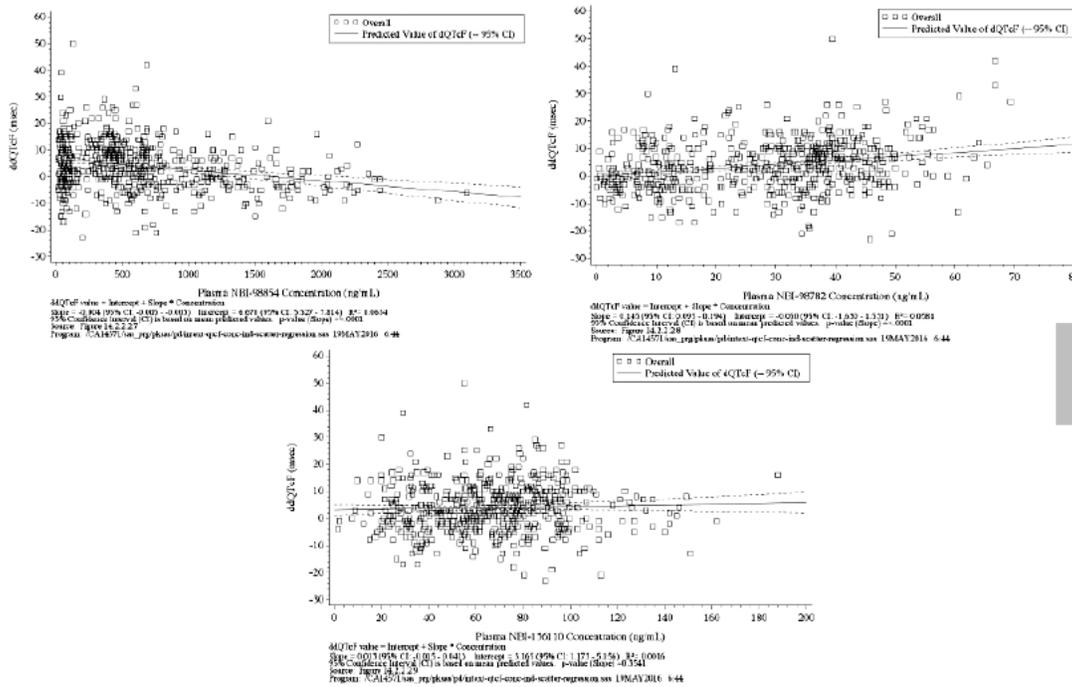
Treatment A: Administration of 160 mg NBI-98854 (4 x 40 mg NBI-98854 capsules) + 1 moxifloxacin placebo tablet
t_{max} and T_{1/2} are presented as Median (Minimum, Maximum)

Source: EDR: nda209241\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\mbi-98854-1401\report-body.pdf , Table 11-4

4.2.8.3.2 Exposure-Response Analysis

The sponsor conducted regression analysis on $\Delta\Delta QTcF$ versus plasma concentrations (Figure 2). The estimated slopes for NBI-98854, NBI-98782, and NBI-136110 were -0.004, 0.145, and 0.013 msec/ng/mL, respectively. The predicted value (90% 2-sided confidence limits) of $\Delta\Delta QTcF$ at the geometric mean value of C_{max} for each of the 3 analytes were -0.438 msec (-1.810, 0.933), 6.300 msec (5.392, 7.209), and 4.432 msec (3.461, 5.403), respectively. Although, $\Delta\Delta QTcF$ increased with increasing concentrations of NBI-98782, the upper limit of the 90% 2-sided CI of the predicted $\Delta\Delta QTcF$ at C_{max} was less than 10 msec.

Figure 2: Corrected change from time-matched baseline in QTcF ($\Delta\Delta QTcF$) versus plasma NBI-98854 (Upper Left), NBI-98782 (Upper Right), or NBI-136110 (Lower) concentrations.



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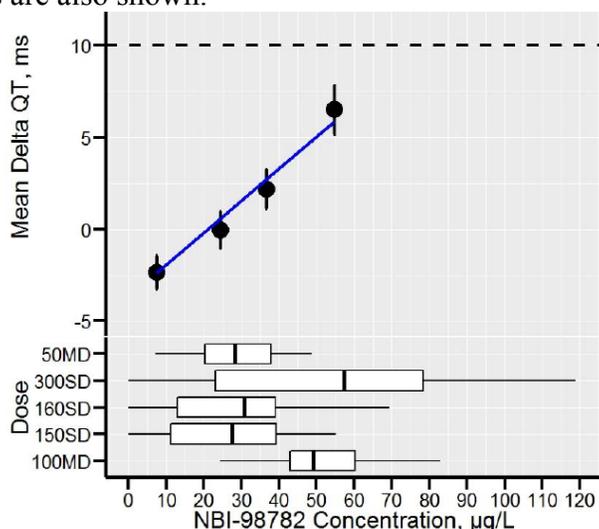
Source: EDR: nda209241\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\mbi-98854-1401\report-body.pdf , Figure 11-16 to Figure 11-18

Reviewer's Analysis: A plot of $\Delta\Delta QTcF$ vs. drug concentrations is presented in Figure 8.

4.3 ADDITIONAL STUDIES AND ANALYSES

The sponsor submitted a concentration-QT report to evaluate the concentration-QT relationships for NBI-98854 and NBI-98782 across studies (1401, 0901 and 1301) and doses.⁴ This analysis showed a lack of relationship between NBI-98854 and QTc, but a significant relationship between NBI-98782 and QTc (Figure 3).

Figure 3: Mean change in Δ QTcF after single dose of 160 mg (Study 1401), multiple doses of 50 mg and 100 mg (Study 0901), and single doses of 150 mg and 300 mg (Study 1301) for each quartile of NBI-98782 Concentrations. The one-sided 95% confidence intervals, the model predicted changes (Blue Line) and a Reference Line (Dash Line) at 10 ms are also shown.



Based on this relationship the sponsor Mean Δ QTcF after 80 mg NBI-98854 in a CYP2D6 non-PM at steady-state C_{max} was estimated to be 3.07 ms and in a CYP2D6 PM at steady-state NBI-98782 C_{max} was estimated to be 8.59 ms (Table 7).

Table 7: Model predicted Δ QTcF after multiple doses of 40 mg and 80 mg in CYP2D6 Non-Poor metabolizers and Poor-Metabolizers based on concentration-QT analysis (Studies 1401, 0901, and 1301, pooled analysis) and population PK modeling.

Dose	Mean NBI-98782 Steady State C_{max} , $\mu\text{g/L}$	Mean Δ QTcF, ms
Non Poor-Metabolizers		
40 mg	19.50	-0.37
80 mg	39.01	3.07
Poor-Metabolizers		
40 mg	35.70	2.48
80 mg	70.41	8.59

The model predicted mean NBI-98782 steady state C_{max} is from population PK model (Report 2016-PK-056).

Reviewer's Comment: The C-QTc model used by the sponsor did not incorporate placebo and included data from study 0901, which could potentially impact the slope of the estimated relationship. For further details see the reviewer's analysis (section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8 (Study 1401), it appears that QTcF and QTcI are equally better than QTcB. Studies 1301 and 0901 provided only QTcB and QTcF correction intervals. QTcF was used as the primary statistical analysis.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods (Study 1401)

Treatment Group	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Placebo	46	0.00617	46	0.00270	46	0.00061
Moxifloxacin 400 mg	48	0.00588	48	0.00283	48	0.00349
NBI-98854 160 mg	46	0.00454	46	0.00156	46	0.00156
All	48	0.00524	48	0.00145	48	0.00165

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for INGREZZA™ (Valbenazine)

The statistical reviewer used a mixed model to analyze the Δ QTcF effect. The model includes treatment as a fixed effect and baseline value as a covariate. The primary analysis is based on Study 1401 which includes 160 mg. The results are listed in Table 9. The largest upper bound of the 2-sided 90% CI for the mean difference between Valbenazine 160 mg and placebo exceed 10 ms (11.7 ms) of the regulatory concern as described in ICH E14 guidelines.

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Valbenazine 160 mg and Moxifloxacin 400 mg (Study 1401 by Pooled Period)

		Treatment Group								
		Moxifloxacin 400 mg					NBI-98854 160 mg			
		Δ QTcF		$\Delta\Delta$ QTcF			Δ QTcF		$\Delta\Delta$ QTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	*Adj. 90% CI	N	LS Mean	LS Mean	90% CI
0.5	-1.9	48	3.7	5.6	(3.5, 7.7)	(2.7, 8.4)	46	-2.7	-0.8	(-2.9, 1.3)
1	-0.2	48	9.9	10.1	(8.2, 11.9)	(7.5, 12.6)	46	-2.2	-2.0	(-4.0, -0.1)
2	0.0	48	11.9	11.8	(9.8, 13.9)	(9.0, 14.7)	46	2.6	2.6	(0.5, 4.7)
3	2.8	48	11.2	8.4	(5.8, 11.0)	(4.9, 11.9)	46	6.0	3.2	(0.6, 5.8)
4	-1.8	48	7.7	9.4	(6.4, 12.4)	(5.3, 13.5)	46	1.3	3.0	(0.0, 6.1)
5	-3.3	47	4.5	7.8	(4.6, 10.9)	(3.5, 12.0)	45	2.2	5.5	(2.4, 8.6)
6	-3.1	47	6.2	9.3	(6.2, 12.4)	(5.1, 13.5)	45	1.9	5.0	(1.9, 8.1)
8	-4.2	47	6.4	10.6	(7.8, 13.3)	(6.8, 14.3)	44	4.7	8.9	(6.1, 11.7)
12	-4.1	47	3.2	7.3	(4.6, 10.0)	(3.6, 11.1)	45	4.2	8.3	(5.6, 11.1)
24	-7.2	47	-2.3	4.9	(2.1, 7.7)	(1.1, 8.7)	44	-1.0	6.1	(3.3, 8.9)
36	-5.3	47	-1.4	3.9	(1.0, 6.8)	(-0.0, 7.9)	46	-2.1	3.2	(0.2, 6.1)
48	-6.5	47	-3.5	3.0	(-0.1, 6.1)	(-1.2, 7.3)	46	-1.3	5.2	(2.1, 8.3)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

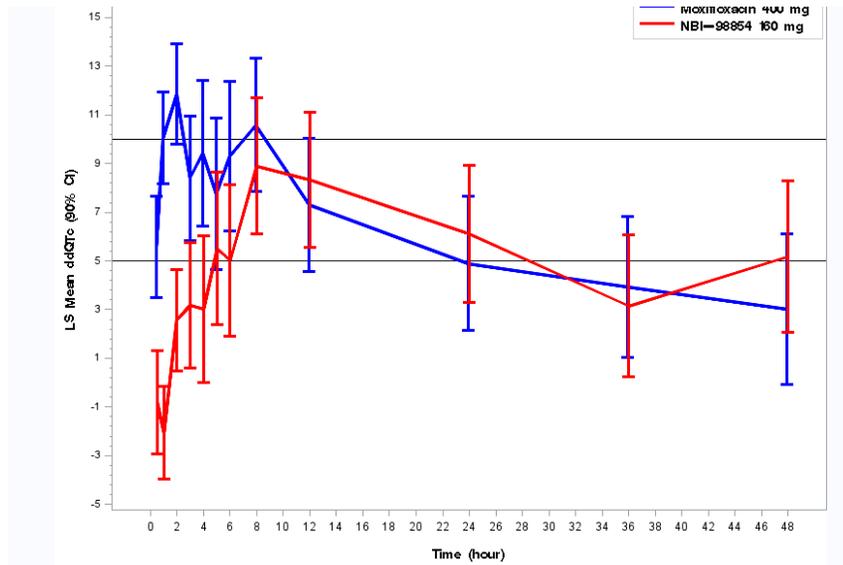
5.2.1.1 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval is 9.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.0 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.2 Graph of $\Delta\Delta$ QTcF over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 4: Mean and 90% CI Δ QTcF Time Course



5.2.1.3 Categorical Analysis

Table 10 and Table 11 list the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and > 500 ms. No subject's QTcF is above 500 ms from Studies 1401 and 1301.

Table 10: Categorical Analysis for QTcF (Study 1401)

Treatment Group	Total N	Value ≤ 450 ms	450 ms $<$ Value ≤ 480 ms	480 ms $<$ Value ≤ 500 ms	Value > 500
Moxifloxacin 400 mg	48	46 (95.8%)	1 (2.1%)	1 (2.1%)	0 (0.0%)
NBI-98854 160 mg	46	44 (95.7%)	2 (4.3%)	0 (0.0%)	0 (0.0%)
Placebo	46	44 (95.7%)	2 (4.3%)	0 (0.0%)	0 (0.0%)

Table 11: Categorical Analysis for QTcF (Study 1301)

Treatment Group	Total N	Value ≤ 450 ms	450 ms $<$ Value ≤ 480 ms	480 ms $<$ Value ≤ 500 ms	Value > 500
150 mg	6	5 (83.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)
300 mg	6	5 (83.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)
Placebo	3	3 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 12 and Table 13 list the number of subjects changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, between 60 ms and 90, and > 90 ms. No subject's change from baseline is above 60 ms from Studies 1401 and 1301.

Table 12: Categorical Analysis of Δ QTcF (Study 1401)

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms	60 ms<Value \leq 90 ms	Value>90 ms
Moxifloxacin 400 mg	48	46 (95.8%)	2 (4.2%)	0 (0.0%)	0 (0.0%)
NBI-98854 160 mg	46	45 (97.8%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Placebo	46	46 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 13: Categorical Analysis of Δ QTcF (Study 1301)

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms	60 ms<Value \leq 90 ms	Value>90 ms
150 mg	6	6 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
300 mg	6	5 (83.3%)	1 (16.7%)	0 (0.0%)	0 (0.0%)
Placebo	3	3 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used a mixed model to analyze the Δ HR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The primary analysis is based on Study 1401 which includes 160 mg. The analysis results are listed in Table 14. The largest upper bound of the 2-sided 90% CI for the mean difference between Valbenazine 160 mg and Placebo is 1.2 bpm. Table 15 and Table 16 present the categorical analysis of HR for Studies 1401 and 1301, respectively. No subject who experienced HR interval greater than 100 bpm is in Valbenazine 160 mg, 150 mg and 300 mg groups.

Table 14: Analysis Results of $\Delta\Delta$ HR for Valbenazine 160 mg and Moxifloxacin 400 mg (Study 1401)

Time (h)	Treatment Group				
	Placebo	NBI-98854 160 mg			
	Δ HR	Δ HR		$\Delta\Delta$ HR	
	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	1.2	46	1.2	0.1	(-1.1, 1.2)
1	1.1	46	-1.3	-2.4	(-3.9, -0.9)
2	0.3	46	-4.5	-4.8	(-6.0, -3.5)
3	10.0	46	-0.3	-10.3	(-12.3, -8.2)
4	8.9	46	1.3	-7.6	(-9.8, -5.4)
5	11.3	45	0.6	-10.7	(-12.9, -8.5)
6	11.1	45	2.7	-8.4	(-10.8, -6.1)
8	8.0	44	-1.4	-9.4	(-11.5, -7.4)
12	7.7	45	-1.6	-9.3	(-11.4, -7.2)
24	8.2	44	0.8	-7.3	(-9.2, -5.4)
36	8.8	46	2.1	-6.7	(-8.9, -4.5)
48	13.9	46	8.1	-5.8	(-7.9, -3.6)

Table 15: Categorical Analysis for HR (Study 1401)

Treatment Group	Total N	HR \leq 100 bpm	HR >100 bpm
Moxifloxacin 400 mg	48	48 (100%)	0 (0.0%)
NBI-98854 160 mg	46	46 (100%)	0 (0.0%)
Placebo	46	45 (97.8%)	1 (2.2%)

Table 16: Categorical Analysis for HR (Study 1301)

Treatment Group	Total N	HR \leq 100 bpm	HR >100 bpm
150 mg	6	6 (100%)	0 (0.0%)
300 mg	6	6 (100%)	0 (0.0%)
Placebo	3	3 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used a mixed model to analyze the Δ PR effect. The model includes treatment as a fixed effect and baseline value as a covariate. The primary analysis is based on Study 1401 which includes 160 mg. The analysis results are listed in Table 17. The largest upper bound of the 2-sided 90% CI for the mean different between Valbenazine 160 mg and Placebo is 11.7 mg (see Table 17). Table 18 and Table 19 present the categorical analysis of PR for Studies 1401 and 1301, respectively. Six subjects who experienced PR interval greater than 200 ms are in Valbenazine 160 mg, 150 mg and 300 mg groups.

Table 17: Analysis Results of $\Delta\Delta$ PR for Valbenazine 160 mg and Moxifloxacin 400 mg (Study 1401 by Pooled Period)

Time (h)	Treatment Group				
	Placebo	NBI-98854 160 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	-1.3	46	-1.2	0.0	(-1.6, 1.6)
1	-0.5	46	0.6	1.1	(-0.8, 2.9)
2	-0.7	46	-1.1	-0.3	(-2.1, 1.4)
3	-4.8	46	-2.6	2.2	(-1.1, 5.5)
4	-6.5	46	-3.9	2.6	(-0.5, 5.8)
5	-9.0	45	-6.4	2.6	(-0.7, 5.9)
6	-9.9	45	-9.8	0.0	(-3.1, 3.1)
8	-7.5	44	-7.6	-0.1	(-2.8, 2.5)
12	-4.1	45	-5.4	-1.4	(-3.9, 1.2)
24	-6.2	44	-9.0	-2.8	(-5.7, 0.1)
36	-4.0	46	-7.8	-3.8	(-6.8, -0.8)
48	-7.1	46	-12.3	-5.2	(-8.7, -1.7)

Table 18: Categorical Analysis for PR (Study 1401)

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
Moxifloxacin 400 mg	48	46 (95.8%)	2 (4.2%)
NBI-98854 160 mg	46	42 (91.3%)	4 (8.7%)
Placebo	46	43 (93.5%)	3 (6.5%)

Table 19: Categorical Analysis for PR (Study 1301)

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
150 mg	6	5 (83.3%)	1 (16.7%)
300 mg	6	5 (83.3%)	1 (16.7%)
Placebo	3	3 (100%)	0 (0.0%)

5.2.4 QRS Analysis

The statistical reviewer used a mixed model to analyze the Δ QRS effect. The model includes treatment as a fixed effect and baseline value as a covariate. The primary analysis is based on Study 1401 which includes 160 mg. The analysis results are listed in Table 20. The largest upper bound of the 2-sided 90% CI for the mean different between Valbenazine 160 mg and Placebo is 11.7 mg. Table 21 and Table 22 present the categorical analysis of QRS for Studies 1401 and 1301, respectively. No subject who experienced QRS interval greater than 110 ms is in Valbenazine 160 mg, 150 mg and 300 mg groups.

Table 20: Analysis Results of $\Delta\Delta$ QRS for Valbenazine 160 mg and Moxifloxacin 400 mg (Study 1401)

	Treatment Group				
	Placebo	NBI-98854 160 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.5	0.9	46	0.7	-0.2	(-1.0, 0.6)
1	0.4	46	0.4	0.0	(-0.7, 0.8)
2	0.1	46	0.3	0.2	(-0.5, 0.8)
3	3.7	46	4.1	0.5	(-1.0, 2.0)
4	2.0	46	2.1	0.1	(-1.4, 1.6)
5	2.1	45	2.4	0.3	(-1.3, 1.8)
6	0.8	45	1.0	0.3	(-1.1, 1.6)
8	-0.5	44	0.7	1.2	(0.0, 2.4)
12	-0.4	45	-0.1	0.2	(-0.8, 1.2)
24	0.9	44	1.2	0.3	(-0.9, 1.6)
36	1.5	46	1.1	-0.4	(-1.5, 0.7)
48	1.8	46	1.6	-0.3	(-1.5, 1.0)

Table 21: Categorical Analysis for QRS (Study 1401)

Treatment Group	Total N	QRS \leq 110 ms	QRS $>$ 110 ms
Moxifloxacin 400 mg	48	48 (100%)	0 (0.0%)
NBI-98854 160 mg	46	46 (100%)	0 (0.0%)
Placebo	46	46 (100%)	0 (0.0%)

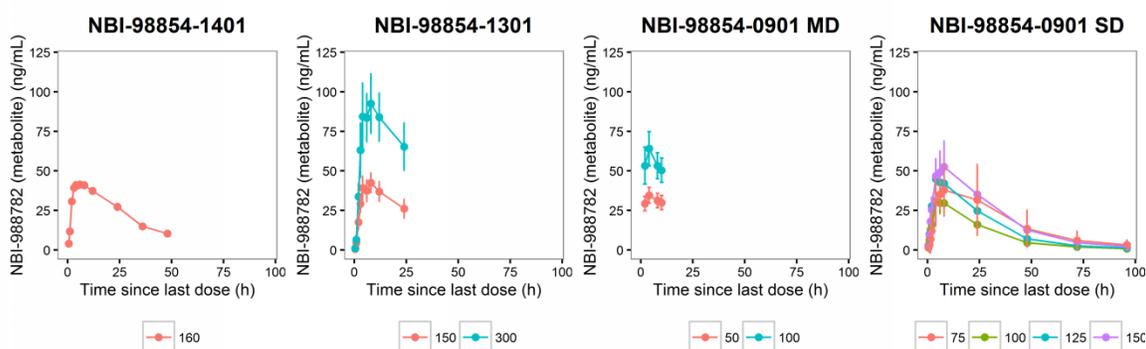
Table 22: Categorical Analysis for QRS (Study 1301)

Treatment Group	Total N	QRS \leq 110 ms	QRS $>$ 110 ms
150 mg	6	6 (100%)	0 (0.0%)
300 mg	6	6 (100%)	0 (0.0%)
Placebo	3	3 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The dose studied in the TQT study (1401) barely covers therapeutic exposure of the active metabolite (section 4.2.6.2 for further details). Therefore, the clinical pharmacology assessment will be based on the pooled analysis of studies 0901, 1301 and 1401 (see section 4.1 for study descriptions). Briefly, study 0901 is a SAD/MAD study including doses up to 150 mg (single dose) 100 mg (multiple doses) and study 1301 is a SAD study including two cohorts: 150 and 300 mg. The PK profiles for the active metabolite by dose for each of the three studies are shown in Figure 5.

Figure 5: Concentration-time profile for the active metabolite by study/dose.



5.3.1 Exploratory assessment

Exploratory assessment of the relationship between PK and QTc by time supports that the metabolite is causing the observed QTc effect in study 1301 and 1401. However study 0901 did not show the same pattern (Figure 6). Further exploratory assessment of the C-QT relationship focusing on linearity is shown in Figure 7, which shows a linear relationship for 1301 and 1401 and no relationship for 0901. It is not clear why 0901 is an outlier in this regard, but it is worth noting that the study was performed at a different site, doses included are in the lower range and that it was a small study. Therefore, the following analysis will focus on assessment of the C-QTc relationship using pooled data from 1301 and 1401.

Figure 6: Exploratory evaluation of the relationship between the timing of plasma concentration of the metabolite (top row) and changes in $\Delta\Delta\text{QTcF}$ (bottom row), by study (column) and dose. The vertical line denotes the average T_{max} across all dose groups within a study. Note, that $\Delta\Delta\text{QTcF}$ is computed by subtracting the average placebo by-time within a study from ΔQTcF .

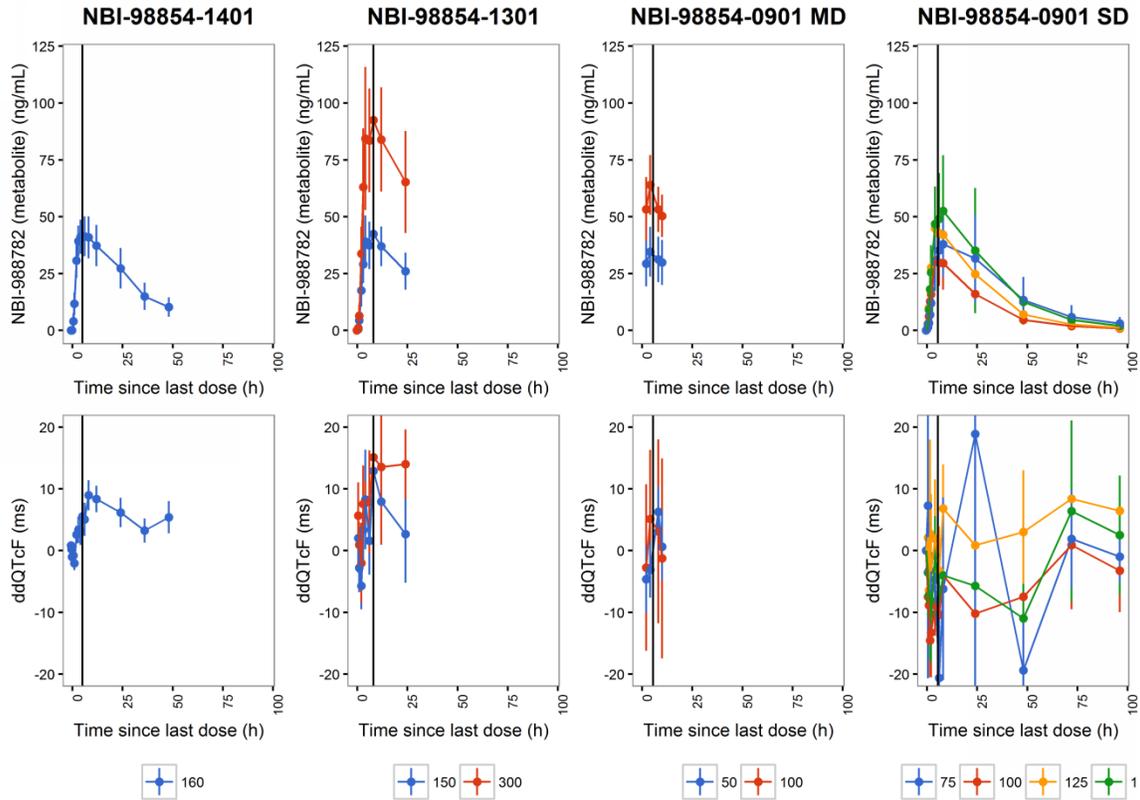
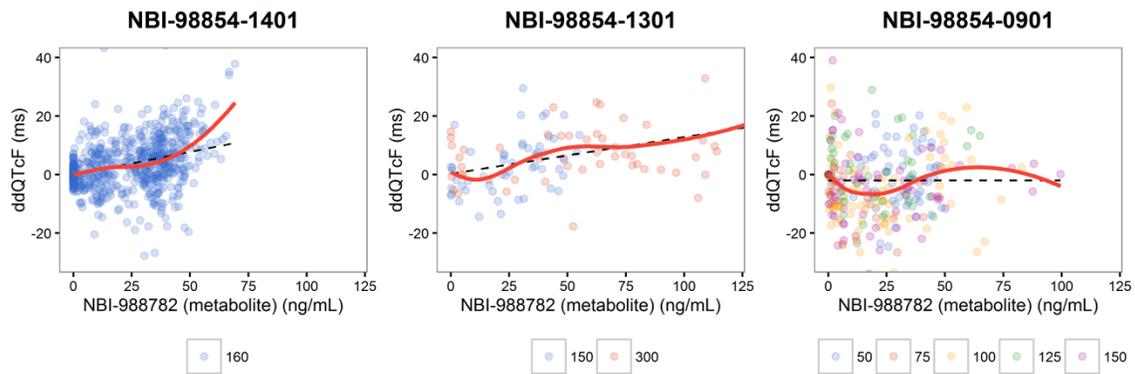


Figure 7: Exploratory assessment of linearity of the concentration-QTc relationship for each of three studies included. Note, that $\Delta\Delta\text{QTcF}$ is computed by subtracting the average placebo by-time within a study from ΔQTcF .



5.3.2 Assessment of the C-QT relationship

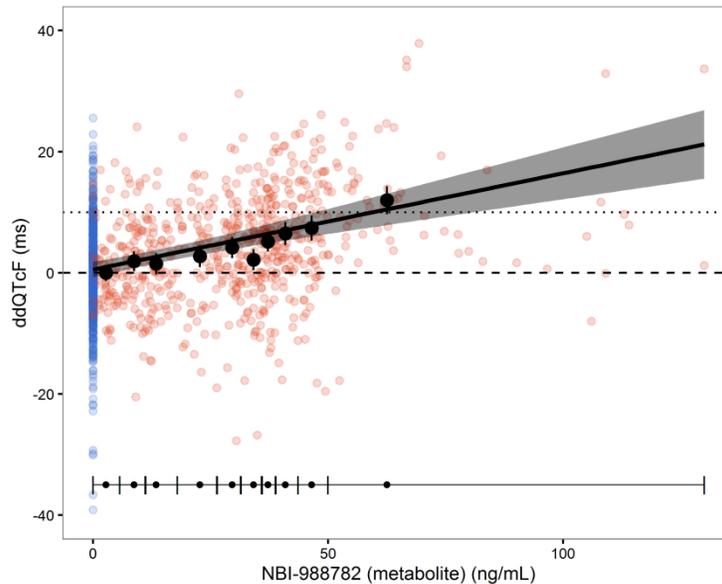
There was no formally prespecified model, therefore an internally recommended model was used for this analysis with the addition of a fixed effect related to the study as well as an interaction between study and slope:

$$dQTc \sim \text{time} + \text{study} + \text{meta} + \text{study}:\text{meta} + \text{treat} + \text{qtcbaseline} + (\text{meta}|\text{usubjid})$$

where time, study and active are three categorical variables representing nominal time post-dose, study and treatment (treat=1 for drug, and treat=0 for placebo) with metabolite concentrations set to 0 for placebo and baseline QTc centered at the combined study average. In this model meta|usubjid (last term) denotes that there is a random effect on both the intercept and the slope with an unstructured covariance.

The goodness-of-fit plot for the model is shown in Figure 8, which shows that the model describes the observed data reasonably well. Further evaluation of model performance using model diagnostic plots (see Appendix 6.2) supports this observation. Lastly, estimated model parameters are included in Appendix 6.3.

Figure 8: Goodness-of-fit plot for the model. The colors correspond to placebo (blue) and treatment (red). The observed $\Delta\Delta QTcF$ is grouped into 10 bins for the treatment data. The solid line and shaded area represents mean \pm 90% confidence interval and the line in the bottom represents the concentration range in the bins, where the dot represents the median for each bin. Note, that $\Delta\Delta QTcF$ is computed by subtracting the average placebo by-time within a study from $\Delta QTcF$.



From the model described above the mean $\Delta\Delta QTcF$ effect and 90% confidence bounds were estimated for the expected steady-state concentration of the metabolite in healthy subjects and subjects on concomitant medication or poor metabolizers and are listed below (see Table 7 for further details):

Table 23: Predicted $\Delta\Delta QTcF$ and 90% CI for concentrations of the active metabolite corresponding to steady-state concentration of 80 mg in healthy subjects and poor metabolizers (Table 7).

Concentration (ng/mL)	$\Delta\Delta QTcF$ (90% CI) (ms)
-----------------------	-----------------------------------

39.01 ng/mL	6.7 (5.1 to 8.4)
70.41 ng/mL	11.7 (8.8 to 14.7)

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

In short term controlled and long term phase 2/3 trials, adverse events identified to be of clinical importance per the ICH E14 guidelines (e.g., syncope, prolong QT and sudden death) occurred in these studies, but the event rates are too low to make any conclusions on the risk of arrhythmia. The majority of subjects in these studies were taking another QT prolonging medication.

- In Phase 2/3 controlled studies, 3 (1%) of 254 subjects treated with NBI-98854 and 1 (<1%) of 178 subjects treated with placebo experienced an AESI of Cardiac Events and QT Prolongation. One event each of chest pain, sudden death, and syncope were reported among subjects who received NBI-98854 and a myocardial infarction was reported in a subject who received placebo. This AESI was associated with study discontinuation in 3 subjects in the Phase 2/3 Controlled Studies pool (1 subject with sudden death, 1 with syncope, and 1 with myocardial infarction); no subject had their dose reduced.
- In Phase 2/3 long term extension studies, 14 (3%) of 427 subjects treated with NBI-98854 experienced an AESI of Cardiac Events and QT Prolongation. The most common AEs associated with this AESI were chest pain (6 subjects, 1%) and syncope (6 subjects, 1%); other events were reported in 1 NBI-98854-treated subject each (<1%). Two fatal events were reported, 1 subject each experienced sudden death and cardiac failure.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in all three studies (1401, 1301, and 0901) appears acceptable.

5.4.3 Other ECG intervals

No clinically relevant effects on heart rate, PR and QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and Exposure ^a (2016-PK-056 Table 22)	40 or 80 mg daily		
	NBI-98854 (parent)	NBI-98782 (metabolite)	
	Mean at the single maximum proposed clinical dose: C_{max} : 461 ng/mL AUC_{0-24} : 3820 ng×hr/mL	Mean at the single maximum proposed clinical dose: <u>CYP2D6 non-PM</u> C_{max} : 21.7 ng/mL AUC_{0-24} : 411 ng×hr/mL <u>CYP2D6 PM</u> C_{max} : 29.2 ng/mL AUC_{0-24} : 585 ng×hr/mL	
	NBI-98854 (parent)	NBI-98782 (metabolite)	
	Mean at the steady state with the maximum proposed clinical dosing regimen: C_{max} : 556 ng/mL AUC_{0-24} : 5350 ng×hr/mL	Mean at the steady state with the maximum proposed clinical dosing regimen: <u>CYP2D6 non-PM</u> C_{max} : 39.0 ng/mL AUC_{0-24} : 775 ng×hr/mL <u>CYP2D6 PM</u> C_{max} : 71.4 ng/mL AUC_{0-24} : 1550 ng×hr/mL	
Maximum tolerated dose	Single Dose	300 mg	
	Multiple Dose	100 mg QD for 8 days in healthy volunteers 100 mg QD for 14 days in subjects with schizophrenia or schizoaffective disorder	
Principal adverse events	Adverse events associated with monoamine reduction: fatigue, insomnia, somnolence, restlessness, akathisia		
Maximum dose tested	Single Dose	300 mg	
	Multiple Dose	100 mg QD for 8 days in healthy volunteers 100 mg QD for 14 days in subjects with schizophrenia or schizoaffective disorder	
Exposures Achieved at Maximum Tested Dose	Single Dose (300 mg) ^b (2.7.2 Section 2.2.2.3 Table 18)	NBI-98854 (parent) Mean (%CV): C_{max} : 2430 (18.5) ng/mL $AUC_{0-\infty}$: 28,600 (18.7) ng×hr/mL	NBI-98782 (metabolite) Mean (%CV): C_{max} : 97.3 (30.8) ng/mL $AUC_{0-\infty}$: 3580 (31.5) ng×hr/mL
	Multiple Dose (100 mg) (2.7.2 Section 3.3.2 Table 35)	NBI-98854 (parent) Mean (%CV): C_{max} : 878 (72.7) ng/mL AUC_{0-24} : 6730 (46.1) ng×hr/mL	NBI-98782 (metabolite) Mean (%CV): C_{max} : 64.0 (20.5) ng/mL AUC_{0-24} : 1110 (22.0) ng×hr/mL
Range of linear PK (NDA Module 2.7.2 Section 3.3.1)	40-150 mg		
Accumulation at steady state (C_{max}) ^c (NBI-98854-0901)	NBI-98854 (parent) 1.16	NBI-98782 (metabolite) 2.22	
Metabolites (NDA Module 2.4.2 Table 1)	NBI-98782 –VMAT2 inhibition K_i 2.6-3.3 nM (Human Platelet VMAT2 assay) NBI-136110 –VMAT2 inhibition K_i 220 nM (Human Platelet VMAT2 assay)		

Absorption	Absolute Bioavailability (NBI-98854-1204)	NBI-98854 (parent) Mean (%CV): 48.6 (10.3)% (Estimated from an IV microdose)	NBI-98782 (metabolite) Not applicable.
	T _{max} (NBI-98854-1504 80 mg)	NBI-98854 (parent) Median (range): 0.63 hrs (0.50-2.0 hrs)	NBI-98782 (metabolite) Median (range): 4.0 hrs (3.0-8.0 hrs)
Distribution	V _d (NBI-98854-1204)	Mean (%CV): 169 (34.9) L (Estimated from an IV microdose)	Not applicable.
	% bound to plasma proteins (277N-1102 and 277N-1101)	NBI-98854 (parent) Mean (%CV): NBI-98854 (1000 ng/mL): 99.9 (0.01) ^d	NBI-98782 (metabolite) Mean (%CV): NBI-98782 (100 ng/mL): 65.2 ^e
Elimination	(Route NBI-98854-1204)	Urine: 61.2% (percent dose eliminated primarily as metabolites) Feces: 29.5% (percent dose eliminated primarily as metabolites)	
	Terminal t _{1/2} (NBI-98854-1504 80 mg)	NBI-98854 (parent) Mean (%CV): 16.0 (10.0) hrs	NBI-98782 (metabolite) Mean (%CV): 17.0 (11.4) hrs
	CL (NBI-98854-1204)	NBI-98854 (parent) Mean (%CV): 7.20 (20.1) L/hr (estimated from an IV microdose)	NBI-98782 (metabolite) Not applicable.
Intrinsic Factors	Age ^f (NBI-98854-1102)	NBI-98854 (parent) C _{max} : ↑ 27.6% in elderly AUC _{0-∞} : ↑ 25.9% in elderly	NBI-98782 (metabolite) C _{max} : ↓ 0.794% in elderly AUC _{0-∞} : ↑ 38.7% in elderly
	Sex (2016-PK-056 Figure 8)	No consistent substantial differences in C _{max} and AUC between male and female for NBI-98854 and NBI-98782	
	Race (2016-PK-056 Figure 8)	No consistent substantial differences in C _{max} and AUC among races for NBI-98854 and NBI-98782	
	Hepatic Impairment (NBI-98854-1303)	NBI-98854 (parent) C _{max} : ↑ 99.4% in moderately impaired; ↑ 150% in severely impaired AUC _{0-∞} : ↑ 87.9% in moderately impaired; ↑ 137% in severely impaired	NBI-98782 (metabolite) C _{max} : ↑ 109% in moderately impaired; ↑ 117% in severely impaired AUC _{0-∞} : ↑ 177% in moderately impaired; ↑ 243% in severely impaired
	Renal Impairment (NBI-98854-1204)	NBI-98854 (parent) Not known (1.8% of the total administered dose excreted in urine as unchanged NBI-98854)	NBI-98782 (metabolite) Not known (1.6% of the total NBI-98854 dose excreted as NBI-98782 in urine)
	CYP2D6 (2016-PK-056 Table 23)	NBI-98854 (parent) The C _{max} and AUC _{0-∞} were similar between PM and non-PM	NBI-98782 (metabolite) C _{max} : ↑ 83% in PM AUC _{0-∞} : ↑ 103% in PM

Extrinsic Factors	Drug Interactions with Ketoconazole (NBI-98854-1302)	NBI-98854 (parent) C _{max} : ↑ 51.1% AUC _{0-∞} : ↑ 114%	NBI-98782 (metabolite) C _{max} : ↑ 62.9% AUC _{0-∞} : ↑ 107%
	Drug Interactions with Rifampin (NBI-98854-1502)	NBI-98854 (parent) C _{max} : ↓ 31.8% AUC _{0-∞} : ↓ 72.3%	NBI-98782 (metabolite) C _{max} : ↓ 51.5% AUC _{0-∞} : ↓ 77.2%
	Food Effect (NBI-98854-1504)	NBI-98854 (parent) C _{max} : ↓ 46.2% with high fat meal AUC _{0-∞} : ↓ 12.6% with high fat meal	NBI-98782 (metabolite) C _{max} : ↓ 18.7% with high fat meal AUC _{0-∞} : ↓ 7.6% with high fat meal
Expected High Clinical Exposure Scenario	NBI-98854 (parent) Subjects taking strong CYP3A4 inhibitor on the highest therapeutic dose (80 mg QD)		NBI-98782 (metabolite) CYP2D6 PM on the highest therapeutic dose (80 mg QD)
	Steady State C _{max} : 1.51-fold Steady State AUC ₀₋₂₄ : 2.14-fold		Steady State C _{max} : 1.83-fold Steady State AUC ₀₋₂₄ : 2.03-fold
Preclinical Cardiac Safety	A standard battery of in vitro and in vivo nonclinical studies, as per ICH S7B guidance, were conducted to investigate the potential impact of NBI-98854 and its active metabolite (NBI-98782) on the cardiovascular system. In vitro, NBI-98854 inhibited hERG tail currents with IC ₅₀ value of 2.0 μM (831 ng/mL), whereas the IC ₅₀ for NBI-98782 was 36.1 μM (11532 ng/mL). These IC ₅₀ values in the absence of protein binding are equivalent to NBI-98854 and NBI-98782 total plasma concentrations of 831000 ng/mL and 33138 ng/mL based on 99.9% and 65.2% human plasma protein binding, respectively. In the definitive in vivo cardiovascular safety study conducted in conscious dogs implanted with telemetry devices, a transient increase in blood pressure was observed at 30 mg/kg NBI-98854 and transient increases in heart rate were observed at ≥ 15 mg/kg NBI-98854 and ≥ 7.5 mg/kg NBI-98782 compared to the vehicle control group. Increased QTc intervals (<7% or 15 msec) were observed in dogs dosed with NBI-98854 (≥15 mg/kg) and NBI-98782 (≥15 mg/kg) compared to vehicle controls. No waveform abnormalities were observed following administration of either NBI-98854 or NBI-98782. Overall, the blood pressure, heart rate, and QTc increases were not considered toxicologically significant due to their minimal magnitude and transient nature and because they were not accompanied by any adverse effect on arrhythmogenesis. Although the cardiovascular effects noted above are not considered adverse, the NOAEL in the dog cardiovascular study was conservatively assigned to be 15 mg/kg for NBI-98854. At the NOAEL dose, NBI-98854 C _{max} and AUC ₀₋₂₄ were estimated to be 6.8 μg/mL and 27.9 μg×hr/mL, respectively based on Day 1 exposures from a 14-day repeat dose toxicity study in dogs.		
Clinical Cardiac Safety	See Appendix 1		

PM= CYP2D6 poor metabolizer; non-PM= CYP2D6 ultrarapid (UM), extensive (EM), or intermediate (IM) metabolizer; ICH=International Conference on Harmonisation; hERG=human ether-a-go-go related gene; IC₅₀=half maximal inhibitory concentration; NOAEL= no observed adverse effect level.

^a Model simulated data using mean population estimates only; values reported herein were rounded to three significant figures.

^b Dose administered with food.

^c Calculated from 50 and 100 mg QD for 8 days in healthy volunteers who completed NBI-98854-0901 study multiple dose cohorts (N=17).

^d Estimated using ultrafiltration methodology.

^e %CV was not calculated due to N=2.

^f PK data from NBI-98854-1102 study excluding CYP2D6 PM.

^g Based on proposed maximum recommended dose of 80 mg (40 mg in subjects with moderate or severe hepatic impairment).

APPENDIX 1. CLINICAL CARDIAC SAFETY

Table 1: NBI-98854 Clinical Trials Reported to NDA 209241

Study	Study Phase	# Subjects Exposed to NBI-98854* (any dose)	# Subjects who Received Placebo	Total # Subjects in Study	Dosing Duration	NBI-98854 Dose
Phase 1 Studies (Healthy Volunteers)						
0801	1	16	14	16	4 single doses	1, 2, 5, 12.5, 25, 50, and 75 mg
0901 ^a	1	Single dose: 8 Multiple dose: 22	Single dose: 5 Multiple dose: 10	40	Single dose: 3 single doses Multiple doses: 8 days	Single dose: 75, 100, 125, and 150 mg Multiple dose: 50 and 100 mg
1102	1	22	0	22	Adults: 3 single doses (n=12) Elderly: 1 single dose (n=10)	25 mg capsule and powder fasted (adults and elderly) and fed (adults)
1203	1	12	0	12	2 single doses; 7 days apart	100 mg capsule and powder, fasted
1204	1	12	0	12	Single dose	50 mg
1301	1	12	3	15	Single dose	150 and 300 mg
1302	1	24	0	24	Single doses on Days 1 and 6; ketoconazole (bid) on Days 5-9	50 mg
1401	1	46	46	48	3 single doses (NBI, placebo, moxifloxacin)	160 mg
1502	1	12	0	12	Single doses on Days 1 and 11; rifampin on Days 5-14	80 mg
1503	1	23	0	24	Multiple doses on Days 10-16; digoxin on Days 1 and 14	80 mg
1504	1	48	0	48	2 single doses; current/proposed formulations or fed/fasted	40 and 80 mg
1507	1	12	0	12	Single dose on Day 1; midazolam on Days 1 and 4	80 mg
Total (Healthy Volunteers Only)		269	78	285		
Phase 1 Studies (Non-Healthy Volunteer Studies)						
1303 ^b	1	24 (6 healthy + 18 hepatic imp.)	0	24	Single dose	50 mg
1403 ^c	1b	28	0	28	14 days	5 and 10 mg in children; 10, 25, and 50 mg in adolescents
Phase 1 Total		321	78	337		

Table 1: NBI-98854 Clinical Trials Reported to NDA 209241 (Continued)

Study	Study Phase	# Subjects Exposed to NBI-98854* (any dose)	# Subjects who Received Placebo	Total # Subjects in Study	Dosing Duration	NBI-98854 Dose
Phase 2/3 Studies (Schizophrenia, Schizoaffective Disorder, Mood Disorder, Gastrointestinal Disorder Subjects with TD)						
1001	2	6	0	6	12 days (4 days at each dose)	12.5, 25, and 50 mg
1101	2	36	35	37	28 days (14 days on NBI-98854 and 14 days on placebo)	12.5 and 50 mg
1201	2	102	54	109	12 weeks	50 and 100 mg
1202	2	51	49	102 (100 exp.)	6 weeks	25, 50, 75 mg
1304	3	220	76	234	Up to 48 weeks; ongoing	40 and 80 mg
1402	3	161	0	168	12 months; ongoing	40 and 80 mg
Total Phase 2/3		576	214	656		
All Subjects		897	292	993		
Unique Subjects Exposed to NBI-98854		846^d	NA	NA		

* Based on the safety analysis set in each study.

Note. Some subjects received both NBI-98854 and placebo.

^a The single-dose group received both NBI-98854 and placebo.

^b Includes subjects with mild, moderate, and severe hepatic impairment.

^c Includes child (6-11 years of age) and adolescent (12-18 years of age) subjects with Tourette syndrome.

^d Excludes 51 subjects who were included in the safety analysis sets in both 1402 and a previous study (1101, 1201, or 1202).

SUMMARY OF CARDIAC SAFETY REVIEW

Overall, there was no difference in AEs associated with the Cardiac Events and QT Prolongation adverse events of special interest (AESI) among subjects treated with NBI-98854 or placebo. There was no clear association of the Cardiac Events and QT Prolongation AESIs and the duration of NBI-98854 treatment.

A Torsades de pointes/QT prolongation MedDRA standardized medical query (SMQ) analysis was conducted along with a medical review of reported preferred terms for cardiac events and QT prolongation for the Phase 2 and 3 studies with at least 6 weeks of NBI-98854 exposure. The medical review included AEs of sudden death, syncope, cardiac failure, chest pain, electrocardiogram (ECG) QT prolonged, and myocardial infarction. The results of both analyses are summarized in [Table 2](#) for the Phase 2/3 Placebo-Controlled Studies pool (up to 6 weeks, Studies 1201, 1202, 1304) and [Table 3](#) for the Long-term Exposure pool (up to 48 weeks, Studies 1201, 1304, 1402).

Table 2: Phase 2/3 Placebo Controlled Studies Pool

Preferred Term ^a	NBI-98854 ^b				All NBI-98854 (N=254) N (%)	Placebo (N=178) N (%)
	<40 mg (N=5) N (%)	40 mg (N=110) N (%)	80 mg (N=112) N (%)	100 mg (N=27) N (%)		
Chest pain	0	1 (0.9)	0	0	1 (0.4)	0
Sudden death ^c	0	0	1 (0.9)	0	1 (0.4)	0
Syncope ^c	0	0	0	1 (3.7)	1 (0.4)	0
Myocardial infarction	0	0	0	0	0	1 (0.6)
Convulsion	0	0	0	0	0	1 (0.6)

Data Source: ISS Tables 1.2.4.1, 1.2.13.2.1, 1.2.13.2.2

^a MedDRA Version 12.0

^b The <40 mg column indicates doses of 25 mg NBI-98854, the 40 mg column includes doses of 40 mg and 50 mg NBI-98854 and the 80 mg column includes doses of 75 mg and 80 mg NBI-98854. Subjects included in the 100 mg column received NBI-98854 100 mg for 2 weeks, followed by 50 mg for 4 weeks in Study 1201.

^c Also included in the Torsades de pointes/QT prolongation SMQ

Table 3: Phase 2/3 Long-term Exposure Pool

Preferred Term ^a	NBI-98854 ^b		All NBI-98854 (N=427) N (%)
	40 mg (N=197) N (%)	80 mg (N=230) N (%)	
Chest Pain	3 (1.5)	3 (1.3)	6 (1.4)
Syncope ^c	4 (2.0)	2 (0.9)	6 (1.4)
Cardiac Failure	0	1 (0.4)	1 (0.2)
Electrocardiogram QT Prolonged ^c	0	1 (0.4)	1 (0.2)
Sudden Death ^c	0	1 (0.4)	1 (0.2)

Data source: ISS Tables 1.2.4.2, 1.2.13.3.1, 1.2.13.3.2

^a MedDRA Version 12.0

^b 40 mg column includes doses of 40 mg and 50 mg NBI-98854.

^c Also included in the Torsades de pointes/QT prolongation SMQ

Table 4 summarizes Fridericia's correction of QT (QTcF) interval and QTcF interval increases from baseline for the Phase 2/3 Controlled Studies pool. A majority of subjects were on concomitant medications known to have a potential to prolong the QT interval at baseline (74% of NBI-98854 and 73% placebo subjects). No subject had QTcF intervals >500 msec. Two subjects in the placebo group had QTcF intervals >480 msec; no subjects treated with NBI-98854 met this threshold. One subject each in the NBI-98854 and placebo group had QTcF interval increases >60 msec from baseline. Similar incidences of QTcF intervals >450 msec and QTcF interval increases >30 msec were observed between subjects who received NBI-98854 and those who received placebo.

Table 4: Electrocardiogram Categorical Summary, QTcF Interval Data: Phase 2/3 Controlled Studies Pool

Parameter (Threshold)	NBI-98854 Dose ^a				All NBI-98854 (N=254) n (%)	Placebo (N=178) n (%)
	<40 mg (N=5) n (%)	40 mg (N=110) n (%)	80 mg (N=112) n (%)	100 mg (N=27) n (%)		
QTcF						
>450 msec	0	11 (10.0)	5 (4.5)	1 (3.7)	17 (6.7)	11 (6.2)
>480 msec	0	0	0	0	0	2 (1.1)
>500 msec	0	0	0	0	0	0
QTcF						
>30 msec increase from BL	0	3 (2.7)	6 (5.4)	2 (7.4)	11 (4.3)	11 (6.2)
>60 msec increase from BL	0	1 (0.9)	0	0	1 (0.4)	1 (0.6)

Data Source: ISS Table 1.4.9.1.

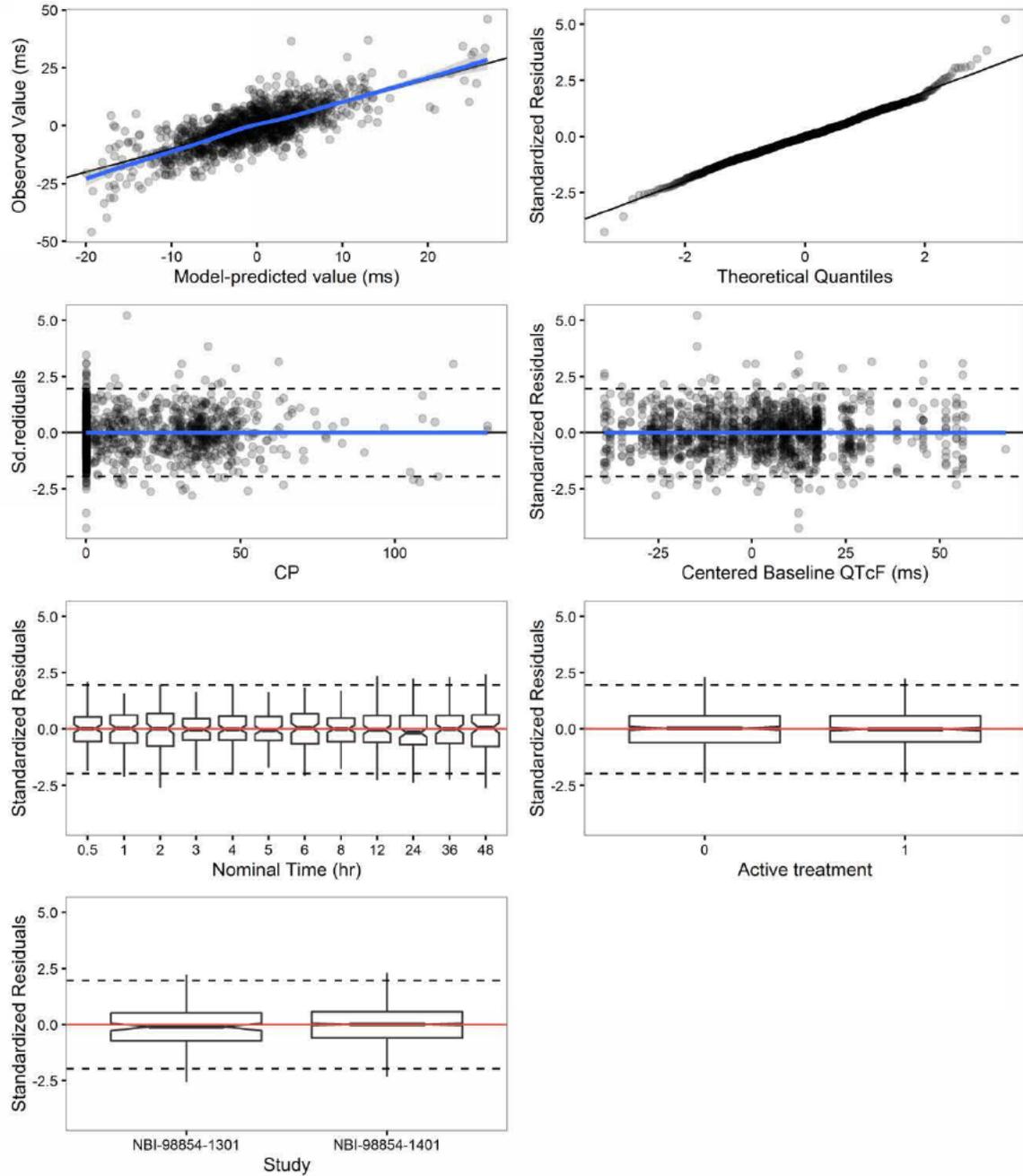
Note: Thresholds for each parameter are based on either the highest value or largest increase from baseline reported from Day 1 through Week 6. Subjects are counted only once within each threshold category.

BL=baseline, QTcF=heart-rate corrected QT interval, Fridericia's formula.

^a The <40 mg column indicates doses of 25 mg NBI-98854, the 40 mg column includes doses of 40 mg and 50 mg NBI-98854 and the 80 mg column includes doses of 75 mg and 80 mg NBI- 98854. Subjects included in the 100 mg column received NBI-98854 100 mg for 2 weeks, followed by 50 mg for 4 weeks in Study 1201.

6.2 MODEL DIAGNOSTICS

Figure 9: Model diagnostic plots for the C-QT model described in 5.3.2



6.3 ESTIMATED MODEL PARAMETERS

Table 24: Model parameters for C-QT model (5.3.2)

Fixed effect parameter	Estimate	Lower 95% CI	Upper 95% CI	Relative standard error (%)	p
(Intercept)	-3.48	-6.68	-0.29	-46.55	0.0331
Study					
NBI-98854-1401	1.14	-2.00	4.28	139.65	0.476
Time					
1	0.31	-1.38	2.00	274.99	0.716
2	0.97	-0.82	2.75	94.08	0.288
3	3.54	1.67	5.41	26.93	<0.001
4	-0.12	-2.03	1.78	-790.32	0.899
5	-0.83	-2.80	1.13	-119.89	0.405
6	-0.52	-2.43	1.38	-185.97	0.591
8	-0.23	-2.15	1.69	-425.58	0.814
12	0.51	-1.37	2.38	188.00	0.595
24	-2.93	-4.72	-1.14	-31.13	0.00136
36	-2.13	-3.92	-0.34	-42.75	0.0195
48	-2.27	-4.04	-0.50	-39.82	0.0122
ACTIVE					
1	0.54	-0.99	2.07	144.82	0.491
QTCF.BS	-0.20	-0.25	-0.15	-13.07	<0.001
META	0.20	0.11	0.29	22.40	<0.001
NBI-98854-1401:META	-0.08	-0.18	0.02	-62.15	0.113

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

/s/

LARS JOHANNESSEN

12/28/2016

Nan Zheng was the primary reviewer.

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CHRISTINE E GARNETT

12/29/2016

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209241

Application Type: NME NDA, fast track, breakthrough therapy

Drug Name(s)/Dosage Form(s): Valbenazine 40mg Capsules

Applicant: Neurocrine Biosciences, Inc.

Receipt Date: 8/11/16

Goal Date: 4/11/17

1. Regulatory History and Applicant's Main Proposals

Valbenazine is a new molecular entity (in the Program) characterized as a selective, orally active vesicular monoamine transporter 2 (VMAT2) indicated for the treatment of tardive dyskinesia (TD). A rolling review for valbenazine was granted on 3/29/16. Valbenazine was also granted fast track designation (January 2012) and breakthrough therapy designation (October 2014).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS**”

Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, (b) (4)

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:
-

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “ Labor and Delivery ”)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “ Nursing Mothers ”)
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

N/A

Selected Requirements of Prescribing Information

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JASMEET K KALSI
10/11/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209241 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Ingrezza (pending a new PNR) Established/Proper Name: Valbenazine Dosage Form: Capsules Strengths: 40mg		
Applicant: Neurocrine Biosciences, Inc. Agent for Applicant (if applicable):		
Date of Application: 8/11/16 Date of Receipt: 8/11/16 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 4/11/16		Action Goal Date (if different):
Filing Date: 10/10/16		Date of Filing Meeting: 9/12/16
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): treatment of tardive dyskinesia (TD)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): [IND 111591](#)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.				
Are the established/proper and applicant names correct in electronic archive?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic				

<i>archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Received 4/29/16
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

questions below:				
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, # years requested:				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English)	<input type="checkbox"/>	<input type="checkbox"/>		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

<input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Signed on 7/22/16
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted on 9/9/16
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Signed 7/18/16
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Signed 8/9/16
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 4/12/2016

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<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted on 8/25/16
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

format? ⁴				
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OPDP PLT DMEPA OSI DPMH CSS IRT-QT
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): 11/4/15 (CMC)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/4/16 (pre-NDA)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): SPA Agreement on 4/3/14	<input type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/12/16

BACKGROUND: Valbenazine is a new molecular entity (in the Program) characterized as a selective, orally active vesicular monoamine transporter 2 (VMAT2) indicated for the treatment of tardive dyskinesia (TD). A rolling review for valbenazine was granted on 3/29/16. Valbenazine was also granted fast track designation (January 2012) and breakthrough therapy designation (October 2014).

- Stamp Date: 8/11/16
- Filing Date: 10/10/16
- Day 74 Letter Date: 10/24/16
- **PDUFA Goal Date: 4/11/17**

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jasmeet Kalsi, PharmD	Y
	CPMS/TL:	Steve Hardeman, RPh and Paul David, RPh	N and Y
Cross-Discipline Team Leader (CDTL)	Javier Muniz, MD		N
Division Director/Deputy	Mitchell Mathis, MD / Tiffany Farchione, MD		Y
Office Director/Deputy	Ellis Unger, MD / Robert Temple, MD		Y
Clinical	Reviewer:	Gioia Guerrieri, DO	Y
	TL:	Javier Muniz, MD	N
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Huixia Zhang, PhD and Di	Y

		Zhou, PhD	
	TL:	Hao Zhu, PhD	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Kevin Krudys	Y
Biostatistics	Reviewer:	Thomas Birkner, PhD	Y
	TL:	Peiling Yang, PhD	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Darren Fegely, PhD and Imran Khan, PhD	Y
	TL:	Aisar Atrakchi, PhD	Y
Statistics (carcinogenicity)	Reviewer:	Steve Thompson, PhD	N
	TL:		
Product Quality (CMC) Review Team:	ATL:	Dave Claffey, PhD	Y
	RBPM:	Grafton Adams	N
• Drug Substance	Reviewer:	Sharon Kelley	Y
• Drug Product	Reviewer:	Rao Khambhampati	N
• Process	Reviewer:	Chunsheng Cai	N
• Microbiology	Reviewer:	Ta-Chen Wu	N
• Facility	Reviewer:	Steven Hertz, Ruth Moore	N
• Biopharmaceutics	Reviewer:	Okpo Eradiri	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	Branch Chief:	Wendy Wilson, PhD	N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Christine Bradshaw	Y
	TL:	Susannah O'Donnell, PharmD	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Lolita White	Y
	TL:	Loretta Holmes	Y
OSE/DRISK (REMS)	Reviewer:	Somya Dunn, MD	Y
	TL:	Kimberly Lehrfield, MD	Y

OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Cara Alfaro, PharmD	Y
	TL:	Janice Pohlman, MD, MPH	N
Controlled Substance Staff (CSS)	Reviewer:	Martin Rusinowitz and Silvia Calderon	Y
	TL:	Corinne Moody	Y
Other reviewers/disciplines			
DPMH Consult	Reviewer:	Carol Kasten	
	TL:	Denise Pico-Branco	
PLT	Reviewer:	Sharon Williams	Y
	TL:	Brantley Dorch	Y
Other attendees	Kalyani Bhatt, AC committee coordinator		Y
	Addy Rosemary, DPMH		
	Vasantha A.		
	Marc Stone, Safety Director		Y
	Tamara Johnson, DPMH		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
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<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
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REGULATORY PROJECT MANAGEMENT

Signatory Authority: [Dr. Ellis Unger](#)

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): **11/16/16**

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

Upcoming Meetings	Dates (subject to change)
Advisory Committee Planning Meetings	9/28/16 @ 9am
Mid-Cycle	11/16/16 @ 11am
Label Planning	11/28/16 @ 9am
Labeling Meetings	Mtg 1: 12/12/16 @ 1pm Mtg 2: 1/3/17 @ 9am Mtg 3: 1/17/17 @ 9am Mtg 4: 1/30/17 @9am
Internal Post Mid-Cycle Communication Meeting	TBD
Post Mid-Cycle Communication	TBD
Pre-Meeting for Late-Cycle Mtg	TBD
Late-Cycle Mtg	TBD
Advisory Committee Mtg	TBD
Wrap-up	2/13/17 @ 9am

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are
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	entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: April 2016

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

/s/

JASMEET K KALSI
09/27/2016

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name: (b) (4)
City, State: (b) (4)
EI Dates: (b) (4)
FDA Participant: (b) (4), Investigator, (b) (4) District
Office (u) (4) - (b) (4)

Inspection Summary

This is a FY2015 PDUFA GLP Surveillance Inspection. At the inspection close-out meeting on (b) (4), no Form FDA 483 was issued to (b) (4) and there were no items discussed with the firm's management. The ORA and the OSIS classifications for the inspection are both no action indicated (NAI). OSIS recommends that the audited studies be accepted for review by the Agency.

Studies Audited during this Inspection

(b) (4) Study No.: AD20XW.2G3R (b) (4)
Study Title: 28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Mice with a Preliminary 5-Day Range Finding Toxicity Study
Study Initiation Date: July 23, 2013
Study Completion Date: October 21, 2013
Test Article: NBI-98854 di-tosylate
Testing Facility: (b) (4)
Study Sponsor: Neurocrine Biosciences, Inc. (San Diego, CA)
Relevant IND: 111591
Review Division: Division of Psychiatry Products (DPP)

Non-Responsive

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/s/

ABHIJIT RAHA
08/24/2015

ZHOU CHEN
08/24/2015

CHARLES R BONAPACE
08/25/2015

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Name:
City, State:
EI Dates:
FDA Participants:

Non-Responsive

Non-Responsive

NON-RESPONSIVE

IND: 111,591
Rev Div.: DPP
Sponsor: Neurocrine Biosciences
Test Article: NBI-98854
Study No.: (b) (4) #624-0012
Study Title: A Six-Month Oral Gavage Toxicity and Toxicokinetic Study with NBI-98854 in Rats with a Six-Week Recovery

(b) (4)

(b) (4)

33 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NIRAJ MEHTA
10/25/2013

ABHIJIT RAHA
10/25/2013

ZHOU CHEN
10/25/2013

CHARLES R BONAPACE
10/25/2013

WILLIAM H TAYLOR
10/28/2013