

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209241Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

# ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>   |                                      |   |
|--|--------------------------------------|---|
| NDA # 209241<br>BLA #  | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:<br><i>(an action package is not required for SE8 or SE9 supplements)</i>  |
| Proprietary Name: <b>Ingrezza</b><br>Established/Proper Name: <b>valbenazine</b><br>Dosage Form: <b>capsules (40mg)</b>  |                                      | Applicant: <b>Neurocrine Biosciences, Inc.</b><br>Agent for Applicant (if applicable):  |
| RPM:   |                                      | Division:   |
| NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)<br>Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)  |                                      | <b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> Date of check: |
| <b>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b>  |                                      |   |
| ❖ Actions  |                                      |   |
| <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <a href="#">April 11, 2017</a></li> </ul>  |                                      | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR  |
| <ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>  |                                      | <input checked="" type="checkbox"/> None  |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____ |                                      | <input type="checkbox"/> Received   |
| ❖ Application Characteristics <sup>3</sup>   |                                      |   |

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): vesicular monamine transporter 2 (VMAT2) inhibitor  
 (confirm chemical classification at time of approval)

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation                     | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

- |   |  |
|---|--|
| NDAs: Subpart H   | BLAs: Subpart E  |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510)                | <input type="checkbox"/> Accelerated approval (21 CFR 601.41)    |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520)             | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I   | Subpart H  |
| <input type="checkbox"/> Approval based on animal studies                     | <input type="checkbox"/> Approval based on animal studies        |
| <input type="checkbox"/> Submitted in response to a PMR                       | REMS: <input type="checkbox"/> MedGuide                          |
| <input type="checkbox"/> Submitted in response to a PMC                       | <input type="checkbox"/> Communication Plan                      |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU                                   |
|   | <input type="checkbox"/> MedGuide w/o REMS                       |
|   | <input checked="" type="checkbox"/> REMS not required            |

Comments:

|  |  |
|--|--|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)  | <input type="checkbox"/> Yes <input type="checkbox"/> No   |
| ❖ Public communications (approvals only)   |  |
| • Office of Executive Programs (OEP) liaison has been notified of action   | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  |
| • Indicate what types (if any) of information were issued  | <input type="checkbox"/> None<br><input checked="" type="checkbox"/> FDA Press Release<br><input checked="" type="checkbox"/> FDA Talk Paper – pending in NEJM<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |
| ❖ Exclusivity  |  |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?                              | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes  |
| • If so, specify the type  |  |
| ❖ Patent Information (NDAs only)   |  |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.                        | <input checked="" type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.   |
| <b>CONTENTS OF ACTION PACKAGE</b>  |  |
| <b>Officer/Employee List</b>   |  |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) | <input checked="" type="checkbox"/> Included   |
| Documentation of consent/non-consent by officers/employees   | <input checked="" type="checkbox"/> Included   |

### Action Letters

|   |   |
|---|---|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i> | Action(s) and date(s) Approval, 4/11/17 |
|---|---|

### Labeling

|  |   |
|--|---|
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>   |   |
| <ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>      | <input type="checkbox"/> Included   |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>   | <input checked="" type="checkbox"/> Included  |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i> | <input type="checkbox"/> Medication Guide<br><input checked="" type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> Device Labeling<br><input type="checkbox"/> None   |
| <ul style="list-style-type: none"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>      | <input type="checkbox"/> Included   |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>   | <input checked="" type="checkbox"/> Included  |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>       |   |
| <ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>   | <input checked="" type="checkbox"/> Included  |
| ❖ Proprietary Name   |   |
| <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul> | 11/14/16<br>11/13/16  |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i>  | RPM: <input type="checkbox"/> None 10/11/17<br>DMEPA: <input type="checkbox"/> None 3/9/17<br>DMPP/PLT (DRISK):<br><input type="checkbox"/> None 3/10/17<br>OPDP: <input type="checkbox"/> None 3/2/17<br>SEALD: <input checked="" type="checkbox"/> None<br>CSS: <input type="checkbox"/> None 2/28/17<br>Product Quality <input checked="" type="checkbox"/> None<br>Other: <input type="checkbox"/> None DPMH – 3/6/17 |

### Administrative / Regulatory Documents

|  |   |
|--|---|
| ❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>   | 9/27/16   |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee   | <input checked="" type="checkbox"/> Not a (b)(2)                    |
| ❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>  | <input checked="" type="checkbox"/> Completed (Do not include)      |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> |   |
| <ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

|   |  |
|---|--|
| <ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>   | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action |
| ❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <a href="#">3/1/17</a><br/>If PeRC review not necessary, explain: _____</li> </ul>  |  |
| ❖ Breakthrough Therapy Designation  | <input type="checkbox"/> N/A   |
| <ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>   | 10/28/14   |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>   | 10/24/14   |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>  |  |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i> ) | - Multiple IRs sent  |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)   | - T-con Memo: 2/21/17  |
| ❖ Minutes of Meetings   |  |
| <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input checked="" type="checkbox"/> N/A or no mtg  |
| <ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>   | <input type="checkbox"/> No mtg 2/4/16   |
| <ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input type="checkbox"/> No mtg 6/24/14  |
| <ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>   | <input type="checkbox"/> N/A 11/29/16  |
| <ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>  | <input type="checkbox"/> N/A 2/7/17  |
| <ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>  | PeRC Meeting Minutes – 3/1/17  |
| ❖ Advisory Committee Meeting(s)   | <input checked="" type="checkbox"/> No AC meeting  |
| <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>   |  |
| <b>Decisional and Summary Memos</b>   |  |
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None 4/11/17  |
| Division Director Summary Review ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None 4/11/17  |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None 4/6/17   |
| PMR/PMC Development Templates ( <i>indicate total number</i> )  | <input type="checkbox"/> None Seven, 4/6/17  |
| <b>Clinical</b>   |  |

|  |  |  |
|--|--|--|
| <b>❖ Clinical Reviews</b>  |  |  |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> No separate review             |
| • Clinical review(s) ( <i>indicate date for each review</i> )  |  | 4/4/17   |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )  |  | <input checked="" type="checkbox"/> None                           |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )   |  | In clinical review, 4/4/17   |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>   |  | <input checked="" type="checkbox"/> None                           |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )   |  | <input type="checkbox"/> N/A 2/28/17<br>not a controlled substance |
| ❖ Risk Management<br>• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )<br>• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )<br>• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> ) |  | <input type="checkbox"/> None 3/22/17                              |
| ❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )  |  | <input type="checkbox"/> None requested 2/14/17                    |
| <b>Clinical Microbiology</b>   |  | <input checked="" type="checkbox"/> None                           |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )   |  | <input type="checkbox"/> No separate review                        |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )   |  | <input type="checkbox"/> None                                      |
| <b>Biostatistics</b>   |  | <input type="checkbox"/> None                                      |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )   |  | <input type="checkbox"/> No separate review                        |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> No separate review             |
| Statistical Review(s) ( <i>indicate date for each review</i> )   |  | <input type="checkbox"/> None 3/16/17, Thomas Birkner              |
| <b>Clinical Pharmacology</b>   |  | <input type="checkbox"/> None                                      |
| ❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> No separate review             |
| Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )   |  | <input checked="" type="checkbox"/> No separate review             |
| Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )   |  | <input type="checkbox"/> None 3/6/17, Di Zhou                      |
| ❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )   |  | <input type="checkbox"/> None requested 2/22/17                    |

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

| <b>Nonclinical</b> <input type="checkbox"/> None  |   |
|---|---|
| ❖ Pharmacology/Toxicology Discipline Reviews  |   |
| • ADP/T Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> No separate review 4/7/17  |
| • Supervisory Review(s) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> No separate review   |
| • Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None 3/7/17  |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None   |
| ❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )   | <input type="checkbox"/> No carc 3/7/17   |
| ❖ ECAC/CAC report/memo of meeting   | <input type="checkbox"/> None 2/14/17<br>Included in P/T review, page   |
| ❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )  | <input checked="" type="checkbox"/> None requested  |
| <b>Product Quality</b> <input type="checkbox"/> None  |   |
| ❖ Product Quality Discipline Reviews <sup>6</sup>   |   |
| • Tertiary review ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None   |
| • Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )  | <input type="checkbox"/> None   |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )   | <input type="checkbox"/> None 2/14/17   |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )   | <input type="checkbox"/> None   |
| ❖ Environmental Assessment (check one) (original and supplemental applications)   |   |
| <input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )  | 2/7/17, in the Integrated Quality Assessment  |
| <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )  |   |
| <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )  |   |
| ❖ Facilities Review/Inspection  |   |
| <input checked="" type="checkbox"/> Facilities inspections ( <i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> ) | <input checked="" type="checkbox"/> Acceptable, 4/6/17<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable |

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

| Day of Approval Activities  |  |
|---|--|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>   | <input type="checkbox"/> No changes<br><input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> ) |
| <ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>   | <input type="checkbox"/> Done  |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>  | <input checked="" type="checkbox"/> Done<br>( <i>Send email to CDER OND IO</i> )                                     |
| ❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> | <input type="checkbox"/> Done  |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email   | <input checked="" type="checkbox"/> Done   |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter  | <input checked="" type="checkbox"/> Done   |
| Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name                              | <input checked="" type="checkbox"/> Done   |
| ❖ Ensure Pediatric Record is accurate   | <input type="checkbox"/> Done  |
| ❖ Send approval email within one business day to CDER-APPROVALS   | <input checked="" type="checkbox"/> Done   |

## Kalsi, Jasmeet (Mona)

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**From:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>  
**Sent:** Tuesday, April 11, 2017 4:58 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Cc:** Mathis, Mitchell; Unger, Ellis; Farchione, Tiffany; David, Paul A; Hardeman, Steven D; Kiedrow, Keith; Patel, Hiren  
**Subject:** RE: NDA 209241 - Action

Received!

Thank you, Mona. And thank you to our DPP review team for your collaboration and long hours spent on this tardive dyskinesia program!

Best regards,  
Kristine

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**From:** Kalsi, Jasmeet (Mona) [<mailto:Jasmeet.Kalsi@fda.hhs.gov>]  
**Sent:** Tuesday, April 11, 2017 1:40 PM  
**To:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>  
**Cc:** Kalsi, Jasmeet (Mona) <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>; Mathis, Mitchell <[Mitchell.Mathis@fda.hhs.gov](mailto:Mitchell.Mathis@fda.hhs.gov)>; Unger, Ellis <[Ellis.Unger@fda.hhs.gov](mailto:Ellis.Unger@fda.hhs.gov)>; Farchione, Tiffany <[Tiffany.Farchione@fda.hhs.gov](mailto:Tiffany.Farchione@fda.hhs.gov)>; David, Paul A <[Paul.David@fda.hhs.gov](mailto:Paul.David@fda.hhs.gov)>; Hardeman, Steven D <[Steven.Hardeman@fda.hhs.gov](mailto:Steven.Hardeman@fda.hhs.gov)>; Kiedrow, Keith <[Keith.Kiedrow@fda.hhs.gov](mailto:Keith.Kiedrow@fda.hhs.gov)>; Patel, Hiren <[Hiren.Patel@fda.hhs.gov](mailto:Hiren.Patel@fda.hhs.gov)>  
**Subject:** NDA 209241 - Action  
**Importance:** High

Dear Kristine:

Your NDA 209241 for valbenazine (Ingrezza) 40 mg capsules has been approved. Please find attached a copy of the approval letter and confirm receipt. An official letter will be mailed to you at:

Neurocrine Biosciences, Inc.  
12780 El Camino Real  
San Diego, CA 92130

It was a pleasure working with you and your team and we look forward to working together in the future.

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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## Kalsi, Jasmeet (Mona)

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**From:** Kim, Kristine <kkim@neurocrine.com>  
**Sent:** Wednesday, April 05, 2017 6:19 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Subject:** RE: Labeling Questions Response - NDA 209241, valbenazine  
**Attachments:** postmarketing-commit-correspondence.pdf; postmarketing-req-correspondence.pdf

Hi Mona,

Thank you for your quick feedback regarding the PMR/PMCs and the 18 month expiry period.

We are in agreement with the proposed PMRs/PMCs with the updated dates and revised PMR 3177-4 as noted in your email below. We have submitted NDA 209241 Sequence 0045 with documentation of agreement filed under Section 1.17.1 Correspondence Regarding PMCs and Section 1.17.2 Correspondence Regarding PMRs. These documents are also attached for your review.

NDA 209241 Sequence 0045 also contains final bottle and sample carton labels, submitted under Section 1.14.2.

If you need anything else, please let me know.

Kind regards,  
Kristine

---

**From:** Kalsi, Jasmeet (Mona) [mailto:Jasmeet.Kalsi@fda.hhs.gov]  
**Sent:** Wednesday, April 5, 2017 8:57 AM  
**To:** Kim, Kristine <kkim@neurocrine.com>  
**Cc:** Kalsi, Jasmeet (Mona) <Jasmeet.Kalsi@fda.hhs.gov>  
**Subject:** RE: Labeling Questions Response - NDA 209241, valbenazine  
**Importance:** High

Hi Kristine,

### PMCs/PMRs:

- We accept your updated dates for the following PMCs:
  - o 3177-5
  - o 3177-6
- Updated PMR 3177-4:
  - o 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.
    - Final Protocol Submission: 01/2018
    - Trial Completion: 01/2019
    - Final Report Submission: 01/2020

Please let me know if you agree with the updated PMR 3177-4 and proposed dates.

**OPQ response on expiration date:**

Based on our review of the additional stability data submitted in the amendment SN-0040 dated March 8, 2017 to NDA 209241 and in accordance with ICH Q1E, we find that the drug product stability data supports an expiration dating period of 18 months when drug product bottles and unit dose blisters are stored at 25°C.

Please let me know if you have any questions or concerns. I am working on getting the label back to you soon.

Thanks,  
Mona

---

**From:** Kim, Kristine [<mailto:kkim@neurocrine.com>]  
**Sent:** Tuesday, April 04, 2017 8:11 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Cc:** Mathis, Mitchell; Farchione, Tiffany; Unger, Ellis  
**Subject:** RE: Labeling Questions Response - NDA 209241, valbenazine

Dear Mona,

Based on FDA's response to our remaining labeling concerns, dated April 4, 2017, Neurocrine accepts FDA's position on these issues and agrees that there is no need for a teleconference on the labeling. We therefore attach the amended prescribing information and the PPI and look forward to receipt of the final draft from the Division before the end of this week.

Would you please confirm that FDA has reviewed and made decisions resolving the following two issues, which we believe are the only outstanding topics:

- On March 29, 2017, FDA sent Neurocrine PMRs/PMCs. Neurocrine responded via e-mail on March 31, 2017 that these were acceptable except for the PMR that required protocol amendments to two trials that have concluded, and changes in dates for two of the PMCs. We are awaiting an FDA response in order to be able to finalize the PMR/PMCs and make a formal submission to the NDA.
- On March 8, 2017, with agreement from OPQ, Neurocrine provided updated stability data on the drug product with a request for a shelf life of 18 months (NDA 209241 Sequence 0040). We are assuming that the data were acceptable and that the expiration date will be 18 months.

We are responding earlier than the requested April 5, 2017 at 11 am EST timeline because we appreciate the importance of meeting the April 11 PDUFA date for both FDA and Neurocrine. We request that if FDA has remaining comments on the PMR/PMCs or the expiration date issue, that we schedule a brief call on Wednesday April 5, 2017 to understand the status and to resolve any outstanding issues in order for DPP to take action by the PDUFA date of April 11, 2017.

Thank you for your assistance.  
Kristine

---

**From:** Kalsi, Jasmeet (Mona) [<mailto:Jasmeet.Kalsi@fda.hhs.gov>]  
**Sent:** Tuesday, April 4, 2017 11:41 AM  
**To:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>  
**Cc:** Kalsi, Jasmeet (Mona) <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>; Mathis, Mitchell <[Mitchell.Mathis@fda.hhs.gov](mailto:Mitchell.Mathis@fda.hhs.gov)>; Farchione, Tiffany <[Tiffany.Farchione@fda.hhs.gov](mailto:Tiffany.Farchione@fda.hhs.gov)>; Unger, Ellis <[Ellis.Unger@fda.hhs.gov](mailto:Ellis.Unger@fda.hhs.gov)>  
**Subject:** Labeling Questions Response - NDA 209241, valbenazine  
**Importance:** High

Hi Kristine,

Enclosed are our responses to your three labeling concerns. Please note, that in order to take action by our PDUFA Goal Date of April 11, 2017, the Division has decided that a teleconference is not needed for addressing these labeling concerns.

Please acknowledge and respond by **11 AM (EST), April 5, 2017**. We will then send out the final draft of the labeling this week.

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products**

**U.S. Food and Drug Administration**  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
04/10/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Wednesday, March 29, 2017 1:29 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** PMC/PMR - NDA 209241, valbenazine

**Importance:** High

Hi Kristine,

Please find below the PMCs/PMRs for NDA 209241, valbenazine. Let me know if you are in agreement with the commitments/requirements and the proposed dates.

### Post-marketing Requirements:

- 3177-1 Conduct an in vitro study to assess the induction potential of NBI-136110 on CYP2B6 enzyme.  
Final Protocol Submission: 12/2017  
Study Completion: 07/2018  
Final Report Submission: 12/2018
- 3177-2 Conduct 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).  
Final Protocol Submission: 11/2017  
Trial Completion: 12/2018  
Final Report Submission: 08/2019
- 3177-3 Conduct a pharmacokinetic trial to assess exposure differences of the parent compound and major metabolites in patients with severe renal impairment and matching subjects with normal renal function receiving the same dose.  
Final Protocol Submission: 12/2017  
Trial Completion: 12/2018  
Final Report Submission: 08/2019
- 3177-4 To evaluate for clinical dependence and withdrawal [REDACTED] (b) (4) administer withdrawal scales and [REDACTED] (b) (4) 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.  
Final Protocol Submission: 01/2018  
Trial Completion: 01/2019  
Final Report Submission: 01/2020

### Post-marketing Commitments:

- 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.

Final Protocol Submission: 10/2017  
Trial Completion: 10/2021  
Final Report Submission: 10/2022

3177-6 To better assess the persistence of valbenazine treatment for TD, perform a trial in which subjects who have demonstrated an adequate response to valbenazine are randomized to receive placebo or continue their current dose. Subjects should be stratified based on whether they are continuing to take an antipsychotic. A significant proportion of subjects should no longer be taking antipsychotics in order to assess the potential for differential persistency.

Final Protocol Submission: 01/2018  
Trial Completion: 01/2020  
Final Report Submission: 01/2021

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.

Final Protocol Submission: 04/2018  
Trial Completion: 04/2020  
Final Report Submission: 04/2021

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products**

**U.S. Food and Drug Administration**

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
03/29/2017

**PeRC Meeting Minutes  
March 1, 2017**

**PeRC Members Attending:**

Lynne Yao  
John Alexander  
Gettie Audain  
Jacqueline Yancy  
Donna Snyder  
Lily Mulugeta  
Robert "Skip" Nelson  
Dionna Green  
Victor Baum  
Rosemary Addy  
Hari Cheryl Sachs  
Kevin Krudys  
Barbara Buch  
Wiley Chambers  
Gil Burkhart  
Gerri Baer  
Adrienne Hornatko-Munoz  
Maura O'leary  
Julia Pinto  
Tom Smith  
Greg Reaman  
Freda Cooner  
Daiva Shetty  
Susan McCune

**Agenda**

NON-RESPONSIVE

|       |            |   |     |  |                    |
|-------|------------|---|-----|--|--------------------|
| 11:20 | NDA 209241 | Valbenazine Capsules (Full Waiver) with Agreed iPSP | DPP | Jasmeet (Mona) Kalsi & Nam (Esther) Chun | Tardive dyskinesia |
|-------|------------|---|-----|--|--------------------|

NON-RESPONSIVE

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

NON-RESPONSIVE

**Valbenazine Capsules (Full Waiver) with Agreed iPSP**

- Proposed indication: Tardive dyskinesia
- The PREA trigger is new active ingredient and indication with a PDUFA date of April 11, 2017.
- The division clarifies that there was an agreed iPSP and the plan remains full waiver because most of the products that cause tardive dyskinesia (older antipsychotic agents) are used less commonly in pediatric patients. New antipsychotic agents approved for use in adolescents have less risk for TD. Additionally, adolescent patients who might develop tardive dyskinesia generally remit after discontinuation of the antipsychotic.
- *PeRC Recommendations:*
  - The PeRC concurs with the division to grant a full waiver of pediatric studies because studies would be highly impracticable as agreed upon in the Agreed

NON-RESPONSIVE

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/s/  
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GETTIE AUDAIN  
03/22/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Friday, March 17, 2017 3:02 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request

Hi Kristine,

You indicated that the active metabolite of valbenazine is one of two enantiomers of alpha-dihydrotetrabenazine [i.e., (+) or (-) alpha-dihydrotetrabenazine]. Please indicate which stereoisomer the metabolite is and provide supportive data (e.g. optical rotation data) by **March 24, 2017**.

(b) (4)

Thank you,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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JASMEET K KALSI  
03/20/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, March 16, 2017 3:12 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hi Kristine,

Please see the response dates for the IR's below:

- *Please provide the submission date(s) and serial number(s) of the SAP and potential SAP amendments for Study 1202.*
  - o **Submit by COB tomorrow, March 17, 2017.**
- *The primary analysis method (i.e., ANCOVA) requires the MCAR (missing completely at random) assumption in the presence of missing data. Please provide some sensible sensitivity/supportive analyses using varying assumptions to help us understand the impact of the exclusion of randomized subjects from the 'ITT' analysis set on the primary efficacy results/conclusions of your study.*
  - o **Submit by COB, March 22, 2017.**

Thanks,  
Mona

---

**From:** Kim, Kristine [mailto:kkim@neurocrine.com]  
**Sent:** Thursday, March 16, 2017 2:27 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hello Mona,

I have a follow-up question regarding the information requests that were cited in Late Cycle Meeting Minutes (Section 3). Since we are currently in label negotiations, what is the FDA's expectation for providing a response (necessity, timing)?

Thank you,  
Kristine

---

**From:** Kalsi, Jasmeet (Mona) [mailto:Jasmeet.Kalsi@fda.hhs.gov]  
**Sent:** Tuesday, March 7, 2017 11:04 AM  
**To:** Kim, Kristine <kkim@neurocrine.com>  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hi Kristine,

We do not anticipate that the submission of additional stability data to support an extended drug product expiry will impact the PDUFA goal date. We will evaluate any additional stability data submitted to the NDA during this review cycle, if time and resources permit.

Thanks,  
Mona

---

**From:** Kim, Kristine [<mailto:kkim@neurocrine.com>]  
**Sent:** Monday, March 06, 2017 1:38 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hi Mona,

I am following up with my email from Friday. Have you heard back from OPQ regarding our request?

Thank you,  
Kristine

---

**From:** Kim, Kristine  
**Sent:** Friday, March 3, 2017 11:34 AM  
**To:** 'Kalsi, Jasmeet (Mona)' <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hi Mona,

Thank you for sending the late-cycle meeting minutes. I will follow-up with a response to the open action items for Study 1202 (Section 3 Info Requests) at a later date. I also have a follow-up question for OPQ:

With respect to the post meeting comment regarding the (b) (4) month drug product expiry period: At this stage of review, would OPQ consider a request of an 18-month expiry period assignment supported by submission of 9-month stability data for the 3 primary drug product batches, without impact to the PDUFA action date?

Kind regards,  
Kristine

---

**From:** Kalsi, Jasmeet (Mona) [<mailto:Jasmeet.Kalsi@fda.hhs.gov>]  
**Sent:** Friday, March 3, 2017 8:09 AM  
**To:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>  
**Cc:** Kalsi, Jasmeet (Mona) <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>  
**Subject:** Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hi Kristine,

Please find attached the final meeting minutes from the Late-Cycle meeting for NDA 209241 held on February 7, 2017.

Please let me know if you have any questions or concerns.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

**U.S. Food and Drug Administration**

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JASMEET K KALSI  
03/16/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, March 16, 2017 3:12 PM  
**To:** Kim, Kristine  
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Mona

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Kristine

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Thanks,  
Mona

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**To:** Kalsi, Jasmeet (Mona)  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

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Thank you,  
Kristine

---

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**Sent:** Friday, March 3, 2017 11:34 AM  
**To:** 'Kalsi, Jasmeet (Mona)' <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>  
**Subject:** RE: Late-Cycle Meeting Minutes - NDA 209241, valbenazine

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Kind regards,  
Kristine

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**Sent:** Friday, March 3, 2017 8:09 AM  
**To:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>  
**Cc:** Kalsi, Jasmeet (Mona) <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>  
**Subject:** Late-Cycle Meeting Minutes - NDA 209241, valbenazine

Hi Kristine,

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Please let me know if you have any questions or concerns.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
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**U.S. Food and Drug Administration**

Tel: (240) 402-8977

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JASMEET K KALSI  
03/16/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, March 16, 2017 6:28 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request

Hi Kristine,

For NDA 209241, in the Study Report for Study 1304, on page 144 in Table 67 entitled "Incidence of Potentially Clinically Significant Laboratory Values during the Placebo-Controlled Period," the incidence of various events is described.

Please provide narratives for all subjects described as having abnormal laboratory values in the VBZ 40 mg and 80 mg columns by **COB March 20, 2017**.

Thank you,  
Mona

### **Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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JASMEET K KALSI  
03/16/2017



James S. Nelson, Director of QA  
Neurocrine Biosciences, Inc.  
12780 El Camino Real  
San Diego, CA 92130

Dear Mr. Nelson:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at Neurocrine Biosciences, Inc. between 11/28/16 and 12/02/16. Investigator Comyar Shoghi representing the FDA, met with you and your staff to review your sponsorship of two clinical investigations (Protocol **NBI-99854-1202**, “A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Titration Study to Assess the Safety, Tolerability, and Efficacy of NBI-99854 for the Treatment of Tardive Dyskinesia” and Protocol **NBI-99854-1304**, “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel, Fixed-Dose Study to Assess the Efficacy, Safety, and Tolerability of NBI-99854 for the Treatment of Tardive Dyskinesia”) of the investigational drug Valbenazine.

This inspection was conducted as a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the FDA Establishment Inspection Report and the documents submitted with that report, we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Shoghi during the inspection. Should you have any questions or concerns about this letter or the inspection, please write to me at the address given below.

Sincerely,

{See appended electronic signature page}

CDR LaKisha Williams, USPHS  
Regulatory Health Project Manager  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Building 51, Room 5374  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0000

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LAKISHA M WILLIAMS  
03/15/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, March 14, 2017 1:12 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Labeling Questions

Hi Kristine,

Please see the response below to your labeling questions submitted on 3/8/17:

### **Section 6 Adverse Reactions:**

- 1) In order for us to understand the derivation of the proposed adverse reaction frequencies we need assistance in identifying the datasets that were used to generate the following values:**
- Variable and Fixed Dose Placebo-Controlled Trial Experience: demographics, concomitant atypical and typical antipsychotic use, adverse reactions leading to discontinuation of treatment, overall Ns for Table 1**

We used the submitted datasets for the individual Studies 1201, 1202, and 1304. Specifically:

- The demographics files (dm.xpt)
- The adverse events files (ae.xpt). Events occurring outside of the controlled trial period were excluded
- The concomitant medications as classified (cm.xpt) by written email agreement 2/9/17 (b) (4)
- Adverse events resulting in discontinuation were individually determined by the reviewer by reviewing the discontinuations (ds.xpt) and adverse event (ae.xpt) files for each of the controlled studies

- 2) Could the FDA provide the SAS program code for the random effects model with a binomial distribution and a logit link that was used to analyze the (3) pooled 6-week controlled periods?**

SAS was not used.

The adverse reactions of interest were tabulated using the following format for each adverse reaction:

| Study | Number of Subjects | Treatment | Subjects with AR |
|-------|--------------------|-----------|------------------|
| 1201  | 54                 | Placebo   |                  |
| 1202  | 51                 | Placebo   |                  |
| 1304  | 80                 | Placebo   |                  |
| 1201  | 55                 | VBZ       |                  |
| 1202  | 51                 | VBZ       |                  |
| 1304  | 154                | VBZ       |                  |

The *melogit* (mixed effects logistic regression) procedure in Stata (version 14.2) was applied to each table with the following command:

```
melogit ar trt ||study:, binomial(n)
```

where ar is the number of subjects with the ar, trt is the treatment (placebo=0 / VBZ=1), study the study number (random effect), and n the number of subjects.

The log odds ratio for placebo was the coefficient for the constant term in the regression model; the log odds ratio for valbenazine was the sum of the coefficients for the constant term and the trt term.

Log odds ratios were converted into incidence rates using the inverse logit formula:  $\exp(\text{lor})/(\exp(\text{lor})+1)$

**3) We would like to discuss the selection of preferred terms that are grouped under the Anticholinergic Effects category.**

The Applicant agreed to the FDA groupings of associated MedDRA Preferred Terms via email on Friday, February 10, 2017 at 8:30 PM. The grouping of terms agreed to are provided again for reference below:

| FDA Grouping            | MedDRA AERTs             |
|-------------------------|--------------------------|
| Anticholinergic effects | Urinary retention        |
|                         | Constipation             |
|                         | Diplopia                 |
|                         | Visual blurred           |
|                         | Dry mouth                |
|                         | Disturbance in attention |
|                         | Amnesia                  |
|                         | Delirium                 |

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**4) For determining the percentages of patients with adverse reactions leading to discontinuation of treatment, we would like to confirm that treatment group assignment is based on treatment at the time of the onset of the adverse reaction. In addition, it would be very helpful to see a listing of the actual patients used in determining these percentages.**

For the controlled trials (1201, 1202, and 1304) discontinuations during the controlled trial period due to adverse reactions are noted as follows:

*Study 1201*

- Subject 1201-141-1001 [Placebo] discontinued on day 42 due to exacerbation of Schizophrenia
- Subject 1201-126-1002 [VBZ 100 mg] discontinued on day 35 due to UTI, syncope

*Study 1202*

- Subject 1202-215-2020 [Placebo] discontinued on day 13 due to MI
- Subject 1202-215-2009 [Placebo] discontinued on day 55 due to urinary retention

*Study 1304*

- Subject 1304-304-3002 [VBZ 80 mg] discontinued on day 31 due to worsening of schizoaffective disorder
- Subject 1304-344-3001 [Placebo] discontinued on day 28 due to nausea
- Subject 1304-312-3006 [VBZ 40 mg] discontinued on day 28 due to uncontrolled type 2 diabetes
- Subject 1304-342-3007 [VBZ 40 mg] discontinued on day 22 due to altered mental status, hostility
- Subject 1304-382-3001 [VBZ 40 mg] discontinued on day 15 due to akathisia, increased anxiety
- Subject 1304-346-3008 [Placebo] discontinued on day 14 due to worsening of Tourette's symptoms
- Subject 1304-312-3016 [VBZ 40 mg] discontinued on day 6 due to elevated creatinine

In total, this yields discontinuations of 5 placebo-treated 6 drug-treated subjects.

**5) We cannot verify a few of the frequencies displayed in Table 2 (Study 1304) for the grouped terms - is it possible that some patients are being counted more than once in determining the grouped adverse reaction term frequency (due to having more than one preferred term being mapped to that grouped term)?**

Subject adverse events were counted as in the following example. Subject A experienced vomiting on day 1, nausea on day 5, and diarrhea on day 10. These are counted as 1 event each of diarrhea, nausea, and vomiting. These, however, are counted as 3 events of a hypothetical MedDRA preferred term grouping of “gastric distress.”

**Section 12 Pharmacodynamics, Cardiac Electrophysiology:**

**6) We would like to better understand the modeling that was performed to calculate the mean QT prolongation and upper bound of the double-sided 95% CI for patients taking an INGREZZA 80 mg dose with increased exposure. Could the FDA provide the assumptions that were used to perform the modeling?**

We performed a pooled concentration-QTc analysis considering data from studies 0901, 1301 and 1401, where the QTc effect was modeled using the change from baseline (dQTc) as the dependent variable [1-3]. Since it is a pooled analysis consideration to study heterogeneity has to be given [4] and we explored the relationship between concentration and QTc by study. From exploratory analysis we observed a lack of a relationship between concentration and QTc in study 0901, and excluded this study from future analysis. A detailed description of the model, model assumptions and derivation of ddQTc and upper confidence intervals are included below.

Model description:

$dQTc \sim \text{Treatment} + QTc_{\text{baseline}} + \text{Time} + \text{Concentration} + \text{Study} + \text{Study} * \text{Concentration}$

where:

- Concentration: metabolite (NBI-98782) concentration, set to zero for placebo observations
- Treatment: 1 for drug and 0 for placebo
- QTcbaseline: QTc baseline centered around the population average
- Time: time as a categorical fixed effect
- Study: Either 1401 or 1301

In addition, the model includes a random effect on the intercept and slope.

Model assumptions

The model has the following assumptions, where assumption 1 through 3 apply to the analysis conducted by the sponsor as well:

1. QTc is independent of RR
2. No delayed effect between concentrations
3. QTc and the relationship between QTc and concentrations are linear
4. There is no significant difference in placebo response between studies

Derivation of double delta

This model can then be used to derive the mean ddQTc (see reference 1 for further details):

- $ddQTc(c) = dQTc(\text{concentration}=c, \text{treatment}=\text{drug}) - dQTc(\text{concentration}=0, \text{treatment}=\text{placebo})$  (1)

For the model described above equation(1) simplifies to:

- $ddQTc(c) = \text{Treatment} + c * \text{concentration}$  (2)

The model was fitted using the lme4 package in R and the mean and 90% confidence intervals were derived using the lsmeans package with the degrees of freedom estimated using Kenward-Rogers.

References:

- [1] – Garnett C, et al. Operational Characteristics of Linear Concentration-QT Models for Assessing QTc Interval in the Thorough QT and Phase I Clinical Studies. *Clin Pharmacol Ther* 2016;100(2):170-8
- [2] – Darpo D, et al. The IQ-CSRC prospective clinical Phase 1 study: “Can early QT assessment using exposure response analysis replace the thorough QT study?”. *Ann Noninvasive Electrocardiol* 2014;19(1):522-31
- [3] – Darpo D, et al. Results from the IQ-CSRC prospective study to support replacement of the thorough QT study by QT assessment in the early clinical phase. *Clin Pharmacol Ther* 2015;97(4):326-35

[4] – ICH E14 Q&A (R3) – section 5.1

Please let me know if you have any questions.

Thanks,  
Mona

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/s/  
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JASMEET K KALSI  
03/14/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, February 28, 2017 3:58 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Overdoses Information Request

Hi Kristine,

We were unable to find any mention of overdoses due to valbenazine in the ISS. Were there any instances of overdose in the valbenazine development program? If so, please describe and provide a narrative by **March 2, 2017**.

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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JASMEET K KALSI  
02/28/2017

## Kalsi, Jasmeet (Mona)

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**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Monday, February 27, 2017 3:03 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Requests - Datasets and Carton Labeling

Hi Kristine,

Please respond to the following information requests for NDA 209241 by **March 2, 2017** or sooner:

- **Professional Sample Carton Labeling:**
  - For consistency with the blister labels and to help minimize the potential for misinterpreting the entire package of 5 capsules as being equal to one 40 mg dose, please revise the statement of strength to read: 40 mg per capsule. After this revision, please submit for Agency review.
- **Datasets**
  - For Studies 1201 and 1202, for the “cdss.xpt” datasets, please resubmit with a “Change From Baseline (CFB)” column, denoting the change from baseline for the CDSS Total Score.
  - For Study 1202, for the “madr.xpt” datasets, please resubmit with a “Change From Baseline (CFB)” column, denoting the change from baseline for the MADRS Total Score.

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

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JASMEET K KALSI  
02/27/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, February 23, 2017 7:18 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request - Datasets

Hi Kristine,

Please submit the following for NDA 209241 by February 27, 2017 or sooner:

- For Study 1202, for the "YMRS.xpt" datasets, please resubmit with a "Change From Baseline (CFB)" column, denoting the change from baseline for the YMRS Total Score.
- For Studies 1201 and 1202, for the "SAS.xpt" datasets, please resubmit with a "Change From Baseline (CFB)" column, denoting the change from baseline for the SAS Global Score.
- For Studies 1201 and 1202, for the "bars.xpt" datasets, please resubmit with a "Change From Baseline (CFB)" column, denoting the change from baseline for:
  - o Each scored subpart of the Barnes-Akathisia Scale (Items 1, 2, 3, 4)
  - o The BARS total score

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

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JASMEET K KALSI  
02/23/2017

## Kalsi, Jasmeet (Mona)

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**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, February 23, 2017 6:49 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request - Controlled Substance Staff

Hi Kristine,

This information request for NDA 209241 is a follow-up from the Feb. 14, 2017 amendment (Response to Information Request), with new questions from Controlled Substance Staff embedded in blue font.

**1. Multiple subjects are listed as early terminated due to Sponsor decision. Please provide any additional information regarding the termination of the following subjects (6 subjects identified by USUBJID):**

- a. NBI-98854-1304-3303009
- b. NBI-98854-1304-3303003
- c. NBI-98854-1304-3303007
- d. NBI-98854-1201-1451001
- e. NBI-98854-1304-3303002
- f. NBI-98854-1304-3303004

**Sponsor Response:**

Subjects from Study 1304, Site 330 (USUBJID 3303009, 3303003, 3303007, 3303002, 3303004) were discontinued from the study due to site non-compliance;

[Question 1 to Sponsor: Were these the only remaining subjects still enrolled at this site? If not, clarify the outcomes for other remaining subjects.]

see Table 1 for additional subject information. The Sponsor was notified by the study bioanalytical laboratory, (b) (4), of unreasonably high plasma concentrations in some samples from Site 330; the observed plasma levels were not physiologically achievable.

[Question 2 to Sponsor: Clarify what is meant by "some samples". Were these samples obtained specifically from the subjects a - f above? If so, were there high plasma concentrations noted for all six subjects? Clarify the term "not physiologically achievable". Provide the test result for plasma level, and compare this to plasma level expected based on the treatment assignment for each subject.]

A full investigation was conducted by the Sponsor Quality Assurance and Clinical Operations teams and a report of the findings was submitted to the Division of Scientific Investigations, Office of Compliance at the FDA on 19-Nov-2015. All 5 subjects at that site were requested to return for safety evaluations;

[Question 3 to Sponsor: Was a copy of this letter provided in the NDA or IND? Provide a copy for our review.]

3 subjects returned for a final study visit and did not report any adverse events associated with an overdose of study drug;

[Question 4 to Sponsor: Was there an expectation that these patients had taken suprathereapeutic doses of the drug based on sample test results referenced above? Clarify the timing of the "final study visit" relative to the timing of blood draws for the samples referenced above. Provide any available details concerning the potential for subjects intentionally taking suprathereapeutic doses of study medication.]

2 subjects withdrew their consent and refused to return to the site but had no adverse events (AEs) to report. Ultimately, the anomalous pharmacokinetic (PK) concentrations were determined to be due to sample tampering and the site was closed.

[Question 5 to Sponsor: Clarify what is meant by “sample tampering” and provide any additional available details surrounding possible sample tampering in question. Clarify if tampering was possibly the actions of study subjects, or study site personnel.]

PK data for all subjects at the previous time points in the study were consistent with predicted exposure based on treatment group randomization. The efficacy and safety data for these 5 subjects had been collected in the proper fashion. As the primary endpoint was based on AIMS video scoring by blinded, Central AIMS Video Raters, subject data were included in the analysis sets. These data included 3 subjects (3303002, 3303003, 3303004) completing the 6-week placebo controlled portion of the study and contributing to the double-blind extension phase and 2 subjects (3303007, 3303009) with early termination (ET) visits at Week 2.

**Table 1: Study 1304 Site 330 Subject Information**

| <b>USUBJID</b> | <b>Treatment Assignment</b> | <b>Final Study Kit Dispensation</b> |
|----------------|-----------------------------|-------------------------------------|
| 3303002        | 40 mg                       | Week 20                             |
| 3303003        | 40 mg                       | Week 16                             |
| 3303004        | 80 mg                       | Week 12                             |
| 3303007        | 40 mg                       | Baseline                            |
| 3303009        | 80 mg                       | Week 2                              |

Please respond to this IR as soon as possible and let me know if you need any clarification.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

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JASMEET K KALSI  
02/23/2017

## Kalsi, Jasmeet (Mona)

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**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, February 21, 2017 1:47 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request - Adverse Events

Hello,

Regarding NDA 209241 please provide any additional information (e.g. clinical narrative, study drug dose and total days of exposure, study day of AE occurrence, severity, follow-up or conclusion of AE) about the following adverse events by **February 23, 2017**:

- Subject 1402-435-4006 is noted as having an AE of "neoplasm left lung"
- Subject 1304-337-3004 is noted as having an AE of "multiple pulmonary nodules"
- Subject 1304-318-3012 is noted as having an AE of "6 mm left thyroid nodule"
- Subject 1304-313-3009 is noted as having an AE of "left adrenal adenoma"
- Subject 1304-337-3023 is noted as having an AE of "multiple adenomatous colon polyps"
- Subject 1304-355-3022 is noted as having an AE of "colon polyp"

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

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JASMEET K KALSI  
02/21/2017

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** 2/3/2017 at 2:15pm (EST)

**Application Number:** NDA 209241

**Product Name:** Valbenazine Capsules

**Sponsor/Applicant Name:** Neurocrine Biosciences, Inc.

**Subject:** Data sets discussion

## **FDA Participants :**

|                            |   |
|----------------------------|---|
| Michael Davis, MD, PhD     | Medical Officer, DPP                              |
| Brian Miller, MD, MBA, MPH | Medical Officer, DPP                              |
| Javier Muniz, MD           | Team Leader, DPP                                  |
| Douglas Warfield, PhD      | Associate Director of Biomedical Informatics, DPP |
| Mona Kalsi, PharmD         | RPM, DPP  |

## **Sponsor/Applicant Participants**

|                            |  |
|----------------------------|--|
| Chris O'Brien, M.D.        | Chief Medical Officer                      |
| Josh Burke, M.S.           | Director, Biostatistics                    |
| Julie Yefchak              | Manager, Biostatistics / Clinical Programs |
| Malcolm Lloyd-Smith, M.Sc. | Chief Regulatory Officer                   |
| Kristine Kim, M.S.         | Director, Regulatory Affairs               |

## **1.0 BACKGROUND:**

The Clinical and Safety medical officers wanted to discuss the structure of the exposure dataset with the Applicant.

## **2.0 DISCUSSION:**

- One question that arose was why there were a different number of subjects in the Study 1402 exposure dataset from the number submitted in the 120 Day Safety Update. The Applicant indicated that a subset of subjects had participated in other studies (e.g., Studies 1201 and 1202) and they were hence not listed twice in the overall exposure dataset.
- The Applicant did confirm, however, that the dataset may have been missing a small number subjects from the 120 Day Safety Update and that they would submit a revised version that included all subjects up to the 120 Day Safety Update.
- The Applicant noted that only subjects who had been exposed to valbenazine were included in the exposure dataset. There were a limited number of subjects in Study 1201 who had been randomized yet never received study drug.

- The treatment variables listed in the exposure dataset reflected the initial treatment arm; while it may have indicated placebo treatment in the dataset, these subjects received valbenazine later in the study.

### **3.0 ACTION ITEMS:**

The Applicant will submit a response regarding the 120-day update with unique subject exposures and additional select concomitant medication information. This submission will be incorporated into the review for NDA 209241.

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/s/

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JASMEET K KALSI  
02/21/2017

## **Executive CAC Final Study Minutes**

**Date of Meeting: February 14, 2017**

Committee: Karen Davis Bruno, PhD, OND IO, Chair  
Abigail Jacobs, PhD, OND IO, Member  
Paul Brown, PhD, OND IO, Member  
Tim McGovern, PhD, OND IO, Member  
Jane Sohn, PhD, DNDP, Alternate Member  
Aisar Atrakchi, PhD, DPP, Pharm Tox Supervisor  
Darren Fegley, PhD, DPP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

### **NDA 209241**

**Drug Name: Valbenazine (NBI-98854; INGREZZA®)**

**Sponsor: Neurocrine Biosciences Inc.**

### **Background:**

NDA 209241 was submitted on August 11, 2016 to pursue marketing approval of valbenazine for the treatment of tardive dyskinesia. Final study reports for a 6-month transgenic mouse and a 2-year rat carcinogenicity study were submitted with the NDA.

### **Mouse Carcinogenicity Study**

Tg.rasH2 mice (25/sex/group) were administered valbenazine ditosylate daily by oral gavage in a vehicle of 0.25% (w/v) methylcellulose in reverse osmosis deionized water for 26 consecutive weeks. Doses of 10, 30, and 75 mg/kg/day (free base equivalent dose of administered di-tosylate salt) were used for males and females. A positive control group (urethane, 1000 mg/kg on days 1, 3, and 5 by IP injection) demonstrated sensitivity of the test system. There were no statistically significant drug-related neoplastic findings in either males or females.

### **Rat Carcinogenicity Study**

Sprague Dawley rats (60/sex/group) were administered valbenazine ditosylate daily by oral gavage in a vehicle of 0.25% (w/v) methylcellulose in reverse osmosis deionized water for 91 consecutive weeks. Doses of 0.5, 1, and 2 mg/kg/day (free base equivalent dose of administered di-tosylate salt) were used for males and females. All male dose groups were terminated during week 91 when only 20 male rats remained in the control group. Females at the 0.5 mg/kg/day dose level were terminated early during week 91 when only 15 rats remained. All remaining female dose groups were terminated later during week 91 when only 20 rats remained in the control group. The sponsor received agreement from the division and the ECAC prior to

termination for these groups. There was a statistically significant increase in survival rates for high dose males (2 mg/kg/day) compared to controls. There were no statistically significant drug-related neoplastic findings in either males or females.

**Executive CAC Conclusions:**

Tg.rasH2 Mouse:

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 6-month Tg.rasH2 mouse study.

Rat:

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the rat carcinogenicity study.

---

Karen Davis Bruno, Ph.D.

Chair, Executive CAC

cc:\

/Division File, DPP

/AAtrakchi, DPP

/DFegley, DPP

/JKalsi, DPP

/SLeuenroth-Quinn, OND IO

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STEPHANIE J QUINN  
02/17/2017

KAREN L DAVIS BRUNO  
02/17/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Monday, February 13, 2017 9:08 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Safety Information Requests

Good Morning Kristine,

Please see the follow information requests for NDA 209241:

1. Multiple subjects are listed as early terminated due to Sponsor decision. Please provide any additional information regarding the termination of the following subjects (6 subjects identified by USUBJID):
  - a. NBI-98854-1304-3303009
  - b. NBI-98854-1304-3303003
  - c. NBI-98854-1304-3303007
  - d. NBI-98854-1201-1451001
  - e. NBI-98854-1304-3303002
  - f. NBI-98854-1304-3303004
2. In your Disposition (or "DS") datasets for each individual study, for subjects who discontinue due to adverse events, the adverse event resulting in termination is specified. This is not included in the disposition dataset for Study 1201. Please specify the adverse events that led to the discontinuation of the following subjects from Study 1201, as specified by the list USUBJIDs:
  - a. NBI-98854-1201-1121005
  - b. NBI-98854-1201-1131003
  - c. NBI-98854-1201-1141002
  - d. NBI-98854-1201-1261002
  - e. NBI-98854-1201-1281012
  - f. NBI-98854-1201-1341001
  - g. NBI-98854-1201-1411001
  - h. NBI-98854-1201-1531001
3. Subject NBI-98854-1304-3613004 is listed as discontinuing due to the Adverse Event of a Social Stay Hospitalization/Psychiatric Hospitalization. Please provide any additional information as to the events triggering hospitalization (including but not limited to suicidal ideation, suicide attempt, depression, etc.)

Please respond by **February 15, 2017.**

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
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Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
02/13/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Friday, February 10, 2017 4:14 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Adverse Events Preferred Term Regrouping IR  
**Attachments:** Adverse events preferred term groupings.xlsx

Hi Kristine,

As we discussed at the late cycle meeting, we are regrouping some of the Adverse Event Preferred Terms to get a better picture of the drug's effect for the purposes of labeling and for our safety analysis. Please see the attached term groupings.

Do you concur?

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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**GI, Endocrine, Constitutional AE Groupings**

| FDA Grouping       | MedDRA AEPTs                         |
|--------------------|--------------------------------------|
| Abdominal pain     | Abdominal pain                       |
|                    | Abdominal pain lower                 |
|                    | Abdominal pain upper                 |
|                    | Abdominal tenderness                 |
| Decreased appetite | Anorexia                             |
|                    | Decreased appetite                   |
| Diabetes           | Diabetes mellitus                    |
|                    | Diabetes mellitus inadequate control |
| Glycosuria         | Glucose urine present                |
|                    | Glycosuria                           |
| Hyponatremia       | Hyponatraemia                        |
|                    | Hyponatraemia syndrome               |
| Weight Loss        | Abnormal loss of weight              |
|                    | Weight decreased                     |

**Hematologic, Respiratory, and Dermatologic AE Groupings**

| FDA Grouping | MedDRA AEPTs                          |
|--------------|---------------------------------------|
| Anemia       | Anaemia                               |
|              | Haematocrit decreased                 |
|              | Haemoglobin decreased                 |
|              | Microcytic anaemia                    |
|              | Red blood cell count decreased        |
| Bronchospasm | Asthma                                |
|              | Chronic obstructive pulmonary disease |
| Leukopenia   | Leukopenia                            |
|              | Neutropenia                           |
|              | Agranulocytosis                       |
| Rash         | Rash                                  |
|              | Rash generalised                      |
|              | Rash maculo-papular                   |
|              | Rash papular                          |
|              | Urticaria                             |
| Sinusitis    | Acute sinusitis                       |
|              | Allergic sinusitis                    |
|              | Rhinitis                              |
|              | Rhinitis allergic                     |
|              | Sinus congestion                      |
|              | Sinusitis                             |

**Psychiatric AE Groupings**

| FDA Grouping | MedDRA AEPTs       |
|--------------|--------------------|
| Depression   | Depressed mood     |
|              | Depression         |
|              | Depressive symptom |
| SI/SA        | Suicidal behaviour |
|              | Suicidal ideation  |
|              | Suicidal attempt   |

**Neurologic AE Groupings**

| FDA Grouping            | MedDRA AEPTs             |
|-------------------------|--------------------------|
| Anticholinergic effects | Urinary retention        |
|                         | Constipation             |
|                         | Diplopia                 |
|                         | Vision blurred           |
|                         | Dry mouth                |
|                         | Disturbance in attention |
|                         | Amnesia                  |
|                         | Delirium                 |
| Balance disorders/Fall  | Balance disorder         |
|                         | Ataxia                   |
|                         | Dizziness                |
|                         | Fall                     |
|                         | Gait disturbance         |

|                     |                         |                                      |
|---------------------|-------------------------|--------------------------------------|
| Drooling            | Drooling                | (Reported as increase from baseline) |
|                     | Salivary Hypersecretion |                                      |
| Dyskinesia          | Dyskinesia              |                                      |
|                     | Tardive dyskinesia      |                                      |
| EPS - Akathisia     | Akathisia               |                                      |
|                     | Restlessness            |                                      |
|                     | Restless legs syndrome  |                                      |
| EPS - Non-Akathisia | Dystonia                |                                      |
|                     | Extrapyramidal disorder |                                      |
|                     | Parkinsonism            |                                      |
|                     | Muscle rigidity         |                                      |
|                     | Tremor                  |                                      |
|                     | Muscle spasms           |                                      |
| Somnolence          | Cogwheel rigidity       |                                      |
|                     | Malaise                 |                                      |
|                     | Sedation                |                                      |
|                     | Somnolence              |                                      |
|                     | Fatigue                 |                                      |

**Infectious AE Groupings**

| FDA Grouping                      | MedDRA AEPTs                   |               |
|-----------------------------------|--------------------------------|---------------|
| Infection - Respiratory           | Bronchitis                     | (Common cold) |
|                                   | Bronchitis chronic             |               |
|                                   | Influenza                      |               |
|                                   | Nasopharyngitis                |               |
|                                   | Parainfluenzae virus infection |               |
|                                   | Pneumonia                      |               |
|                                   | Pneumonia aspiration           |               |
|                                   | Respiratory track congestion   |               |
| Upper respiratory tract infection |                                |               |
| Infection - Soft tissue           | Abscess limb                   |               |
|                                   | Abscess soft tissue            |               |
|                                   | Cellulitis                     |               |
|                                   | Cellulitis staphylococcal      |               |
|                                   | Furuncle                       |               |
|                                   | Staphylococcal infection       |               |
| Infection - GU                    | Subcutaneous abscess           |               |
|                                   | Dysuria                        |               |
|                                   | Prostatitis                    |               |
|                                   | Pyelonephritis acute           |               |
| Infection - Other                 | Urinary tract infection        |               |
|                                   | Vulvovaginal mycotic infection |               |
|                                   | Acute tonsillitis              |               |
|                                   | Pharyngitis                    |               |
|                                   | Body tinea                     |               |
|                                   | Tinea cruris                   |               |
|                                   | Tooth abscess                  |               |
|                                   | Ear infection                  |               |
|                                   | Otitis externa                 |               |
|                                   | Eye infection                  |               |
|                                   | Gingival infection             |               |
|                                   | Onychomycosis                  |               |
| Oral herpes                       |                                |               |
| Infection - GI                    | Viral infection                |               |
|                                   | Gastric infection              |               |
|                                   | Gastroenteritis                |               |
|                                   | Gastroenteritis viral          |               |

**GI, Endocrine, Constitutional AE Groupings**

| FDA Grouping       | MedDRA AEPTs                         |
|--------------------|--------------------------------------|
| Abdominal pain     | Abdominal pain                       |
|                    | Abdominal pain lower                 |
|                    | Abdominal pain upper                 |
|                    | Abdominal tenderness                 |
| Decreased appetite | Anorexia                             |
|                    | Decreased appetite                   |
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| Leukopenia   | Leukopenia                            |
|              | Neutropenia                           |
|              | Agranulocytosis                       |
| Rash         | Rash                                  |
|              | Rash generalised                      |
|              | Rash maculo-papular                   |
|              | Rash papular                          |
|              | Urticaria                             |
| Sinusitis    | Acute sinusitis                       |
|              | Allergic sinusitis                    |
|              | Rhinitis                              |
|              | Rhinitis allergic                     |
|              | Sinus congestion                      |
|              | Sinusitis                             |

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| Anticholinergic effects | Urinary retention        |
|                         | Constipation             |
|                         | Diplopia                 |
|                         | Vision blurred           |
|                         | Dry mouth                |
|                         | Disturbance in attention |
|                         | Amnesia                  |
|                         | Delirium                 |
| Balance disorders/Fall  | Balance disorder         |
|                         | Ataxia                   |
|                         | Dizziness                |
|                         | Fall                     |
|                         | Gait disturbance         |

|                     |                         |                                      |
|---------------------|-------------------------|--------------------------------------|
| Drooling            | Drooling                | (Reported as increase from baseline) |
|                     | Salivary Hypersecretion |                                      |
| Dyskinesia          | Dyskinesia              |                                      |
|                     | Tardive dyskinesia      |                                      |
| EPS - Akathisia     | Akathisia               |                                      |
|                     | Restlessness            |                                      |
|                     | Restless legs syndrome  |                                      |
| EPS - Non-Akathisia | Dystonia                |                                      |
|                     | Extrapyramidal disorder |                                      |
|                     | Parkinsonism            |                                      |
|                     | Muscle rigidity         |                                      |
|                     | Tremor                  |                                      |
|                     | Muscle spasms           |                                      |
| Somnolence          | Cogwheel rigidity       |                                      |
|                     | Malaise                 |                                      |
|                     | Sedation                |                                      |
|                     | Somnolence              |                                      |
|                     | Fatigue                 |                                      |

**Infectious AE Groupings**

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|-----------------------------------|--------------------------------|---------------|
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|                                   | Bronchitis chronic             |               |
|                                   | Influenza                      |               |
|                                   | Nasopharyngitis                |               |
|                                   | Parainfluenzae virus infection |               |
|                                   | Pneumonia                      |               |
|                                   | Pneumonia aspiration           |               |
|                                   | Respiratory track congestion   |               |
| Upper respiratory tract infection |                                |               |
| Infection - Soft tissue           | Abscess limb                   |               |
|                                   | Abscess soft tissue            |               |
|                                   | Cellulitis                     |               |
|                                   | Cellulitis staphylococcal      |               |
|                                   | Furuncle                       |               |
|                                   | Staphylococcal infection       |               |
| Infection - GU                    | Subcutaneous abscess           |               |
|                                   | Dysuria                        |               |
|                                   | Prostatitis                    |               |
|                                   | Pyelonephritis acute           |               |
| Infection - Other                 | Urinary tract infection        |               |
|                                   | Vulvovaginal mycotic infection |               |
|                                   | Acute tonsillitis              |               |
|                                   | Pharyngitis                    |               |
|                                   | Body tinea                     |               |
|                                   | Tinea cruris                   |               |
|                                   | Tooth abscess                  |               |
|                                   | Ear infection                  |               |
|                                   | Otitis externa                 |               |
|                                   | Eye infection                  |               |
|                                   | Gingival infection             |               |
|                                   | Onychomycosis                  |               |
|                                   | Oral herpes                    |               |
| Viral infection                   |                                |               |
| Infection - GI                    | Gastric infection              |               |
|                                   | Gastroenteritis                |               |
|                                   | Gastroenteritis viral          |               |

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, February 09, 2017 1:21 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241, valbenazine - Label and MedGuide Information Request

Hi Kristine,

This information request is regarding NDA 209241. The division would like to note that a Medication Guide is not necessary for this application and to please resubmit the carton and container label. The following information request and updated carton and container label should be submitted by **February 15, 2017** or sooner.

### 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. Delete the Medication Guide (MG) statement.

### 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 statement of strength to read: "40 mg per capsule". Alternatively, consider placing the capsule strength over each capsule compartment on the blister label.
  - b. The blister label does not provide instructions on how to remove the capsules. We are concerned that the user may have difficulty removing the capsules from the blister package. To increase clarity, add brief instructions to the blister label that describe how the capsules should be removed (e.g., "Push capsule through foil" or similar verbiage).
2. Carton Labeling
  - a. Delete the MG statement.
3. Packaging Design
  - a. The instructions for opening the package are on the back panel and can be obscured by the placement of the Prescribing Information leaflet which is glued to the back of the package. To increase the visibility of the instructions for opening the package, have you considered the following:
    - Placing the instructions for opening the package and the "press down" tab on the principal display panel (PDP) or, alternatively, placing a statement on the PDP that instructs the patient to look on the back of the package for the instructions

- b. When opening the professional sample, the back side of the blister faces the principal display panel, which may lead to confusion. The back side of the blister lacks product identifier information. Patients must flip the blister over to positively identify the capsules. This orientation is not optimal for patients' viewing of important product information contained on the blister label. Have you considered the following:
- Reversing the position of the blister (by flipping it over) so that the product identifying information on the blister label faces the PDP when the package is opened

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products**

**U.S. Food and Drug Administration**

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JASMEET K KALSI  
02/10/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, February 07, 2017 1:50 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Concomitant Medications Information Request  
**Attachments:** Key CM antipsychotics dataset.xlsx

Hi Kristine,

Upon review of the concomitant medications, we noticed several errors [REDACTED] (b) (4)  
The attached dataset - exported to Microsoft Excel for convenience - represents the joining of the submitted concomitant medication datasets for Studies 1201, 1202, 1304, and 1402. We then eliminated all medications that were not antipsychotics, and classified the remaining as typical or atypical antipsychotics.

Do you agree?

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
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JASMEET K KALSI  
02/07/2017

## Kalsi, Jasmeet (Mona)

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**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Friday, February 03, 2017 9:17 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Valbenazine - NonClinical Information Request

Hi Kristine,

Please see the following IR from the non-clinical team and respond by **February 9, 2017:**

Please provide historical control data for the incidence of the benign and malignant tumors of the skin/subcutis observed in the 104-day carcinogenicity study in rat (study No. 8299648) conducted at [REDACTED] (b) (4). In particular we are interested in the incidence of trichoepithelioma, sebaceous cell carcinoma, and fibrosarcoma.

Thank you,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

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JASMEET K KALSI  
02/03/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Monday, January 30, 2017 8:01 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Urgent Information Request

**Importance:** High

Good Morning Kristine,

Please submit a response to the following IR for NDA 209241 by **COB today, 5 PM EST:**

*On page 23 of the ISS, you list 846 subjects as being exposed to the study drug. Upon examination of the ISS ADEX dataset, only 599 unique subjects are listed as exposed as the dataset only includes Studies 1201, 1202, 1304, and 1402.*

*Please submit a new ISS ADEX dataset inclusive of exposures for all 20 investigative trials as specified in the ISS. To be specific, this includes:*

- 1. Phase 1 trials: Studies 801, 901, 1102, 1203, 1204, 1301, 1302, 1303, 1401, 1403, 1502, 1503, 1504, 1507*
- 2. Phase 2 trials: Studies 1001, 1101, 1201, 1202*
- 3. Phase 3 trials: Studies 1304, 1402*

Thank you for the quick turnaround. Please let me know if you have any questions.

Regards,  
Mona

### **Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
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JASMEET K KALSI  
01/30/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Friday, January 27, 2017 1:26 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Valbenazine - Safety Information Request

Hi Kristine,

Regarding NDA 209241, and adding on to the IR sent on January 26, 2017, we would appreciate any additional information on these events, specifically, if it is related to a fall or balance disorders.

In study 1304, Subject 354-3003 is noted as having a broken second left toe.  
In study 1304, Subject 332-3001 is noted as having a broken foot and a fractured patella.  
In study 1304, Subject 335-3004 is noted as having a fractured left foot.  
In study 1201, Subject 139-1009 is noted as having a foot fracture.  
In study 1402, Subject 132-4003 is noted as having a fractured right foot.

Please respond by **January 30, 2017**.

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

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/s/  
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JASMEET K KALSI  
01/27/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, January 24, 2017 10:51 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request - Study 1304

Hi Kristine,

The following information requests are in reference to the long-term extension period of Study 1304 for NDA 209241:

1. The protocol indicates that all subjects were to receive valbenazine, but the subject and investigator would be blinded to actual treatment. Please clarify the extent of knowledge that the subjects and investigators had about the long-term treatment (e.g., did the subjects all know they would be receiving active treatment and just not know the specific dose, or did they think that they could potentially be receiving long-term placebo treatment?)
2. What were the logistics of the central video rating for the extension period? We assume they rated an initial batch of videos for the placebo-controlled period and later rated a batch of videos at the end of the study (since complete data from the initial 6-week period was submitted prior to the 120-day update). If this was indeed the case, how did the blinding-to-visit work (e.g., did the raters know that the videos would be from the set of visits Weeks 8, 16, 32, 48, and 52, or did they believe that baseline and Weeks 2, 4, 6 videos were also included?)

Please respond by **January 27, 2017**.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

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/s/  
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JASMEET K KALSI  
01/26/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, January 26, 2017 12:21 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 Valbenazine - Clinical Information Request

Hi Kristine,

Please respond to the following IR for NDA 209241 by **COB January 27, 2017**:

Regarding study 1202, the Study Protocol (Amendment 2 version, page 25) indicates that blinded central video raters would score the AIMS items 1-7 at Baseline and the end of Weeks 2, 4, 6, and 8. However, the submitted tabulation and analysis datasets (AIMS\_CR.XPT and A\_AIMSCR.XPT) appear to only include central rater scores for Baseline and Week 6. Please clarify whether central video raters scored the other listed visits, and if so, please amend the submitted datasets to facilitate analysis.

Thank you,  
Mona

### **Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

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Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
01/26/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, January 19, 2017 8:43 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Valbenazine - Information Request

Good Morning Kristine,

This Information Request is in reference to Study 1202 and the proposed INGREZZA labeling. In the Study 1202 Clinical Study Report (Table 14.9.2, p. 491), the dose titration information suggests that at Week 6, 34 subjects would be receiving 75 mg, 10 subjects would be receiving 50 mg, and 1 subject would be receiving 25 mg valbenazine. However, in

(b) (4) Please help us resolve this discrepancy for the purpose of data interpretation and accurate labeling.

Please respond by COB 1/20/17.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
01/19/2017

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, January 17, 2017 7:21 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241, valbenazine - Safety Information Request

Good Morning Kristine,

Please see the information request below for NDA 209241 and respond officially to the NDA and via e-mail by **COB January 20, 2017**. If possible, please submit sooner.

*Upon examining the 120-day safety update, there appear to be errors in the ADEX dataset. Study 1304 is a 6 week controlled trial followed by a 42 week open label extension. Thus, maximum drug exposure is 48 weeks, or 336 days. Study 1402 is an open label study lasting 48 weeks, or 336 days. Multiple subjects in both trials have a listed duration of treatment exceeding this period. For example, Subject ID 382-3002 in Study 1304 has a listed exposure of 356 days and Subject ID 448-4001 in Study 1402 has a listed exposure of 342 days.*

- 1. Please explain how subjects have listed drug exposure durations greater than the trial duration (comprised of the sum of the controlled and open label extension) specified in the study protocol for Study 1304.*
- 2. Please explain how subjects have listed drug exposure durations greater than the trial duration specified in the study protocol for open-label long-term Study 1402.*
- 3. It is unclear how exposure is calculated in ADEX dataset for the extension periods. For calculating the extension exposure, does the calculated drug exposure include or exclude the double blind period? Please explain how the "AVALC" and "AVAL" columns are calculated.*

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

Regulatory Project Manager

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, December 27, 2016 2:13 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - CSS Information Request

Hi Kristine,

Please see the following Information Request from the Controlled Substance Staff:

1. Provide the information including narratives for all cases of drug diversion, misuse, overdose, and drug stolen, missed or otherwise not accounted for during all phases.
2. Provide more information related to dependence and withdrawal:
  - We note that withdrawal data includes only 94 patients whereas the phase Phase 2/3 Long-term Exposure Pool included 427 patients. Provide the data for the rest of the patients or the clarification why the data was not provided.
  - Explain how the withdrawal data was collected, at what specific time points after drug discontinuation the information on adverse events was collected. Were any withdrawal scales used?
  - The table 1.2.15 in ISS does not provide information for placebo group. Please clarify why.
  - Provide the updated table for discontinuation/withdrawal adverse events which accounts for ALL adverse events for all System Organ Classes and that uses format found for example in the studies NBI-98854-1301 and NBI-98854-1503 and not the one used in ISS that the Sponsor describes as:  
If a subject experienced more than 1 event in a given System Organ Class, that subject is counted once for the class. If a subject experienced more than 1 event within a given preferred term, that subject is counted only once for that term.
3. Provide the table with all adverse events for phase 2/3 for all neurological and psychiatric adverse events, and for general disorders only for fatigue, asthenia, irritability and energy increased. Provide this data using the same format you used for the study # NBI-98854-1503, which includes a number of all adverse events and number of all subjects affected.

Please submit a response by **January 10, 2017.**

Thanks,  
Mona

### **Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
12/27/2016



NDA 209241

**MID-CYCLE COMMUNICATION**

Neurocrine Biosciences, Inc.  
Attention: Kristine Kim, M.S.  
Director, Regulatory Affairs  
12780 El Camino Real  
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valbenazine 40mg Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on November 29, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jasmeet (Mona) Kalsi, Regulatory Project Manager at (240) 402-8977.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, MD  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** November 29, 2016  
10:00 AM (EST) to 11:00 AM (EST)

**Application Number:** 209241  
**Product Name:** Valbenazine 40mg Capsules  
**Indication:** Treatment of Tardive Dyskinesia (TD)  
**Applicant Name:** Neurocrine Biosciences, Inc.

**Meeting Chair:** Javier Muniz, MD  
**Meeting Recorder:** Jasmeet (Mona) Kalsi, PharmD

**FDA ATTENDEES**

|                                |   |
|--------------------------------|---|
| Ellis Unger, MD                | Director, Office of Drug Evaluation I                     |
| Mitchell Mathis, MD            | Director, Division of Psychiatry Products (DPP)           |
| Tiffany Farchione, MD          | Deputy Director, DPP                                      |
| Javier Muniz, MD               | Clinical Team Leader, DPP                                 |
| Michael Davis, MD              | Clinical Reviewer, DPP                                    |
| Hao Zhu, PhD                   | Team Leader, Office of Clinical Pharmacology (OCP)        |
| Di Zhou, PhD                   | Reviewer, OCP   |
| Gopichand Gottipati, PhD       | Reviewer, Division of Pharmacometrics, OCP                |
| Ofir (Noah) Nevo, PharmD, BCPP | Safety Evaluator, Division of Pharmacovigilance I (DPV I) |
| Vicky Chan                     | Safety Evaluator, DPV I                                   |
| Darren Fegley, PhD             | Pharmacology/Toxicology Reviewer, DPP                     |
| Somya Dunn, MD                 | Risk Management Analyst, Division of Risk Management      |
| Marc Goldstein                 | Independent Assessor, Eastern Research Group              |

**APPLICANT ATTENDEES**

|                          |  |
|--------------------------|--|
| Chris O'Brien, MD        | Chief Medical Officer                    |
| Haig Bozigian, PhD       | Chief Development Officer                |
| Gordon Loewen, PhD       | VP, Preclinical Development              |
| Joshua Burke, MS         | Director, Biostatistics                  |
| Grace Liang, MD          | Medical Director                         |
| Dao Thai, PharmD         | Director, Clinical Drug Safety           |
| Jay Thiele, PhD          | Sr. Director, Pharmaceutical Development |
| Scott Zook, MSc          | VP, Development                          |
| Malcolm Lloyd-Smith, MSc | Chief Regulatory Officer                 |
| Alessandro Lobbia, PhD   | Executive Director, Regulatory Affairs   |
| Kristine Kim, MS         | Director, Regulatory Affairs             |



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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## **1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## **2.0 SIGNIFICANT ISSUES**

No significant issues have been identified at this time.

## **3.0 INFORMATION REQUESTS**

### **Clinical**

- The Division inquired about obtaining data for items 8-10 on the AIMS scale. The Applicant indicated that this data was not included for the following reasons:
  - Item 10 (patient's awareness of abnormal movements) was not directly asked to subjects as the AIMS scoring was performed on video recordings by central raters.
  - Item 8 (overall severity of abnormal movements) is unreliable because it is used differently by clinicians (e.g., many, but not all raters use the highest score on other items for the overall severity score). The CGI-TD was used as an overall clinical impression of TD severity.
  - Patients have variable levels of insight on their TD symptoms. The Applicant tried to capture this with the Patient Global Impression of Change (PGIC) measure as an exploratory efficacy endpoint.
- The Division was satisfied with the Applicant's rationale for not including AIMS items 8-10 data.

## **4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

At this time, based on the information currently available, we do not believe that a REMS will be necessary to ensure the benefits of the drug outweigh the risks.

## **5.0 ADVISORY COMMITTEE MEETING**

The applicant was updated on the date of the Advisory Committee meeting, which is scheduled for February 16, 2017. More details will be available in the upcoming weeks.

## **6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES**

The applicant was updated on the following milestone dates for valbenazine:

- February 02, 2017 – Late Cycle Communication meeting
- February 28, 2017 – communication of proposed labeling and if necessary, any postmarketing commitment requests if major deficiencies are not identified during the review.
- April 11, 2017 – on track to take action by PDUFA date.

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/s/  
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MITCHELL V Mathis  
12/22/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Wednesday, December 21, 2016 6:23 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Valbenazine - Information Request

Hi Kristine,

Please submit the following information request for NDA 209241 by **January 10, 2017**:

1. Please provide your calculation regarding the statement in the label: (b) (4)
2. Please provide your evidence (i.e.. bioassay data, and HPLC Chromatograph) regarding the statement in the summary of clinical pharmacology studies: "the ability of the chromatographic method used for metabolite profiling to resolve NBI-98782 from its secondary alcohol epimer (NBI-98795) was tested and confirmed. Furthermore, NBI-98795 was not detected in human plasma (or excreta) indicating no in vivo evidence for chiral inversion of NBI-98782."

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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JASMEET K KALSI  
12/21/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Monday, December 19, 2016 12:12 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request - Financial Disclosures

Hi Kristine,

In reference to NDA 209241, we were unable to find details related to financial disclosures in Module 1.3.4; only Form 3454 and a complete list of investigators were included. Please respond to the following Information Request officially to the application and via e-mail to me by January 3, 2017.

1. Were there any investigators who were or are NBI employees?
2. Were there any investigators with disclosable financial interests or arrangements?
3. If there were investigators with disclosable financial interests or arrangements, please provide information on the number of investigators and details regarding 1) compensation to investigators for conducting the study where the value could be influenced by the outcome of the study; 2) significant payments of other sorts; 3) proprietary interest in the product tested held by investigators; and 4) significant equity interest in NBI held by investigators.
4. If there are any disclosures, please describe steps you have taken to minimize the potential bias related to the disclosures.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**  
*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration  
Tel: (240) 402-8977  
[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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JASMEET K KALSI  
12/19/2016

MEMORANDUM

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

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DATE: 11/23/2016

TO: Division of Psychiatry Products  
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209241

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

**Rationale**

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

| Facility Type | Facility Name | Facility Address                    |
|---------------|---------------|-------------------------------------|
| Clinical      | Celerion Inc. | 2420 W. Baseline Road,<br>Tempe, AZ |

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SHILA S NKAH  
11/23/2016



NDA 209241

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Neurocrine Biosciences, Inc.  
12780 El Camino Real  
San Diego, CA 92130

ATTENTION: Malcolm Lloyd-Smith  
Chief Regulatory Officer

Dear Mr. Lloyd-Smith:

Please refer to your New Drug Application (NDA) dated and received August 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Valbenazine Capsule, 40 mg.

We also refer to your correspondence dated and received August 25, 2016, requesting review of your proposed proprietary name, Ingrezza.

We have completed our review of the proposed proprietary name, Ingrezza and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your August 25, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Alycia Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4270. For any other information regarding this application, contact Jasmeet Kalsi, Regulatory Project Manager in the Office of New Drugs, at (240) 402-8977.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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LUBNA A MERCHANT on behalf of TODD D BRIDGES  
11/14/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, November 10, 2016 11:06 AM  
**To:** 'Kim, Kristine'  
**Subject:** RE: NDA 209241 - Valbenazine Information Request

**Importance:** High

Good Morning Kristine,

This is a follow-up from the Information Request sent on 9/14/16 for NDA 209241. The review team still needs clarification on the following:

- [Study 1301 dataset hecg.xpt](#) with updated EGTM down to the second.  
-----The new submitted hecg.xpt dataset is the same as the old one. Please resubmit a new one with EGTM down to the second to match those in the ECG Warehouse.
- [Study 0901 subject map file](#) to link the subjects in the ECG warehouse to those in the clinical datasets. To facilitate review, the file is sorted both by ECG\_ID and Subject ID (from the clinical study report).  
-----The map file is in PDF format, please submit a map file in SAS XPT format.

Please submit the requested information to the IND by COB 11/17/16.

Thanks,  
Mona

---

**From:** Kim, Kristine [<mailto:kkim@neurocrine.com>]  
**Sent:** Wednesday, September 14, 2016 5:28 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Cc:** Kiedrow, Keith; Kiedrow, Keith; Hardeman, Steven D  
**Subject:** RE: NDA 209241 - Valbenazine Information Request

Hello Mona,

We will submit the requested information to the NDA and by email to you by Monday, September 19.

Best regards,  
Kristine

---

**From:** Kalsi, Jasmeet (Mona) [<mailto:Jasmeet.Kalsi@fda.hhs.gov>]  
**Sent:** Wednesday, September 14, 2016 10:43 AM  
**To:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>  
**Cc:** Kiedrow, Keith <[Keith.Kiedrow@fda.hhs.gov](mailto:Keith.Kiedrow@fda.hhs.gov)>; Kiedrow, Keith <[Keith.Kiedrow@fda.hhs.gov](mailto:Keith.Kiedrow@fda.hhs.gov)>; Hardeman, Steven D <[Steven.Hardeman@fda.hhs.gov](mailto:Steven.Hardeman@fda.hhs.gov)>  
**Subject:** NDA 209241 - Valbenazine Information Request

Hi Kristine,

This is in reference to your NDA submitted on August 11, 2016. The review team has the following Information Request:

- Please complete the attached ClinPharm and Cardiac Safety Table.

- Please provide a copy of the most recent Investigator's Brochure.
- For Study 1301, EGTM (ECG Time) in the analysis dataset (hecg.xpt) are only down to minute, no way to match those in the ECG warehouse, please update the EGTM down to second and resubmit the dataset.
- For Study 0901, please submit a subject map file to link the subjects in the ECG warehouse to those in the clinical datasets.

Please submit the information electronically to the NDA as well as in an e-mail to me by **9/19/16**.

Thank you,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products**

**U.S. Food and Drug Administration**

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
11/10/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, November 10, 2016 4:47 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request - Due 11/14/16

Hi Kristine,

In your NDA 209241 submission, you have included a listing for important protocol deviations for Studies 1202 and 1304. Please provide a listing for all protocol deviations for these two studies. Please provide these listings by COB Monday, November 14, 2016.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
11/10/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Monday, October 24, 2016 12:08 PM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - Information Request

Hi Kristine,

The review team would like the following for NDA 209241:

- Please confirm that both NBI-98854 and NBI-98782 are enantiopure (ie. composed of only one enantiomer) and provide their chemical structures and IUPAC names.

Please submit to the NDA by COB 10/26/16.

Thanks,  
Mona

### **Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products**

**U.S. Food and Drug Administration**

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
10/24/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Thursday, October 13, 2016 10:03 AM  
**To:** 'Kim, Kristine'  
**Subject:** RE: NDA 209241 - Valbenazine - Information Request

Good Morning Kristine,

Thank you for your response and clarification of study numbers. However, we do ask that you resubmit the ae.xpt and dm.xpt SDTM datasets for studies 1304, 1202, 1201, and 1402 to include the information listed below. While you did meet filing checklist criteria with the submission of the SDTM datasets, the SDTM datasets are lacking some of the required fields we need to review your application :

- Please include a column to indicate whether the subject was in the safety population in both datasets (ae.xpt and dm.xpt) for each of the studies mentioned above.
- Please add a treatment emergent adverse events (TEAE) column to the AE data set (ae.xpt).
- Please include a column to the ae.xpt files to indicate what phase of the trial the TEAE took place (AEPHASE)
- Please include a column to the ae.xpt files to indicate what **dose** of medication (active or placebo) the subject was on when the TEAE took place.
- A "Last Dose" variable would be helpful. However, the aforementioned requests are most critical.

We understand that this will take some time and kindly ask that you have these changes submitted no later than November 1, 2016.

Thanks,  
Mona

---

**From:** Kim, Kristine [mailto:kkim@neurocrine.com]  
**Sent:** Thursday, October 06, 2016 1:51 PM  
**To:** Kalsi, Jasmeet (Mona)  
**Cc:** Kiedrow, Keith; Patel, Hiren; David, Paul A; Hardeman, Steven D  
**Subject:** RE: NDA 209241 - Valbenazine - Information Request

Hello Mona,

I have followed up with our programming team. First, we are requesting clarification: **Please confirm the studies of interest to be 1304, 1202, 1201, and 1402** (stated as 1401 in your email below)..

We understand that the reviewers are utilizing the individual study datasets to recreate the pooled analysis. We propose 2 options to address the reviewer's requests.

Option 1: In order to merge the SDTM and analysis datasets, we suggest a modification to USUBJID in both the SDTM and analysis datasets. The resulting merged datasets will provide all of the data that has been requested. The recommended modification is the following SAS code: **SUBJ=compress(USUBJID,'-');** This approach appears to be the simplest way to obtain the required data.

Option 2: If the programmers' preference is not to modify USUBJID, the ISS ADaM datasets can be accessed to provide the requested information with the exception of the dose at time of TEAE. We have identified the requested variables within the ISS ADaMs; please see below in yellow highlight. Regarding the bullet item pertaining to the dose at time of TEAE, we will provide this data as described below, upon FDA confirmation that the plan is acceptable.

If Option 1 is followed, this request for information will be considered completed; no additional submission will be performed.

If Option 2 is followed, in order to meet the October 12 submission date, we request rapid confirmation from the FDA review team regarding our proposal concerning the provision of the dose at time of TEAE.

Best regards,  
Kristine

Kristine Kim  
Regulatory Affairs Director  
Neurocrine Biosciences, Inc.  
(858) 617-7785

---

**From:** Kalsi, Jasmeet (Mona) [<mailto:Jasmeet.Kalsi@fda.hhs.gov>]

**Sent:** Wednesday, October 05, 2016 4:41 AM

**To:** Kim, Kristine <[kkim@neurocrine.com](mailto:kkim@neurocrine.com)>

**Cc:** Kalsi, Jasmeet (Mona) <[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)>; Kiedrow, Keith <[Keith.Kiedrow@fda.hhs.gov](mailto:Keith.Kiedrow@fda.hhs.gov)>; Patel, Hiren <[Hiren.Patel@fda.hhs.gov](mailto:Hiren.Patel@fda.hhs.gov)>; David, Paul A <[Paul.David@fda.hhs.gov](mailto:Paul.David@fda.hhs.gov)>; Hardeman, Steven D <[Steven.Hardeman@fda.hhs.gov](mailto:Steven.Hardeman@fda.hhs.gov)>

**Subject:** NDA 209241 - Valbenazine - Information Request

Good Morning Kristine,

This e-mail is in reference to your NDA 209241 submitted on August 11, 2016. The review team has requested the following information:

- Please resubmit the ae.xpt and dm.xpt SDTM datasets for studies 1304, 1202, 1201, and 1401 to include the following information:
  - Please include a column to indicate whether the subject was in the safety population (recommended column title SAFEPOP) in both datasets (ae.xpt and dm.xpt) for each of the studies. See ADaM Dataset ADSL / Variable SAFFL (safety population flag for all subjects). Please see ISS Reviewer's Guide Section 3.6 for the ADSL SAFFL derivation. For the AE data see ADaM Dataset ADAE / Variable SAFFL (safety population flag).
  - Please add a treatment emergent adverse events (TEAE) column to the AE data set (ae.xpt). See Dataset ADaM ADAE / Variable TRTEMFL (treatment emergent AE flag). Please see ISS define.xml Page 21 for derivation.
  - Please include a column to the ae.xpt files to indicate what phase of the trial the TEAE took place (AEPHASE). See ADaM Dataset ADAE / Variable APHASE (Phase). Please see ISS define.xml Page 20 for derivation.
  - Please include a column to the ae.xpt files to indicate what **dose** of medication (active or placebo) the subject was on when the TEAE took place. **NEED FDA CONFIRMATION OF ACCEPTABILITY:** We can program a variable called LASTDOSE, which is the dose of medication the subject was on when the TEAE took place, by merging on this variable from our analysis datasets to the ADaM ADAE dataset. For studies 1202, 1304, 1402, this variable exists as LASTDOSE in analysis dataset. For study 1201, this variable exists as LTREAT. We would add this new variable LASTDOSE on to the current ADaM dataset ADAE and resubmit this dataset.

- Because your analysis sets use different values for the Unique Subject ID (USUBJID) than the SDTM domains, we are unable to join the datasets together and use the treatment emergent AE data.
- In addition, please include the derivations used for providing the above information.

Please submit this information electronically to the NDA and via e-mail to me by COB October 12, 2016.

Thanks,  
Mona

**Jasmeet (Mona) Kalsi, PharmD**

*Regulatory Project Manager*

**Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products**

**U.S. Food and Drug Administration**

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
10/13/2016

## Kalsi, Jasmeet (Mona)

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**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Tuesday, October 11, 2016 9:58 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona)  
**Subject:** NDA 209241 - valbenazine - Information Request

Good Morning Kristine,

Please provide a response to the following information request for your NDA 209241, valbenazine, by COB October 18, 2016:

1. In study NBI-98854-1303, one subject (SUBJID= 303-3005) was reported as "SCREEN FAILURE" in the SDTM data file (DM.xpt). However, this subject was included in the final analyses in the clinical report.
2. In study NBI-98854-1504, AUClast were incorrectly reported in the submitted SDTM data file (PP.xpt). Each subject has 2 values of AUClast reported. The study conclusion of bioequivalence between formulations cannot be confirmed without the correct datasets.
3. The PK parameters in several studies (eg. NBI-98854-0801, NBI-98854-1102, NBI-98854-1203, NBI-98854-1204 and NBI-98854-1401) were not specified in terms of their categories (eg. parent drug, metabolite, study period, etc) in the SDTM data file (PP.xpt).

Thank you,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

Tel: (240) 402-8977

[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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/s/  
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JASMEET K KALSI  
10/11/2016

## Kalsi, Jasmeet (Mona)

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**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Wednesday, October 05, 2016 7:41 AM  
**To:** Kim, Kristine  
**Cc:** Kalsi, Jasmeet (Mona); Kiedrow, Keith; Patel, Hiren; David, Paul A; Hardeman, Steven D  
**Subject:** NDA 209241 - Valbenazine - Information Request

Good Morning Kristine,

This e-mail is in reference to your NDA 209241 submitted on August 11, 2016. The review team has requested the following information:

- Please resubmit the ae.xpt and dm.xpt SDTM datasets for studies 1304, 1202, 1201, and 1401 to include the following information:
  - Please include a column to indicate whether the subject was in the safety population (recommended column title SAFEPOP) in both datasets (ae.xpt and dm.xpt) for each of the studies.
  - Please add a treatment emergent adverse events (TEAE) column to the AE data set (ae.xpt).
  - Please include a column to the ae.xpt files to indicate what phase of the trial the TEAE took place (AEPHASE)
  - Please include a column to the ae.xpt files to indicate what **dose** of medication (active or placebo) the subject was on when the TEAE took place.
- Because your analysis sets use different values for the Unique Subject ID (USUBJID) than the SDTM domains, we are unable to join the datasets together and use the treatment emergent AE data.
- In addition, please include the derivations used for providing the above information.

Please submit this information electronically to the NDA and via e-mail to me by COB October 12, 2016.

Thanks,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

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/s/  
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JASMEET K KALSI  
10/05/2016

## Kalsi, Jasmeet (Mona)

---

**From:** Kalsi, Jasmeet (Mona)  
**Sent:** Wednesday, September 14, 2016 1:43 PM  
**To:** 'Kim, Kristine'  
**Cc:** Kiedrow, Keith; Kiedrow, Keith; Hardeman, Steven D  
**Subject:** NDA 209241 - Valbenazine Information Request  
**Attachments:** Highlights\_ClinPharm\_and\_Cardiac\_Safety.doc

Hi Kristine,

This is in reference to your NDA submitted on August 11, 2016. The review team has the following Information Request:

- Please complete the attached ClinPharm and Cardiac Safety Table.
- Please provide a copy of the most recent Investigator's Brochure.
- For Study 1301, EGTM (ECG Time) in the analysis dataset (hecg.xpt) are only down to minute, no way to match those in the ECG warehouse, please update the EGTM down to second and resubmit the dataset.
- For Study 0901, please submit a subject map file to link the subjects in the ECG warehouse to those in the clinical datasets.

Please submit the information electronically to the NDA as well as in an e-mail to me by **9/19/16**.

Thank you,  
Mona

### Jasmeet (Mona) Kalsi, PharmD

*Regulatory Project Manager*

Center for Drug Evaluation and Research  
Office of Drug Evaluation I  
Division of Psychiatry Products

U.S. Food and Drug Administration

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[Jasmeet.Kalsi@fda.hhs.gov](mailto:Jasmeet.Kalsi@fda.hhs.gov)



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**Table 1. Highlights of Clinical Pharmacology and Cardiac Safety**

|   |   |   |
|---|---|---|
| Therapeutic dose and exposure             | <p>Include maximum proposed clinical dosing regimen</p> <p>Mean (%CV) C<sub>max</sub> and AUC at the single maximum proposed clinical dose</p> <p>Mean (%CV) C<sub>max</sub> and AUC at the steady state with the maximum proposed clinical dosing regimen</p>  |   |
| Maximum tolerated dose                    | <p>Include if studied or NOAEL dose</p>   |   |
| Principal adverse events                  | <p>Include most common adverse events; dose limiting adverse events</p>   |   |
| Maximum dose tested                       | Single Dose   | Specify dose  |
|   | Multiple Dose   | Specify dosing interval and duration  |
| Exposures Achieved at Maximum Tested Dose | Single Dose   | Mean (%CV) C <sub>max</sub> and AUC   |
|   | Multiple Dose   | Mean (%CV) C <sub>max</sub> and AUC   |
| Range of linear PK                        | <p>Specify dosing regimen</p>   |   |
| Accumulation at steady state              | <p>Mean (%CV); specify dosing regimen</p>   |   |
| Metabolites                               | <p>Include listing of all metabolites and activity</p>  |   |
| Absorption                                | Absolute/Relative Bioavailability   | Mean (%CV)  |
|   | T <sub>max</sub>  | <ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul> |
| Distribution                              | V <sub>d</sub> /F or V <sub>d</sub>   | Mean (%CV)  |
|   | % bound   | Mean (%CV)  |
| Elimination                               | Route   | <ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>      |
|   | Terminal t <sub>1/2</sub>   | <ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>         |
|   | CL/F or CL  | Mean (%CV)  |
| Intrinsic Factors                         | Age   | Specify mean changes in C <sub>max</sub> and AUC  |
|   | Sex   | Specify mean changes in C <sub>max</sub> and AUC  |
|   | Race  | Specify mean changes in C <sub>max</sub> and AUC  |
|   | Hepatic & Renal Impairment  | Specify mean changes in C <sub>max</sub> and AUC  |
| Extrinsic Factors                         | Drug interactions   | Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC                                    |
|   | Food Effects  | Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)                      |
| Expected High Clinical Exposure Scenario  | <p>Describe worst case scenario and expected fold-change in C<sub>max</sub> and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p>  |   |
| Preclinical Cardiac Safety                | <p>Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.</p>   |   |
| Clinical Cardiac Safety                   | <p>Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).</p> |   |

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/s/  
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JASMEET K KALSI  
09/15/2016



IND 111591

**MEETING MINUTES**

Neurocrine Biosciences, Inc.  
Attention: Kristine Kim, M.S.  
Manager, Regulatory Affairs  
12780 El Camino Real  
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NBI-98854, valbenazine tosylate.

We also refer to the meeting between representatives of your firm and the FDA on February 4, 2016. The purpose of the meeting was to discuss the proposed valbenazine tosylate NDA contents, associated analysis plans, and timeline for NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LCDR Sharonjit Sagoo, Pharm.D., Regulatory Project Manager at (301) 796-0431.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** February 4, 2016 at 10:00AM – 11:00AM Eastern Time  
**Meeting Location:** White Oak Building 22, Conference Room: 1421

**Application Number:** IND 111591  
**Product Name:** NBI-98854, valbenazine tosylate  
**Indication:** Tardive Dyskinesia  
**Sponsor/Applicant Name:** Neurocrine Biosciences, Inc.

**FDA ATTENDEES**

|                                     |  |
|-------------------------------------|--|
| Ellis Unger, M.D.                   | Director, Office of New Drugs – Office of Drug Evaluation I (ODE I)    |
| Robert Temple, M.D.                 | Deputy Director, Office of New Drugs – ODE I                           |
| Mitchell Mathis, M.D.               | Director, Division of Psychiatry Products (DPP)                        |
| Tiffany Farchione, M.D.             | Deputy Director, DPP   |
| Kavneet-Ripi Kohli-Chhabra, M.D.    | Clinical Reviewer, DPP   |
| Lucas Kempf, M.D.                   | Clinical Team Leader, DPP  |
| Hao Zhu, Ph.D.                      | Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP) |
| Huixia Zhang, Ph.D.                 | Clinical Pharmacology Reviewer, OCP                                    |
| Kevin Krudys, Ph.D.                 | Pharmacometrics Reviewer, OCP  |
| Xiaofeng Wang, Ph.D.                | Pharmacometrics Reviewer, OCP  |
| Jeffrey Kraft, Ph.D.                | Genomics & Targeted Therapy Reviewer, OCP                              |
| Aisar Atrakchi, Ph.D.               | Pharmacology/Toxicology Supervisor, DPP                                |
| Imran Khan, Ph.D.                   | Pharmacology/Toxicology Reviewer, DPP                                  |
| Thomas Birkner, Ph.D.               | Biometrics Reviewer  |
| Peiling Yang, Ph.D.                 | Biometrics Team Lead   |
| James Laurenson, Ph.D.              | Reviewer, OPQ  |
| Mariappan Chelliah, Ph.D.           | Reviewer, OPQ  |
| Silvia Calderon, Ph.D.              | Pharmacologist, Controlled Substance Staff                             |
| Somya Dunn, M.D.                    | Risk Management Analyst, Division of Risk Management (DRISK)           |
| Jenn Sellers, M.D., Ph.D., F.A.A.P. | Senior Medical Officer, Office of Scientific Investigations            |
| Sharonjit Sagoo, Pharm.D.           | Regulatory Project Manager, DPP  |

## EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor

## SPONSOR ATTENDEES

|                            |   |
|----------------------------|---|
| Chris O'Brien, M.D.        | Chief Medical Officer                   |
| Josh Burke, M.S.           | Director, Biostatistics                 |
| Haig Bozigian, Ph.D.       | Chief Development Officer               |
| Ajay Madan, Ph.D., DABT    | Vice President, Preclinical Development |
| Sha Luo, M.S.              | Director, DMPK                          |
| Adam Grobin, Ph.D.         | Sr. Director, Analytical Development    |
| Malcolm Lloyd-Smith, M.Sc. | Chief Regulatory Officer                |
| Kristine Kim, M.S.         | Director, Regulatory Affairs            |
|                            | (b) (4)                                 |
| Scott Zook, M.Sc.          | Vice President CMC Development          |

## 1.0 BACKGROUND

Neurocrine Biosciences, Inc. (the sponsor) is developing valbenazine tosylate (also referred to as NBI-98854 or valbenazine) for the treatment of tardive dyskinesia (TD). The development program for this product received Breakthrough Therapy Designation in October, 2014.

TD is a neurological condition characterized by involuntary movements. It primarily affects the orofacial region (i.e., tongue, lips, jaw, face) and choreoathetoid movements in the limbs and trunk. TD develops with long-term neuroleptic use and often persists after discontinuation of the offending medication. There are no products approved for the treatment of TD.

Valbenazine as an orally active vesicular monoamine transporter 2 (VMAT2) inhibitor. VMAT2 plays a role in presynaptic dopamine release, regulating monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. The sponsor's data suggests that valbenazine is rapidly absorbed and relatively slowly converted to the active moiety NBI-98782. NBI-98782 is a potent stereoisomer of dehydrotetrabenazine, a metabolite of tetrabenazine; tetrabenazine is currently approved by the FDA for the treatment of Huntington's chorea. Tetrabenazine was originally approved with a Risk Evaluation and Mitigation Strategy (REMS) communication plan due to drug-associated depression and suicidality. The REMS was eliminated in August, 2015; however, its current label includes a boxed warning for depression and suicidality.

The sponsor reports that results from two completed Phase 2 studies in subjects with TD and schizophrenia, schizoaffective disorder, or mood disorder indicated an improvement in the Abnormal Involuntary Movement Scale (AIMS) score after continuous dosing of valbenazine (1) 50 mg once daily for 6 weeks, (2) 100 mg once daily for 2 weeks followed by 50 mg once daily for 4 weeks, or (3) 6 weeks of titrated doses from 25 mg up to 75 mg once daily (Studies NBI-98854-1201 and NBI-98854-1202). The sponsor also states that, in the 6-week dose-titration study (NBI-98854-1202), patients treated with valbenazine showed a statistically significant reduction in the AIMS dyskinesia total score in the valbenazine group compared to placebo. A

statistically significant higher responder rate (i.e.,  $\geq 50\%$  improvement in AIMS dyskinesia total score from baseline) was also observed in the valbenazine group compared with placebo.

The sponsor has recently analyzed data from its Phase 3 Study NBI-98854-1304 (Kinect 3), double-blind, parallel-group, six-week, placebo-controlled trial; the long-term extension phase of the study is ongoing. Subjects with moderate or severe neuroleptic-induced TD and underlying schizophrenia, schizoaffective disorder, or mood disorder were randomized 1:1:1 (placebo: 40 mg NBI-98854: 80 mg NBI-98854, once daily). NBI-98854 80 mg resulted in a statistically significant improvement in AIMS score vs. placebo. The AIMS score was also significantly reduced in the 40 mg group vs. placebo (supportive analyses). Adverse events were similar among all groups and were consistent with those of prior studies.

The Sponsor requested this Type B, pre-NDA meeting to review the proposed valbenazine NDA content, associated analysis plans, and timeline for the 505(b)(1) new drug application (NDA) submission. Their stated objectives for the meeting are the following:

- Discuss the drug product dissolution data package to be submitted in support of the NBI 98854 40 mg capsules;
- Obtain FDA agreement that the proposed nonclinical and clinical packages are sufficient for the planned valbenazine NDA submission;
- Obtain FDA agreement on the proposed statistical analysis plans for the Integrated Summary of Efficacy and the Integrated Summary of Safety;
- Discuss the plan for the valbenazine NDA to be submitted as a rolling submission;
- Obtain feedback from the FDA regarding the applicability of Priority Review and an Expedited Review for the valbenazine NDA; and
- Obtain FDA concurrence that the proposed content and format for the valbenazine NDA constitutes a fileable marketing application.

FDA sent Preliminary Comments to Neurocrine on February 2, 2016.

## 2. DISCUSSION

### 2.1. Chemistry, Manufacturing and Controls Package

**Question 1:** Does the Division agree the dissolution method and parameters are appropriate?

**FDA Response to Question 1:** *The briefing package does not contain the data and information necessary to fully respond to this question. The FDA will assess the proposed dissolution method during NDA review, as presented in the dissolution method development report. However, your proposed Tier 1 and Tier 2 testing strategy as well as the planned S1, S2, and S3 testing, per USP <711>, are appropriate.*

**Meeting Discussion on Question 1:** *No further discussion.*

**Question 2:** We believe that for the rapidly dissolving product, testing 12 vessels per analysis at 10, 15, 20, 30, 45, and 60 minutes would be appropriate to adequately characterize the ascending and plateau phases of the dissolution curve. Does the FDA agree?

**FDA Response to Question 2:** *Yes, the FDA agrees that the use of 12 vessels per dissolution testing at the proposed sampling schedule of 10, 15, 20, 30 and 45 min is appropriate to characterize the dissolution profile of your drug product.*

**Meeting Discussion on Question 2:** *No further discussion.*

**Question 3:** *The Sponsor has determined the EIC of NBI-98854 to be introduced into the aquatic environment will be less than 1 part per billion and therefore qualifies for a categorical exclusion for an environmental assessment. Does the FDA agree?*

**FDA Response to Question 3:** *The Agency will require additional information to support the claim of categorical exclusion from an EA in the NDA before making this determination. While the calculated EIC of (b)(4) ppb complies with this claim per 21 CFR 25.31(b), the lowest NOAEL in your Toxicology Written Summary, 3 mg/kg/day (Section 2.6.6.4.1), results from a reproductive/fertility and early embryonic development study in rats and is relatively low compared to your EIC. See FDA's recently published draft environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid activity (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf>) for guidance on providing additional information in your NDA to support a claim of categorical exclusion and the statement of no extraordinary circumstances.*

**Meeting Discussion on Question 3:** *The sponsor noted that their EIC was very conservative, with no correction for the salt form of the drug, actual market penetration data, and reduction in the environment such as from metabolism prior to excretion and dilution and degradation in the environment. In addition, reproductive/developmental toxicity in the rat was noted as being associated with a blood AUC with a several orders of magnitude margin to aquatic organism AUC at the EIC. The sponsor asked whether providing such data would be sufficient for supporting the claim for the categorical exclusion. FDA agreed that any such fate and extrapolation or "read-across" toxicity data would be useful for providing the additional support needed for the categorical exclusion, and that such data are in line with the draft guidance noted above.*

## 2.2. Nonclinical Package

*Please note that we moved question 3 from this section to the CMC package section above because it is not a nonclinical topic.*

**Non-clinical Comment:** *The nonclinical studies listed in Module 4 / Appendix E appear to be adequate to file the NDA and are in agreement with the Type B meeting minutes held between the Division and the sponsor on April 13, 2015. We note however, that Segment III reproductive study is pending; we remind you that final report should be submitted with the NDA. The adequacy and completeness of all of the nonclinical studies will be a matter of review.*

**Meeting Discussion:** *The sponsor intends to provide the Segment III study report with the Safety modules rolling submission. No further discussion at meeting.*

### 2.3. Clinical Package

**Question 4:** Does the FDA agree that the proposed plan to assess cardiac risk in the TD patient population is sufficient?

**FDA Response to Question 4:** *The QT assessment is not adequate. The proposed plan to assess cardiac risk in the TD patient population is not able to rule out small clinically relevant QTc prolongation (10 ms).*

**Meeting Discussion on Question 4:** *The sponsor indicated that they will have data to cover an adequate range of clinically relevant exposures, including that observed due to poor metabolizer status and relevant drug-drug interactions. This package will include in vitro data, in vivo safety pharmacology study (dog), safety data collection from Phase 2 (1201, 1202) and Phase 3 studies (1304, 1402). The Phase 1 data includes a study with a positive control (1401); all studies include extensive digital Holter monitoring and ECGs (0901, 1301, 1401).*

*The sponsor claimed that they believe the metabolite (NBI-98782) is a QT prolonger at the clinically relevant exposure. This will be a review issue. If QT prolongation at the clinically relevant exposure can be confirmed after the sponsor submits the data and report, a TQT study will then not be needed.*

**Question 5:** Does the FDA require submission of ECG waveforms collected for the valbenazine Phase 1 studies with digital monitoring to the ECG Warehouse?

**FDA Response to Question 5:** *Yes, ECG waveforms should be collected for NBI-98854-1401 and other Phase 1 studies, and study report and dataset should be submitted to the FDA for further review.*

**Meeting Discussion on Question 5:** *No further discussion.*

**Question 6:** Does the FDA agree that the pharmacology and mechanism of action of valbenazine is well understood, and, therefore, that the Sponsor does not need to conduct a formal 8-factor analysis to evaluate abuse potential of valbenazine?

**FDA Response to Question 6:**

1. *An 8-factor analysis is written by the FDA for transmittal by the Assistant Secretary of Health at the Department of Health and Human Services (ASH/HHS) to the Drug Enforcement Administration when making a scheduling recommendation under the Controlled Substances Act (CSA). Sponsors do not need to provide an 8-factor analysis. However, sponsors must collect, evaluate and include in the NDA all data available related to the abuse potential of the drug under development, and a proposal for*

*scheduling if deemed appropriate. Of note, a recommendation for not scheduling a drug is also considered a recommendation for scheduling.*

- 2. Although the sponsor has presented data maintaining that valbenazine is not a drug of abuse and lacks abuse potential, an assessment of the abuse potential of a drug is required in the NDA. Your assessment of abuse potential should comprise a comprehensive evaluation of the chemistry, pharmacology, pharmacokinetic and pharmacodynamic profile of the drug, and evaluation of clinical data. For guidance on the characterization of the abuse potential of a drug, we refer you to the Agency's Draft Guidance for Industry on the Assessment of Abuse Potential of Drugs. This guidance can be accessed at:  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>*
- 3. CSS is available to review non-clinical and clinical protocols prior to initiation of studies on abuse potential.*

**Meeting Discussion on Question 6:** *The sponsor intends to submit an assessment which will include a comprehensive evaluation of the chemistry, pharmacology, pharmacokinetic and pharmacodynamic profile of the drug, and evaluation of clinical data, per the guidance referenced in the Agency's preliminary comment. The Agency confirmed that an 8-factor analysis will not be necessary and encouraged the sponsor to follow the guidance in completing their assessment. The Controlled Substance Staff reiterated their availability to review protocols prior to initiation of studies on abuse potential.*

#### **2.4. Data Analysis Plans**

**Question 7:** Does the FDA agree the proposed population PK analysis plan is sufficient?

**FDA Response to Question 7:** *Your proposed population PK analysis plan seems reasonable. However, please note that the population PK analysis results regarding PK interaction between NBI-98854 and NBI-98782 and concomitant drugs are informative only if the clinical studies are adequately designed to detect significant changes in drug exposure due to drug-drug interactions with optimal study procedures and sample collection protocols. Detailed information on the dose given and time of administration should be documented for the co-administered drugs.*

**Meeting Discussion on Question 7:** *No further discussion.*

**Question 8:** Does the FDA agree the proposed exposure-response analysis plan is sufficient?

**FDA Response to Question 8:** *On face, the proposed exposure-response analysis plan seems reasonable based on limited information provided. However, we do have some concerns.*

*In your exposure-efficacy analysis conducted at the end of Phase 2, observed NBI-98782 C<sub>max,ss</sub> concentration was used as the exposure metric. However, based on the sparse sampling scheme in study NBI-98854-1304, we are concerned that you may not have collected adequate PK data in each individual to accurately estimate C<sub>max,ss</sub>. You should*

*either provide assurances that you are able to accurately characterize  $C_{max,ss}$  in NBI-98854-1304 or you may consider using model-predicted PK parameters, such as steady state average concentration as your exposure metric.*

*For exposure-safety analysis, you should provide justification for the cutoff points which are used to convert certain safety endpoints to binary outcomes including BARS, CDSS, MADRS, and SAS and explore if the results are sensitive to these cutoff points. If a trend between the exposure measure and any safety endpoint is observed, you should employ proper modeling techniques, such as logistic regression for ordinal responses, to further describe such relationships.*

**Meeting Discussion on Question 8:** *No further discussion.*

**Additional Clinical Pharmacology Comments:**

*We request that you submit, with your NDA, a pharmacogenomics dataset (.xpt) which includes subject level CYP2D6 genotype information and a description of genotyping methodologies and quality controls.*

*The following are the general expectations for submitting pharmacometric data and models:*

*All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*

*Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).*

*A model development decision tree and/or table which gives an overview of modeling steps should be submitted.*

*For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.*

*In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file*

as the revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

**Clinical Pharmacology Post-Meeting Comment:**

1. Please clarify if there is any inter-enantiomer conversion for the prodrug and active metabolite in vivo; if so, how much.
2. Please provide the **Clinical Pharmacology Summary** as review aid according to the template provided. This review aid will allow us to perform the regulatory review more efficiently and in a timely manner. Should you have any questions please contact us via the Regulatory Project Manager.

**Question 9:** Given the design of the valbenazine clinical program, does the FDA agree that the body of the Integrated Summary of Efficacy can serve as the Summary of Clinical Efficacy?

**FDA Response to Question 9:** Yes.

**Meeting Discussion on Question 9:** No further discussion.

**Question 10:** Does the FDA agree with the proposed statistical analysis plan for the Integrated Summary of Efficacy?

**FDA Response to Question 10:** In general, the proposed SAP appears acceptable as we consider the Integrated Summary of Efficacy exploratory. However, trial should be included as a factor in your analyses of pooled trials. Consider using MMRM for the analyses of the pooled trials if the assessment schedule was common for the three trials. Please include analyses of the primary and key secondary efficacy endpoints by study center, where possible, for the individual trials.

**Meeting Discussion on Question 10:** FDA agrees to the 'Question 10 Follow-Up' in the 'Sponsor Follow-Up Response to FDA Preliminary Comments' document (attached). No further discussion.

**Question 11:** Does the FDA agree with the proposed statistical analysis plan for the Integrated Summary of Safety?

**FDA Response to Question 11:** We request you to conduct standardized MedDRA queries (SMQs) for signal detection and risk management for depression and suicide/self-injury. We have no objection to the proposed integrated summary of safety (ISS) analysis because of its exploratory nature; however, we may ask for more explorations during our NDA reviews. As proposed, the ISS only gives means and distribution but does not all provide descriptive information about clinically significant outliers, for example clinically significant

*hyponatremia or hypernatremia, that will be of interest to the clinical review. Additionally, the categorical conversions of dimensional scales, such as the Barnes, need to be clinically justified in the application and presented alongside of the descriptive statistics.*

**Meeting Discussion on Question 11:** *No further discussion.*

## 2.5. NDA Submission Timeline, Format, and Review

**Question 12:** Does the FDA agree that data presented to-date support the granting of both a Priority Review and an Expedited Review for the proposed valbenazine NDA indicated for the treatment of tardive dyskinesia?

**FDA Response to Question 12:** *The data and information provided to date appear to support a Priority Review, although that final determination will be made once the NDA is submitted. Furthermore, we plan at this time, based on the available information/data and assuming a priority review designation, to act early on this application under an expedited review, provided no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action. However, these preliminary determinations will be reexamined when the safety and efficacy data are received/NDA is submitted and, as such, are subject to change.*

**Meeting Discussion on Question 12:** *No further discussion.*

**Question 13:** The Sponsor proposes to submit additional long-term data in the 120-day safety update as updated adverse event (AE) tables, updated tables to demonstrate long-term efficacy, and any new data informative to the benefit/risk profile. In addition, the Sponsor will provide full narratives for any additional deaths, serious AEs, and discontinuations due to AEs. Does the FDA agree?

**FDA Response to Question 13:** *Yes, we agree. Along with providing full narratives, please include CRFs for cases of death, serious adverse events, and discontinuations due to adverse events.*

**Meeting Discussion on Question 13:** *No further discussion.*

**Question 14:** Does the FDA agree that the proposed content and format for the valbenazine NDA constitutes a fileable marketing application?

**FDA Response to Question 14:** *Yes, we agree that the proposed submission should support an NDA filing.*

**Meeting Discussion on Question 14:** *No further discussion.*

***Additional Comments:*** *In your future NDA submission, please include a listing of all interactions with the Agency pertaining to this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

*Regarding the submission of video files for review, please refer to the Specifications for File Format Types Using eCTD Specifications for acceptable file types: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM347471.pdf>*

*Submit video files to the appropriate eCTD module, and link the file(s) into the backbone and also provide a PDF file of the video for archival purposes.*

*Video files should not be sent separately to individual reviewers, nor left out of the eCTD backbone. Any files submitted for review should always be linked into the backbone. Please include the word "video" in the leaf title of the video file, so reviewers can quickly identify the file.*

### **3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. The sponsor is planning for rolling review. The sponsor intends to submit the safety and quality modules in Q2 2016, with the efficacy modules following in Q3 2016. All major components of the NDA will be provided per module. All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for a REMS was held. The sponsor intends to propose a Medication Guide. The sponsor was encouraged to provide data to support their risk management strategy for the Division's review.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The sponsor stated an intention to submit a complete application; therefore, there are no agreements for late submission of application components.
- The Division encouraged the sponsor to include subgroup analyses in the efficacy and safety summaries, including how many patients achieve a score of 0 on the AIMS and whether there is anything unique about non-responders that may allow for early identification. We also encouraged the sponsor to examine any potential predictors of outcome (e.g., chlorpromazine equivalents of antipsychotic dose, time since diagnosis, time on antipsychotic treatment, etc.).

- The sponsor is interested in submitting videos to support an NDA application for this product but has not yet determined whether to submit all videos or a subset thereof. The Division asked the sponsor to submit the rationale for choosing which videos to submit if a subset is selected. Following the meeting, the Division inquired about the appropriate format for such a submission. The response from the document room was as follows:
  - Refer to the Specifications for File Format Types Using eCTD Specifications for acceptable file types:  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM347471.pdf>. If reviewing divisions request video files in modules 2 to 5, sponsors should link the file(s) into the backbone and also provide a PDF file of the video for archival purposes.
  - Video files should not be sent separately to individual reviewers, nor left out of the eCTD backbone. Any files submitted for review should always be linked into the backbone.
  - Sponsors should include the word "video" in the leaf title of the video file so that reviewers can quickly identify the file.

### **3.1 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **3.2 PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **3.3 ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

### **3.4 Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

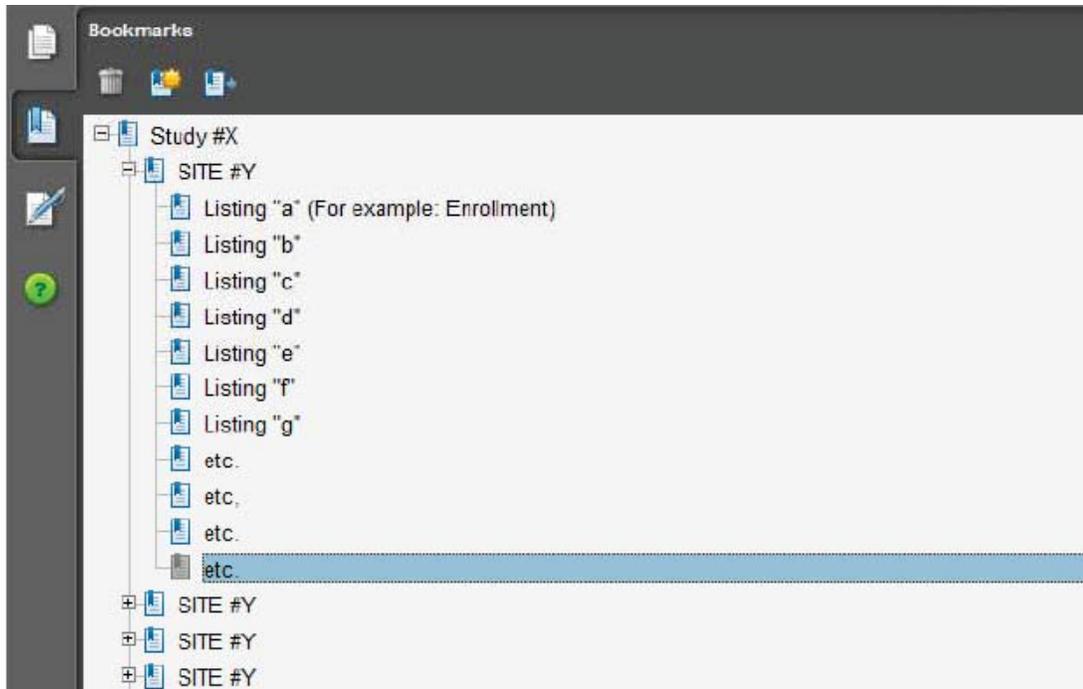
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records,

IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
  5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> ) for the structure and format of this data set.

**Attachment 1**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

| <b>DSI Pre-NDA Request Item<sup>1</sup></b> | <b>STF File Tag</b>          | <b>Used For</b>                                  | <b>Allowable File Formats</b> |
|---|------------------------------|--|-------------------------------|
| I   | data-listing-dataset         | Data listings, by study                          | .pdf                          |
| I   | annotated-crf                | Sample annotated case report form, by study      | .pdf                          |
| II  | data-listing-dataset         | Data listings, by study (Line listings, by site) | .pdf                          |
| III   | data-listing-dataset         | Site-level datasets, across studies              | .xpt                          |
| III   | data-listing-data-definition | Define file                                      | .pdf                          |

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

#### **4.0 ATTACHMENTS AND HANDOUTS**

Sponsor's response document

Clinical Pharmacology Summary

We thank the Division for the thoughtful, thorough preliminary comments for the IND 111591 NBI-98854 Type B pre-NDA meeting scheduled on February 4, 2016. We would like to modify the proposed meeting agenda as outlined below.

| <b>Agenda Item</b>  | <b>Time</b> |
|---------------------|-------------|
| <b>Introduction</b> | 5 minutes   |
| <b>CMC</b>          | 5 minutes   |
| <b>Clinical</b>     | 40 minutes  |
| <b>Wrap-up</b>      | 10 minutes  |

Specifically, we would like to focus our discussions on the following items:

- Question 3: Categorical Exclusion for an Environmental Assessment
- Question 4: Proposed Plan for QT Assessment
- Question 6: Assessment of Abuse Potential
- Preliminary Discussion on Risk Management

The following document contains the Sponsor follow-up comments to the FDA preliminary responses, where applicable. Items that do not require additional discussion at the pre-NDA meeting have been indicated.

## **2.1. Chemistry, Manufacturing and Controls Package**

**Question 1:** Does the Division agree the dissolution method and parameters are appropriate?

***FDA Response to Question 1:*** *The briefing package does not contain the data and information necessary to fully respond to this question. The FDA will assess the proposed dissolution method during NDA review, as presented in the dissolution method development report. However, your proposed Tier 1 and Tier 2 testing strategy as well as the planned S1, S2, and S3 testing, per USP <711>, are appropriate.*

**Question 1 Follow-Up:** No additional discussion needed.

**Question 2:** We believe that for the rapidly dissolving product, testing 12 vessels per analysis at 10, 15, 20, 30, 45, and 60 minutes would be appropriate to adequately characterize the ascending and plateau phases of the dissolution curve. Does the FDA agree?

***FDA Response to Question 2:*** *Yes, the FDA agrees that the use of 12 vessels per dissolution testing at the proposed sampling schedule of 10, 15, 20, 30 and 45 min is appropriate to characterize the dissolution profile of your drug product.*

**Question 2 Follow-Up:** No additional discussion needed.

**Question 3:** The Sponsor has determined the EIC of NBI-98854 to be introduced into the aquatic environment will be less than 1 part per billion and therefore qualifies for a categorical exclusion for an environmental assessment. Does the FDA agree?

**FDA Response to Question 3:** *The Agency will require additional information to support the claim of categorical exclusion from an EA in the NDA before making this determination. While the calculated EIC of (b) (4) ppb complies with this claim per 21 CFR 25.31(b), the lowest NOAEL in your Toxicology Written Summary, 3 mg/kg/day (Section 2.6.6.4.1), results from a reproductive/fertility and early embryonic development study in rats and is relatively low compared to your EIC. See FDA's recently published draft environmental guidance related to drugs with potential estrogenic, androgenic, or thyroid activity (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf>) for guidance on providing additional information in your NDA to support a claim of categorical exclusion and the statement of no extraordinary circumstances.*

**Question 3 Follow-Up:** We will discuss this topic at the meeting.

## **2.2. Nonclinical Package**

**Non-clinical Comment:** *The nonclinical studies listed in Module 4 / Appendix E appear to be adequate to file the NDA and are in agreement with the Type B meeting minutes held between the Division and the sponsor on April 13, 2015. We note however, that Segment III reproductive study is pending; we remind you that final report should be submitted with the NDA. The adequacy and completeness of all of the nonclinical studies will be a matter of review.*

**Follow-Up:** The final Segment III study report will be submitted with the Safety modules rolling submission. No additional discussion needed.

## **2.3. Clinical Package**

**Question 4:** Does the FDA agree that the proposed plan to assess cardiac risk in the TD patient population is sufficient?

**FDA Response to Question 4:** *The QT assessment is not adequate. The proposed plan to assess cardiac risk in the TD patient population is not able to rule out small clinically relevant QTc prolongation (10 ms).*

**Question 4 Follow-Up:** We understand the Division recommends data from Phase 1 evaluations that addresses small, clinically relevant QT prolongation. We will have data to cover an adequate range of clinically relevant exposures, including that observed due to poor metabolizer status and relevant drug-drug interactions. This package will include in vitro data, in vivo safety pharmacology study (dog), safety data collection from Phase 2 (1201, 1202) and Phase 3 studies (1304, 1402). The Phase 1 data includes a study with a positive control (1401); all studies include extensive digital Holter monitoring and ECGs (0901, 1301, 1401). We look forward to further discussion on this topic at the meeting.

**Question 5:** Does the FDA require submission of ECG waveforms collected for the valbenazine Phase I studies with digital monitoring to the ECG Warehouse?

**FDA Response to Question 5:** *Yes, ECG waveforms should be collected for NBI-98854-1401 and other Phase I studies, and study report and dataset should be submitted to the FDA for further review.*

**Question 5 Follow-Up:** No additional discussion needed.

**Question 6:** Does the FDA agree that the pharmacology and mechanism of action of valbenazine is well understood, and, therefore, that the Sponsor does not need to conduct a formal 8-factor analysis to evaluate abuse potential of valbenazine?

**FDA Response to Question 6:**

1. *An 8-factor analysis is written by the FDA for transmittal by the Assistant Secretary of Health at the Department of Health and Human Services (ASH/HHS) to the Drug Enforcement Administration when making a scheduling recommendation under the Controlled Substances Act (CSA). Sponsors do not need to provide an 8-factor analysis. However, sponsors must collect, evaluate and include in the NDA all data available related to the abuse potential of the drug under development, and a proposal for scheduling if deemed appropriate. Of note, a recommendation for not scheduling a drug is also considered a recommendation for scheduling.*
2. *Although the sponsor has presented data maintaining that valbenazine is not a drug of abuse and lacks abuse potential, an assessment of the abuse potential of a drug is required in the NDA. Your assessment of abuse potential should comprise a comprehensive evaluation of the chemistry, pharmacology, pharmacokinetic and pharmacodynamic profile of the drug, and evaluation of clinical data. For guidance on the characterization of the abuse potential of a drug, we refer you to the Agency's Draft Guidance for Industry on the Assessment of Abuse Potential of Drugs. This guidance can be accessed at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>*
3. *CSS is available to review non-clinical and clinical protocols prior to initiation of studies on abuse potential.*

**Question 6 Follow-Up:** We will discuss at the meeting.

#### **2.4. Data Analysis Plans**

**Question 7:** Does the FDA agree the proposed population PK analysis plan is sufficient?

**FDA Response to Question 7:** *Your proposed population PK analysis plan seems reasonable. However, please note that the population PK analysis results regarding PK interaction between NBI-98854 and NBI-98782 and concomitant drugs are informative only if the clinical studies are adequately designed to detect significant changes in drug exposure due to drug-drug interactions with optimal study procedures and sample collection protocols. Detailed information on the dose given and time of administration should be documented for the co-administered drugs.*

**Question 7 Follow-Up:** No additional discussion needed.

**Question 8:** Does the FDA agree the proposed exposure-response analysis plan is sufficient?

**FDA Response to Question 8:** *On face, the proposed exposure-response analysis plan seems reasonable based on limited information provided. However, we do have some concerns.*

*In your exposure-efficacy analysis conducted at the end of Phase 2, observed NBI-98782  $C_{max,ss}$  concentration was used as the exposure metric. However, based on the sparse sampling scheme in study NBI-98854-1304, we are concerned that you may not have collected adequate PK data in each individual to accurately estimate  $C_{max,ss}$ . You should either provide assurances that you are able to accurately characterize  $C_{max,ss}$  in NBI-98854-1304 or you may consider using model-predicted PK parameters, such as steady state average concentration as your exposure metric.*

*For exposure-safety analysis, you should provide justification for the cutoff points which are used to convert certain safety endpoints to binary outcomes including BARS, CDSS, MADRS, and SAS and explore if the results are sensitive to these cutoff points. If a trend between the exposure measure and any safety endpoint is observed, you should employ proper modeling techniques, such as logistic regression for ordinal responses, to further describe such relationships.*

**Question 8 Follow-Up:** No additional discussion needed.

**Additional Clinical Pharmacology Comments:**

*We request that you submit, with your NDA, a pharmacogenomics dataset (.xpt) which includes subject level CYP2D6 genotype information and a description of genotyping methodologies and quality controls.*

*The following are the general expectations for submitting pharmacometric data and models:*

*All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*

*Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).*

*A model development decision tree and/or table which gives an overview of modeling steps should be submitted.*

*For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.*

*In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1\_ctl.txt, run1\_lst.txt, plot1\_R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the*

*revieweraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.*

**Follow-Up:** No additional discussion needed.

**Question 9:** Given the design of the valbenazine clinical program, does the FDA agree that the body of the Integrated Summary of Efficacy can serve as the Summary of Clinical Efficacy?

**FDA Response to Question 9:** *Yes.*

**Question 9 Follow-Up:** No additional discussion needed.

**Question 10:** Does the FDA agree with the proposed statistical analysis plan for the Integrated Summary of Efficacy?

**FDA Response to Question 10:** *In general, the proposed SAP appears acceptable as we consider the Integrated Summary of Efficacy exploratory. However, trial should be included as a factor in your analyses of pooled trials. Consider using MMRM for the analyses of the pooled trials if the assessment schedule was common for the three trials. Please include analyses of the primary and key secondary efficacy endpoints by study center, where possible, for the individual trials.*

**Question 10 Follow-Up:** Trial will be used as a factor in analysis of the pooled trials. The three trials (1201, 1202, and 1304) have common blinded central AIMS video rating timepoints only at Baseline and Week 6, therefore MMRM for analyses of the pooled trials cannot be applied. The Sponsor will include analyses of the primary and key secondary efficacy endpoints by study center for each individual trial.

No additional discussion needed.

**Question 11:** Does the FDA agree with the proposed statistical analysis plan for the Integrated Summary of Safety?

**FDA Response to Question 11:** *We request you to conduct standardized MedDRA queries (SMQs) for signal detection and risk management for depression and suicide/self-injury. We have no objection to the proposed integrated summary of safety (ISS) analysis because of its exploratory nature; however, we may ask for more explorations during our NDA reviews. As proposed, the ISS only gives means and distribution but does not all provide descriptive information about clinically significant outliers, for example clinically significant hyponatremia or hypernatremia, that will be of interest to the clinical review. Additionally, the categorical conversions of dimensional scales, such as the Barnes, need to be clinically justified in the application and presented alongside of the descriptive statistics.*

**Question 11 Follow-Up:** No additional discussion needed.

## **2.5. NDA Submission Timeline, Format, and Review**

**Question 12:** Does the FDA agree that data presented to-date support the granting of both a Priority Review and an Expedited Review for the proposed valbenazine NDA indicated for the treatment of tardive dyskinesia?

***FDA Response to Question 12:*** *The data and information provided to date appear to support a Priority Review, although that final determination will be made once the NDA is submitted. Furthermore, we plan at this time, based on the available information/data and assuming a priority review designation, to act early on this application under an expedited review, provided no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action. However, these preliminary determinations will be reexamined when the safety and efficacy data are received/NDA is submitted and, as such, are subject to change.*

**Question 12 Follow-Up:** No additional discussion needed.

**Question 13:** The Sponsor proposes to submit additional long-term data in the 120-day safety update as updated adverse event (AE) tables, updated tables to demonstrate long-term efficacy, and any new data informative to the benefit/risk profile. In addition, the Sponsor will provide full narratives for any additional deaths, serious AEs, and discontinuations due to AEs. Does the FDA agree?

***FDA Response to Question 13:*** *Yes, we agree. Along with providing full narratives, please include CRFs for cases of death, serious adverse events, and discontinuations due to adverse events.*

**Question 13 Follow-Up:** No additional discussion needed.

**Question 14:** Does the FDA agree that the proposed content and format for the valbenazine NDA constitutes a fileable marketing application?

***FDA Response to Question 14:*** *Yes, we agree that the proposed submission should support an NDA filing.*

**Question 12 Follow-Up:** No additional discussion needed.

***Additional Comment:*** *In your future NDA submission, please include a listing of all interactions with the Agency pertaining to this IND/NDA including serial numbers and submission dates of the protocols, SAPs, amendments, and any relevant meetings.*

**Follow-up:** The Sponsor will include the requested listing in the NDA submission. No additional discussion needed.

### 3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 4, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later

than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

**Follow-up:** We look forward to discussion on this topic at our meeting.

# CLINICAL PHARMACOLOGY SUMMARY AID

## 1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

## 2. Question Based Review

### 2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

### 2.2 General Attributes of the Drug

#### 2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug

products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

**2.2.2 What are the proposed mechanism of action and therapeutic indications?**

**2.2.3 What are the proposed dosages and routes of administration?**

**2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?**

**2.3 General Clinical Pharmacology**

**2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?**

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

**2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

**2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal  $t_{1/2}$  and AUC.

## 2.4 Exposure-Response

### 2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

### 2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex,

race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C<sub>max</sub> or C<sub>min</sub> is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C<sub>max</sub> and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

#### **2.4.3 Does this drug prolong QT/QTc Interval?**

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

#### **2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?**

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

### **2.5 What are the PK characteristics of the drug?**

#### **2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?**

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C<sub>max</sub>, t<sub>max</sub>, AUC, C<sub>max,ss</sub>, C<sub>min,ss</sub>, C<sub>max,ss</sub>/C<sub>min,ss</sub>, t<sub>max,ss</sub>, AUC<sub>0-τ</sub>, CL/F, V/F and t<sub>1/2</sub> (half-life determining accumulation factor), accumulation factor,

fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

**2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?**

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

**2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?**

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C<sub>max</sub>, C<sub>min</sub>, CL/F and t<sub>1/2</sub> of the parent drug and relevant metabolites after single doses and at steady-state.

**2.5.4 What are the characteristics of drug absorption?**

Indicate absolute and relative bioavailability, lag time, t<sub>max</sub>, t<sub>max,ss</sub>, C<sub>max</sub>, C<sub>max,ss</sub> and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

**2.5.5 What are the characteristics of drug distribution?**

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

**2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

**2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?**

Provide identification for  $\geq 90\%$  of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to

be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

#### **2.5.8 What are the characteristics of drug metabolism?**

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

#### **2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?**

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

#### **2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?**

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

#### **2.5.11 What are the characteristics of drug excretion in urine?**

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m<sup>2</sup>) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

#### **2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?**

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C<sub>max</sub> and AUC values in healthy subjects and patients with the target

disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

### **2.5.13 How do the PK parameters change with time following chronic dosing?**

Indicate whether the mean ratio of AUC<sub>0-τ</sub> at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

### **2.5.14 Is there evidence for a circadian rhythm of the PK?**

Indicate whether C<sub>max</sub> and C<sub>min</sub> of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

## **2.6 Intrinsic Factors**

### **2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C<sub>max</sub>, C<sub>min</sub>) in patients with the target disease and how much of the variability is explained by the identified covariates?**

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C<sub>max</sub>, clearance, volume of distribution and t<sub>1/2</sub> for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

### **2.6.2 Based upon what is known about E-R relationships in the target**

## **population and their variability, what dosage regimen adjustments are recommended for each group?**

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

### **2.6.2.1 Severity of Disease State**

### **2.6.2.2 Sex**

### **2.6.2.3 Body Weight**

### **2.6.2.4 Elderly**

### **2.6.2.5 Pediatric Patients**

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

### **2.6.2.6 Race/Ethnicity**

### **2.6.2.7 Renal Impairment**

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C<sub>max</sub> and t<sub>1/2</sub> of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C<sub>max</sub> and CL/F on Cl<sub>r</sub> for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly

altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

### **2.6.2.8 Hepatic Impairment**

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C<sub>max</sub>, t<sub>max</sub> and t<sub>1/2</sub> of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C<sub>max</sub>, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

### **2.6.2.9 What pregnancy and lactation use information is available?**

### **2.6.3 Does genetic variation impact exposure and/or response?**

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

### **2.6.4 Immunogenicity (NOT applicable to small molecule drugs)**

#### **2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the**

**rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

**2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

**2.6.4.3 Do the anti-product antibodies have neutralizing activity?**

**2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?**

**2.6.4.5 What is the impact of anti-product antibodies on clinical safety?**

Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

## **2.7 Extrinsic Factors**

**2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

**2.7.2 Is the drug a substrate of CYP enzymes?**

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to  $K_m$ , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

**2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?**

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for  $K_i$ ,  $IC_{50}$  and  $V_{max}$  for each

relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/K<sub>i</sub> ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

#### **2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?**

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

#### **2.7.5 Are there other metabolic/transporter pathways that may be important?**

#### **2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?**

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

#### **2.7.7 What are the drug-drug interactions?**

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t<sub>1/2</sub>, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C<sub>max</sub> for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report  $t_{1/2}$ , point estimates and 90% confidence intervals of the geometric mean ratios of AUC and  $C_{max}$  for each of the co-administered drugs in the presence and absence of the drug of interest.

**2.7.8 Does the label specify co-administration of another drug?**

**2.7.9 What other co-medications are likely to be administered to the target population?**

**2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

**2.8 General Biopharmaceutics**

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and  $C_{max}$  after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

**IR Product**

**2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

**2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?**

**2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

**2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and**

**efficacy data support the approval of the to-be-marketed product?**

**2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?**

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

**2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?**

**2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?**

**MR product (if an IR is already marketed)**

**2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?**

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C<sub>max</sub>, AUC and C<sub>min</sub> of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

**2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?**

**2.8.8 What is evidence that MR formulation displays less variability in C<sub>max</sub>, AUC and C<sub>min</sub> than IR formulation?**

**2.8.9 Does the MR product show dose dumping *in vivo*?**

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

**2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?**

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

**2.8.11 Are the MR and IR products marketed simultaneously?**

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

**2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?**

**2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?**

**2.9 Analytical Section**

**2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?**

List all assays used and briefly describe the individual methods.

**2.9.2 Which metabolites have been selected for analysis and why?**

**2.9.3 For all moieties measured, is free, bound, or total measured?**

Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

**2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?**

Identify all studies that used a particular assay method. For each assay report

indicate the corresponding assay validation report.

**2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?**

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

**2.9.5.1 What are the lower and upper limits of quantitation?**

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

**2.9.5.2 What are the accuracy, precision, and selectivity at these limits?**

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

**2.9.5.3 What is the sample stability under conditions used in the study?**

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at  $\leq -20^{\circ}$  C.

**2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?**

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

**2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?**

**Applicable to therapeutic proteins only**

**2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?**

Briefly describe the methods and summarize the assay performance.

**2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?**

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

**2.9.5.8 What is the performance of the neutralizing assay(s)?**

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/s/  
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MITCHELL V Mathis  
03/04/2016



IND 111591

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Neurocrine Biosciences  
Attention: Kristine Kim, MS  
Director, Regulatory Affairs  
12780 El Camino Real  
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NBI-98854.

We also refer to your September 5, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that NBI-98854 for (b) (4) tardive dyskinesia meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of NBI-98854 for (b) (4) tardive dyskinesia to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

In terms of next steps, please submit a Type B meeting request. This meeting will be for a comprehensive multidisciplinary discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting.<sup>2</sup> Please refer to the *Guidance for Industry: Formal Meetings*

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup> <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

*between FDA or Sponsors and Applicants*<sup>3</sup> for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for NBI-98854 for [REDACTED] (b) (4) tardive dyskinesia is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Sharonjit Sagoo, Pharm.D., Regulatory Project Manager, at [sharonjit.sagoo@fda.hhs.gov](mailto:sharonjit.sagoo@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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<sup>3</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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/s/  
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MITCHELL V Mathis  
10/28/2014

## Benton, Sandra J

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**From:** Benton, Sandra J  
**Sent:** Thursday, October 23, 2014 7:53 AM  
**To:** Woodcock, Janet; Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Sagoo, Sharonjit; Kronstein, Phillip; Zhang, Jing; Farchione, Tiffany; Mathis, Mitchell  
**Subject:** RE: October 24, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 111591

As the Council agrees with DPP's recommendation to grant Neurocrine Biosciences' breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the October 24, 2014 meeting agenda.

Please let me know if you have any questions. Thanks!

Sandy Benton  
Senior Policy Analyst  
CDER/Office of Medical Policy  
301-796-1042  
[sandra.benton@fda.hhs.gov](mailto:sandra.benton@fda.hhs.gov)

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**From:** Woodcock, Janet  
**Sent:** Friday, October 17, 2014 1:07 PM  
**To:** Benton, Sandra J; Temple, Robert; Jenkins, John K; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Sagoo, Sharonjit; Kronstein, Phillip; Zhang, Jing; Farchione, Tiffany; Mathis, Mitchell  
**Subject:** RE: October 24, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 111591

Agree w division. Would also like to add that one dimension of "serious" ought to be "socially disabling" which these symptoms clearly can be. jw

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**From:** Benton, Sandra J  
**Sent:** Friday, October 17, 2014 10:59 AM  
**To:** Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Griebel, Donna; Mahoney, Karen M (Deputy DD, DNDP); Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Sagoo, Sharonjit; Kronstein, Phillip; Zhang, Jing; Farchione, Tiffany; Mathis, Mitchell  
**Subject:** October 24, 2014 - Medical Policy Council – Breakthrough Therapy Designation - IND 111591

Hi! OMP has scheduled a Medical Policy Council discussion on October 24, 2014 regarding the breakthrough therapy designation request from Neurocrine Biosciences, Inc for its IND 111591, NBI-98854 for the treatment of Neuroleptic-induced Tardive Dyskinesia (TD).

DPP recommends that this breakthrough therapy request be granted. Attached is DPP's background on the breakthrough therapy designation with its rationale for granting the request.

DPP has asked if this request can be reviewed by email.

Would you please review DPP's recommendation and let me know by COB Tuesday, October 21 if –

- You agree with DPP's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DPP's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DPP's recommendation regarding this breakthrough therapy request.

If the Council agrees with bullet 1, I will cancel the discussion for IND 111591.

Please let me know if you have any questions. Thank you.

Sandy Benton  
Senior Policy Analyst  
CDER/Office of Medical Policy  
301-796-1042  
[sandra.benton@fda.hhs.gov](mailto:sandra.benton@fda.hhs.gov)

<< File: CDER Medical Policy Council Brief Breakthrough Therapy Designation\_10\_16\_14.docx >> << File: IND 111591 BTDR.PDF >>

**CDER Medical Policy Council Brief**  
**Breakthrough Therapy Designation**  
*Division of Psychiatry Products*  
*October 24, 2014.*

Summary Box

1. IND Number – 111591
2. Company name – Neurocrine Biosciences, Inc.
3. Drug name – NBI-98854
4. Indication – (b) (4) Tardive Dyskinesia (TD)
5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? – Yes
6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? – There is no standard treatment regimen or approved drug for TD

Division: Psychiatry Products  
Medical officer: Phillip Kronstein, MD  
Clinical Team Leader: Jing Zhang, MD

### 1. Brief description of the drug

NBI-98854 is an orally active valine ester prodrug of a vesicular monoamine transporter 2 (VMAT2) inhibitor (NBI-98782) and is currently under development at Neurocrine Biosciences Inc. (NBI) for the treatment of (b) (4) tardive dyskinesia (TD). NBI-98782 ([+] $\alpha$ -dihydrotetrabenazine) is the most potent and selective of the four stereoisomers of dihydrotetrabenazine (DHTBZ) formed upon reduction of tetrabenazine (Xenazine<sup>®</sup> Lundbeck, Inc.), a FDA approved drug for the treatment of Huntington's chorea. NBI-98854 was designed to deliver NBI-98782 in a controlled fashion, with reduced peak plasma concentrations and pharmacokinetic (PK) variability that the sponsor states should limit off-target binding and allow for an improved safety profile in human subjects.

Twelve clinical studies with NBI-98854 have been completed to date (in a total of 419 subjects, 347 of whom have received at least one dose of NBI-98854); eight Phase 1 studies in healthy male and female subjects, including elderly, non-elderly, and hepatically impaired adults; and four Phase 2 studies in subjects with TD and a clinical diagnosis of schizophrenia or schizoaffective disorder, mood disorder, or gastrointestinal (GI) disorder.

### 2. Brief description of the disease and intended population

Tardive dyskinesia is a neurological condition characterized by involuntary movements of the orofacial region (i.e., tongue, lips, jaw, face) and choreoathetoid movements in the extremities and trunk. These signs and

symptoms develop due to long-term neuroleptic drug use and often persist after discontinuation of the offending medication. Tardive dyskinesia generally emerges as mild intensity involuntary movements with subsequent progression in severity and disability. While isolated case reports of TD even after short-term exposure exist, most often TD emerges after long-term neuroleptic treatment over months to years. The persistent and sometimes progressive nature of this involuntary movement disorder poses a significant clinical problem and therapeutic challenge for both patients and health care providers. Treating physicians are faced with the dilemma of how to balance the continuing therapeutic benefits of neuroleptic therapy with the onset of potentially disabling TD symptoms.

Second generation antipsychotics (SGA, atypicals) were introduced with the hope of avoiding side effects such as extrapyramidal symptoms or TD associated with first generation antipsychotics (FGA, typical). However, there is some evidence that the incidence of TD caused by SGAs may be similar to that caused by FGAs<sup>1</sup>. The prevalence of TD in schizophrenia patients persists at 1.1% (NIMH) and this value does not reflect the large number of psychiatric patients with other diagnoses, in particular elderly or pediatric patients, who are also at risk for developing TD due to chronic use of antipsychotics, on- or off-label.

While often of mild intensity, moderate to severe TD can be disabling and significantly impact essential day-to-day functioning and quality of life. Orofacial involuntary movements can interfere with speech, the ability to eat, and cause swallowing difficulties, which increase the risk for choking episodes. With severe cases of TD, these involuntary movements can cause bodily harm such as lip or tongue lacerations, bruises, joint inflammation, and falls<sup>2</sup>.

The pathophysiology of TD is not fully understood; however, post-synaptic dopamine hypersensitivity in the striatum is the most prominent feature. Dysregulation of dopaminergic systems is an integral component of several CNS disorders, including other hyperkinetic movement disorders and conditions such as schizophrenia and bipolar disorder. The transporter protein VMAT2 plays an important role in presynaptic dopamine release, regulating monoamine uptake from the cytoplasm to the synaptic vesicle for storage and release. The differential expression of VMAT2 in human brain (versus endocrine tissue) makes agents that selectively target VMAT2 potentially useful for the treatment of CNS disorders.

### **3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area**

For the endpoints used in the available clinical data, please see Section 6 (Description of Preliminary Clinical Evidence). At the End of Phase 2 Meeting, the FDA agreed to the use of the same endpoints in the Phase 3 study (NBI-98854-1304). This included the use of a modified Abnormal Involuntary Movement Scale (AIMS) as in the positive Phase 2 study (NBI-98854-1202).

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<sup>1</sup> Woods SW, Morgenstern H, Saks JR, Walsh BC, Sullivan MC, Money R, Hawkins KA, Gueorguieva RV, Glazer WM. Incidence of tardive dyskinesia with atypical versus conventional antipsychotic medications: a prospective cohort study. *J Clin Psychiatry*. 2010 Apr;71(4):463-74.

<sup>2</sup> Factor SA, Lang AE, Weiner WJ. Drug induced movement disorders. 2nd Edition, Wiley- Blackwell, 2005: 24.

#### **4. Brief description of available therapies (if any)**

There is no standard treatment regimen or approved drug for TD. Treatments proposed based on anecdotal evidence have failed to demonstrate efficacy when assessed in larger controlled trials (e.g., Vitamin E)<sup>3</sup>. The first step in treatment is generally to stop or minimize the use of the neuroleptic drug suspected of causing the condition. However, the therapeutic strategy of discontinuing neuroleptics in the schizophrenia and bipolar disorder patient populations typically results in an acute exacerbation of TD symptoms and an increased risk for harmful psychotic decompensation. When a change in medication can be tolerated, replacement of the offending drug with an alternative antipsychotic drug may be beneficial. However, the alternative drug may not be as effective, and there is a risk of agranulocytosis with clozapine (which appears to have a lower risk of TD).

#### **5. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation**

N/A

#### **6. Description of preliminary clinical evidence**

Most important with regard to this application for “breakthrough therapy” designation are the results of Study NBI-98854-1202, a Phase 2, randomized, double-blind, placebo-controlled, 6-week dose-titration study. A total of 100 subjects with schizophrenia/schizoaffective disorder, mood disorder, or GI disorder and TD were randomized (51 to NBI-98854, 49 to placebo). The starting NBI-98854 once daily dose was 25 mg, which was escalated (if allowed according to escalation criteria) in increments of 25 mg every 2 weeks to a maximum of 75 mg in order to achieve an optimal dose of NBI-98854 for each subject.

The primary efficacy endpoint was the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score (items 1-7) change from baseline at Week 6, based on the blinded, central AIMS video raters’ assessment and using the PP analysis set. Of note, a modified AIMS was used, with an alternate version of score descriptors. For the AIMS dyskinesia total score and change from baseline by visit, see Table 1.

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<sup>3</sup> Adler LA, Rotrosen J, Edson R, Lavori P, Lohr J, Hitzemann R, Raisch D, Caligiuri M, Tracy K. Vitamin E treatment for tardive dyskinesia. Veterans Affairs Cooperative Study #394 Study Group. Arch Gen Psychiatry. 1999 Sep;56(9):836-41.

**Table 1 AIMS Dyskinesia Total Score and Change from Baseline by Visit and Treatment (Central Video Raters)**

| Visit             | Statistic or Category | Placebo <sup>a</sup><br>N=44 | PP Analysis Set<br>NBI-98854<br>N=32 | ITT Analysis Set<br>NBI-98854<br>N=45 |
|-------------------|-----------------------|------------------------------|--------------------------------------|---------------------------------------|
| Baseline (Day -1) | Mean (SEM)            | 7.9 (0.7)                    | 8.0 (0.6)                            | 8.0 (0.5)                             |
|                   | SD                    | 4.5                          | 3.3                                  | 3.5                                   |
|                   | Median                | 7.0                          | 7.0                                  | 7.0                                   |
|                   | Min, max              | 1, 23                        | 3, 17                                | 3, 18                                 |
| Week 6            | Mean (SEM)            | 6.8 (0.6)                    | 3.8 (0.6)                            | 4.4 (0.5)                             |
|                   | SD                    | 4.1                          | 3.6                                  | 3.4                                   |
|                   | Median                | 7.0                          | 3.5                                  | 4.0                                   |
|                   | Min, max              | 1, 21                        | 0, 13                                | 0, 13                                 |
| Week 6 CFB        | Mean (SEM)            | -1.1 (0.6)                   | -4.3 (0.6)                           | -3.6 (0.5)                            |
|                   | SD                    | 3.7                          | 3.2                                  | 3.5                                   |
|                   | Median                | -0.5                         | -4.0                                 | -3.0                                  |
|                   | Min, max              | -11, 7                       | -11, 1                               | -11, 3                                |

Data source: NBI-98854-1202 Clinical Study Report, Tables 14.14.1 and 14.14.2.

AIMS=Abnormal Involuntary Movement Scale; CFB=change from baseline; ITT=intent-to-treat; PP=per protocol.

<sup>a</sup>The placebo group is the same for the PP and ITT analysis sets.

The results for the primary efficacy endpoint are shown in Table 2 (ANCOVA was the pre-specified analysis).

**Table 2 Analysis of the Central Video Raters AIMS Dyskinesia Total Score Change from Baseline at Week 6 (PP and ITT Analysis Set)**

| Statistic  | PP Analysis Set  |                   | ITT Analysis Set |                   |
|--|------------------|-------------------|------------------|-------------------|
|  | Placebo<br>N=44  | NBI-98854<br>N=32 | Placebo<br>N=44  | NBI-98854<br>N=45 |
| Mean (SEM)   | -1.1 (0.6)       | -4.3 (0.6)        | -1.1 (0.6)       | -3.6 (0.5)        |
| SD   | 3.7              | 3.2               | 3.7              | 3.5               |
| Median   | -0.5             | -4.0              | -0.5             | -3.0              |
| Min, max   | -11, 7           | -11, 1            | -11, 7           | -11, 3            |
| LS mean (SEM) <sup>a</sup>                           | -0.3 (1.1)       | -3.4 (1.2)        | -0.2 (1.1)       | -2.6 (1.2)        |
| 95% Confidence interval                              | (-2.5, 1.8)      | (-5.7, -1.0)      | (-2.4, 2.0)      | (-4.9, -0.3)      |
| LS mean difference<br>NBI-98854 vs. placebo<br>(SEM) | -3.0 (0.7)       |                   | -2.4 (0.7)       |                   |
| 95% Confidence interval                              | (-4.5, -1.6)     |                   | (-3.7, -1.1)     |                   |
| <b>p-value<sup>b</sup></b>                           | <b>&lt;.0001</b> |                   | <b>0.0005</b>    |                   |

Data source: NBI-98854-1202 Clinical Study Report, Tables 14.14.6 and 14.14.7.

AIMS=Abnormal Involuntary Movement Scale; ITT=Intent-to-Treat; LS=least squares; PP=Per Protocol.

<sup>a</sup>Least-squares mean based on the analysis of covariance (ANCOVA) model, which includes baseline AIMS dyskinesia total score value as a covariate and treatment group and disease category as fixed effects.

<sup>b</sup>p-value for test of null hypothesis that difference between treatment group LS means is equal to zero.

The pre-specified responder rate at Week 6 ( $\geq 50\%$  improvement from baseline) was 59.4% in the NBI-98854 group compared with 18.2% in the placebo group for the PP analysis set ( $p=0.0002$ ; 95% CI: 20.7, 61.7) and 48.9% compared with 18.2% in the ITT analysis set ( $p=0.0022$ ; 95% CI: 12.2, 49.2).

The improvement in Week 6 AIMS was also corroborated by a pre-specified key secondary endpoint, CGI-TD, which showed 67% of the subjects taking NBI-98854 were “much improved” or “very much improved” at Week 6 compared to only 16% of the placebo subjects ( $p<0.0001$ ; PP analysis set). Comparable statistical significance was demonstrated for the ITT analysis set.

While most schizophrenia subjects with TD appear to have limited insight into their dyskinetic movements, the sponsor notes that study subjects with TD appear to be quite capable of detecting change (e.g., when scoring the Patient Global Impression of Change (PGIC)) in a manner consistent with the CGI-TD and supportive of clinical meaningfulness. The PGIC responder rate (i.e., much improved or very much improved) for subjects randomized to NBI-98854 was 58% vs. 32% for placebo recipients.

## **7. Division’s recommendation and rationale**

- Recommendation: We recommend that the request for “breakthrough therapy” designation be granted.
- Rationale: Neuroleptic-induced tardive dyskinesia (TD) is clearly a serious condition in some patients. The FDA found the preliminary evidence for the efficacy of NBI-98854 in TD to be promising, based on the results of the Phase 2 Study NBI-98854-1202.

## **8. Division’s next steps and sponsor’s plan for future development**

The sponsor has recently received clinical and stats comments for their Phase 3 study (NBI-98854-1304) and are expected to start enrolling patients shortly. At the End-of-Phase 2 meeting, the FDA stated that the positive Phase 2 study (NBI-98854-1202) could potentially serve as a second pivotal trial.

## **9. References (if any)**

Please see footnotes.

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/s/  
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SANDRA J BENTON  
10/24/2014

MITCHELL V Mathis  
10/24/2014



IND 111591

**MEETING MINUTES**

Neurocrine Biosciences, Inc.  
Attention: Kristine Kim, M.S.  
Manager, Regulatory Affairs  
12780 El Camino Real  
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NBI-98854.

We also refer to the meeting between representatives of your firm and the FDA on June 24, 2014. The purpose of the meeting was to discuss and obtain Agency agreement on the NBI-98854 nonclinical and clinical development plan to support a new drug application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sharonjit Sagoo, Pharm.D., Regulatory Project Manager at [sharonjit.sagoo@fda.hhs.gov](mailto:sharonjit.sagoo@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** June 24, 2014 at 9:30 AM – 11:30 AM EDT  
**Meeting Location:** FDA, White Oak Building 22, Conference Room 1419

**Application Number:** IND 111591  
**Product Name:** NBI-98854  
**Indication:** (b) (4) tardive dyskinesia  
**Sponsor/Applicant Name:** Neurocrine Biosciences, Inc.

### FDA ATTENDEES

|                           |   |
|---------------------------|---|
| Ellis Unger, M.D.         | Director, Office of New Drugs – Office of Drug Evaluation I (ODE I)   |
| Robert Temple, M.D.       | Deputy Director, Office of New Drugs – ODE I                          |
| Mitchell Mathis, M.D.     | Director, Division of Psychiatry Products (DPP)                       |
| Silvana Borges, M.D.      | Acting Medical Team Leader, DPP                                       |
| Kofi Kumi, Ph.D.          | Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP) |
| Huixia Zhang, Ph.D.       | Clinical Pharmacology Reviewer, OCP                                   |
| Kevin Krudys, Ph.D.       | Pharmacometrics Reviewer, OCP   |
| Aisar Atrakchi, Ph.D.     | Pharmacology/Toxicology Supervisor, DPP                               |
| Imran Khan, Ph.D.         | Pharmacology/Toxicology Reviewer, DPP                                 |
| Sharonjit Sagoo, Pharm.D. | Regulatory Project Manager, DPP                                       |

### SPONSOR ATTENDEES

|                         |   |
|-------------------------|---|
| Chris O'Brien, M.D.     | Chief Medical Officer                   |
| Haig Bozigian, Ph.D.    | Chief Development Officer               |
| Ajay Madan, Ph.D., DABT | Vice President, Preclinical Development |
| Josh Burke, M.S.        | Director, Biostatistics                 |
| Rosa Luo, MS            | Director, CMC API                       |
| Cheryl Chen             | Sr. Director of Clinical Operations     |
| Kristine Kim, MS        | Director, Regulatory Affairs            |
| Antonie Horton          | Associate, Regulatory Affairs           |

(b) (4)

## 1.0 BACKGROUND

NBI-98854 is a prodrug of the vesicular monoamine transporter 2 (VMAT2) inhibitor NBI-98782, under development for the treatment of (b) (4) tardive dyskinesia (TD). NBI-98782 is a potent stereoisomer of dehydrotetrabenazine, a metabolite of tetrabenazine, currently approved by the FDA for the treatment of Huntington's chorea. This development program received Fast Track designation on January 24, 2012.

The sponsor states that NBI-98854 was designed to deliver NBI-98782 in a controlled fashion with reduced peak plasma concentrations and pharmacokinetic (PK) variability to limit off-target binding and allow for an improved safety profile in human subjects. The metabolism of NBI-98854 is characterized by esterase-dependent conversion of NBI-98854 to NBI-98782, and CYP3A4/5-dependent mono-oxidation of NBI-98854. The elimination of NBI-98782 is in part catalyzed by CYP2D6. NBI-98854 appears to cause little or no cytochrome P450 (CYP) enzyme inhibition or induction at pharmacologically relevant concentrations.

To date, several Phase 1 clinical studies and four Phase 2 studies have been conducted in healthy subjects and in patients with schizophrenia, schizoaffective disorder, mood disorder, or gastrointestinal disorder and TD with NBI-98854 single doses up to 300 mg and multiple doses up to 100 mg for up to 2 weeks:

1. **Study 1001** (n = 6) was a 12-day open-label, dose-titration study of NBI-98854 12.5, 25, and 50 mg QD in subjects with schizophrenia or schizoaffective disorder and TD. Efficacy analysis showed an improvement in TD as measured by the abnormal involuntary movement scale (AIMS).
2. **Study 1101** (n=37) was a double-blind, placebo-controlled, 2 period crossover, 2- week study of NBI-98854 12.5 mg and 50 mg QD in patients with schizophrenia or schizoaffective disorder with TD. No statistical difference between NBI-98854 and placebo was observed on the study primary endpoint: change from baseline on the AIMS (items 1-7).
3. **Study 1201** (n=157) was a double-blind, placebo-controlled, 6-week study of NBI-98854 50 mg and 100 mg QD in patients with schizophrenia or schizoaffective disorder with TD. No statistical difference between NBI-98854 and placebo was observed on the study primary endpoint: change from baseline on the AIMS (items 1-7).

In light of the results of studies 1101 and 1201 and while Study 1202 was ongoing, a Scientific Advisory Board (SAB) was convened and provided advice to:

- Employ blinded, central raters by 2 movement disorder neurologists
- Generate consensus scores for items 1-7 of the AIMS
- Randomize the sequence of videos to score
- Use a modified AIMS with alternate version of score descriptors

The items on the AIMS are scored as follows: 0= None, 1=minimal, 2=mild, 3=moderate, 4=severe. A score of 1 is given when the movement is minimal (may be extreme normal), while a score of 2 is given when slight dyskinesia is present. After advice from the SAB, the sponsor proposed to score slight dyskinesia as 1 (together with minimal movement that could be considered normal), reserving a score of 2 for movements of low amplitude present during most of the exam or of moderate amplitude present during some of the exam).

4. **Study 1202** (n=102) was a double-blind, placebo-controlled, 6-week, flexible-dose study of NBI-98854 25-75 mg QD in patients with schizophrenia, schizoaffective disorder, mood disorder, or GI disorder with TD. This study was amended to modify the way the AIMS was scored following SAB recommendations. NBI-98854 showed superiority over placebo on the study primary endpoint, change from baseline on AIMS (1-7): Placebo -1.1, NBI-98854 -3.6, p=0.0005.

Regarding NBI-98854 safety profile, thirteen treatment-emergent serious adverse events (SAEs) among 10 subjects have been reported, including TD, schizophrenia, schizoaffective disorder, suicidal ideation, fall, chest pain, bronchitis, and chronic obstructive pulmonary disease in patients receiving NBI-98854. Serum prolactin was typically increased with NBI-98854 single and multiple doses. No other cardiovascular, laboratory, or vital sign-related safety signals have been identified.

As part of NBI-98854 development program, the sponsor is proposing to conduct one Phase 3 pivotal trial and two safety studies as follows:

- **Proposed Phase 3 study (Study 1304)** (n=200): double-blind, placebo-controlled, 8-week, flexible-dose study of NBI-98854 40-80 mg QD in patients with schizophrenia, schizoaffective disorder, mood disorder, or GI disorder with TD. Primary endpoint: Change from baseline on AIMS (1-7) with modified AIMS score descriptors. Key Secondary endpoint: percentage of responders based on CGI-I TD.
- **Proposed Safety studies**
  - 40 week extension of study 1304
  - Study 1402 (n=100): an open-label, 48-week study of NBI-98854 40-80 mg QD in patients with schizophrenia, schizoaffective disorder, mood disorder, or GI disorder with TD.

The sponsor estimates that, at the time of the NDA submission, the NBI-98854 safety database would include approximately 847 subjects exposed to at least one single dose of NBI-98854, approximately 182 subjects exposed to NBI-98854 for 6 months, and approximately 197 subjects exposed to NBI-98854 for 40 weeks.

The purpose of this Type B, End of Phase 2 meeting is to discuss and obtain Division agreement on the NBI-98854 nonclinical and clinical development plan to support a New Drug Application (NDA).

## 2. DISCUSSION

### 2.1. Nonclinical

**Question 1:** Does the Division agree with the proposed study design for in vitro Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 Mouse Fibroblasts?

**FDA Response to Question 1:**

*On face the design for the in vitro Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 Mouse Fibroblasts appears to be appropriate; however, the validity of the design and adequacy of the study results will be a matter of review upon submission of your NDA.*

**Discussion at Meeting:**

*No further discussion.*

**Question 2:** All abundant circulating metabolites in humans are produced in the rat and dog and the completed toxicology studies provide adequate qualification of NBI-98854 and its major metabolites. Does the Division agree?

**FDA Response to Question 2:**

*Yes, based on the information provided in the Briefing Package as well as previously submitted pharmacokinetic study reports it appears that all abundant circulating metabolites in humans are produced in the rat and dog and the completed toxicology studies could provide adequate qualification of NBI-98854 and its metabolites. However, the final assessment and adequacy of the data will be a matter of review upon submission of your NDA.*

**Discussion at Meeting:**

*No further discussion.*

**Question 3:** The segment 3 prenatal and postnatal development study will be conducted in rats. Does the Division agree?

**FDA Response to Question 3:**

*Yes, this approach appears adequate.*

**Discussion at Meeting:**

*No further discussion.*

**Question 4:** Based on the absence of immune-related adverse signals from toxicity studies conducted to date, does the Division agree that immunotoxicity studies need not be conducted for NBI-98854?

**FDA Response to Question 4:**

*On face, based on the submitted studies in the briefing package it appears that additional immunotoxicity studies may not be needed. However, the final assessment and adequacy of the data will be a matter of review upon submission of your NDA.*

**Discussion at Meeting:**

*No further discussion.*

**Question 5:** Does the Division agree that the data package presented for the ongoing and completed nonclinical studies is sufficient to support conduct of Phase 3 clinical studies for NBI-98854?

**FDA Response to Question 5:**

*On face, the data package presented for the ongoing and completed nonclinical studies appears sufficient to support conduct of Phase 3 clinical studies for NBI-98854. However, the adequacy of the submitted data to support phase 3 studies will be a matter of review upon submission of the full protocols for phase 3 studies under your IND.*

**Discussion at Meeting:**

*No further discussion.*

**Question 6:** Does the Division agree that the planned, ongoing, and completed nonclinical studies will support an NDA for NBI-98854 for the treatment of tardive dyskinesia?

**FDA Response to Question 6:**

*On face, it appears that the planned, ongoing, and completed nonclinical studies would support submission of an NDA for NBI-98854 for the treatment of tardive dyskinesia. However, the adequacy of the submitted data will be a matter of review of the studies upon submission of your NDA.*

**Discussion at Meeting:**

*No further discussion.*

## 2.2. Clinical

**Question 7:** Does the Division agree that the completed, ongoing and planned drug-drug interaction studies, special populations, and TQT studies are sufficient to support an NDA for NBI-98854?

**FDA Response to Question 7:**

*On face, your clinical pharmacology program appears to be sufficient to support an NDA filing. However, if the commercial formulation is different from what is to be used in the proposed Phase 3 trials, a bioequivalence study and food effect study will be required.*

**Discussion at Meeting:**

*No further discussion.*

**Question 8:** Does the Division agree with the Sponsor's proposal to not quantitate NBI-136110 in the proposed pivotal Phase 3 and open-label safety studies?

**FDA Response to Question 8:**

*On face, this approach appears acceptable.*

**Discussion at Meeting:**

*No further discussion.*

**Question 9:** Does the Division agree with the Sponsor's proposed conduct of a single pivotal study to confirm efficacy of NBI-98854?

**FDA Response to Question 9:**

*No, we do not agree. Two or more studies demonstrating efficacy of NBI-98854 for the treatment of TD would be required.*

**Neurocrine Response to FDA Preliminary Response on Question 9:**

The Sponsor will discuss the adequacy of the 1202 trial as a demonstration of efficacy in addition to the proposed 1304 study at the meeting.

**Neurocrine Follow-Up to Question 9:**

Does the Division agree that the 1202 study is an adequate and well controlled trial?

**Discussion at Meeting:**

*The sponsor stated that they considered study 1202 to be a valid study to support NBI-98854 registration for the treatment of TD. We raised several concerns regarding the merits of study 1202 to serve as one of the pivotal studies in support of NBI-98854 registration for the treatment of TD, including the flexible-dose design of the study and the change in the rating methods for the primary endpoint (i.e. change from on-site raters to central raters, and change in the AIMS score descriptors) while the study was ongoing. The sponsor argued that the changes in the rating methods for the primary endpoint for study 1202 were conducted preceding any efficacy analysis. We stated that the evaluation of the sponsor's arguments could not be possible without evaluating the data from study 1202. The sponsor proposed to submit the study report for study 1202 before the meeting minutes for this meeting were finalized.*

**Post meeting note:**

*On July 7, 2014 the sponsor submitted the draft Clinical Study Report for study 1202 to the IND. After a preliminary review of this document, we believe that study 1202 could potentially provide evidence in support of NBI-98854 registration for the treatment of TD. However, we have concerns about the change in the AIMS score descriptors for the evaluation of study 1202 primary outcome. We recommend that you submit your detailed rationale in support of such change.*

*A comprehensive review of the study 1202 design, methods, and results is beyond the scope of these meeting minutes. We do have some concern that this flexible-dose study, in which most patients needed a dose increase up until week 4, does not truly describe the dose-response relationship. Additional comments regarding study design and dose selection for your phase 3 trials are provided under question #10.*

**Question 10:** Does the Division agree with the Sponsor's proposed doses and regimen for the Phase 3 studies?

**FDA Response to Question 10:**

*No, we do not agree. Your plan to study flexible doses of NBI-98854 40-80 mg is less than optimal to fully explore the effective dose range. It is important to establish the full dose-response relationship of your drug to appropriately label the product with respect to both safety and efficacy. We recommend that you select a wider range of doses to capture both the minimal effective dose as well as maximal effective dose (without significant side-effects). We also note that fixed-dose studies would be more informative in the evaluation of NBI-98854 dose-response relationship.*

**Neurocrine Response to FDA Preliminary Response on Question 10:**

1. The Sponsor is proposing a fixed-dose study design, rather than a flexible dose study, with a fixed-dose of 40 mg with possible up titration for non-responders. This trial design reflects intended clinical practice and will provide evidence to support adequate directions for use in the labeling.
2. The Sponsor plans to discuss the available exposure safety and efficacy data set. (Refer to Figure 15 on page 82 in the briefing package.)

**Discussion at Meeting:**

*We recommended that the sponsor conduct a fixed-dose study in which patients are randomized to one of two doses (e.g. 40 mg or 80 mg) or placebo from the beginning of the study. A brief titration period (not to exceed two weeks) for patients in the 80 mg group would be acceptable. The possibility for patients in the 80 mg group to have their dose decreased for safety reasons would also be acceptable. Regarding the second phase 3 trial, the sponsor proposed a flexible-dose study of NBI-98854 40 mg and 80 mg, similar to the first phase 3 trial. We reiterated our thoughts on the flexible-dose design.*

**Post meeting note:**

*Regarding the study design for your phase 3 clinical trials, we would like to emphasize that, in order to evaluate NBI-98854 efficacy at different doses, patients should be kept on the studied dose (e.g. 40 mg) for the entire duration of the study, unless the dose is not tolerated. With regard to the dose selection for your second phase 3 trial, we strongly recommend that you study additional doses (b) (4). As mentioned in our preliminary comments, we recommend that you select a wider range of doses to capture both the minimal effective dose as well as the maximal effective dose (without significant side-effects). Additionally, given our comments on study design, dose selection, rating methods, and frequency of study visits, we encourage you to submit your phase 3 trial protocols to the IND for review and to obtain our feedback prior to initiation of the studies.*

**Question 11:** Does the Division agree with the proposed study design and study population for the pivotal Phase 3 efficacy study?

**FDA Response to Question 11:**

*We agree with the inclusion of patients with schizophrenia, schizoaffective disorder, or mood disorder with antipsychotic-induced TD as the study population for your pivotal clinical trials. However, we are not convinced that patients with GI disorders and metoclopramide-induced TD belong to the same study population as patients with psychiatric disorders. It is*

*also not clear what indication you would pursue with the inclusion of patients with GI disorders and TD. Additionally, given that the pharmacological profile of NBI-98854 is closely related to that of antipsychotic agents, it could be expected for NBI-98854 to improve symptoms in patients who are acutely ill. Therefore, it is critical that patients with schizophrenia, schizoaffective disorder, or mood disorder have their symptoms controlled upon enrollment in the studies in order to discriminate NBI-98854 effect on acute symptoms from its effect on TD. In previous communications with you, it was recommended that symptom severity threshold scores, for instance, in the CGI-S, individual items of the PANSS, and PANSS total score be used for selecting patients with schizophrenia for enrollment. We also note that, in your proposed 8-week pivotal trial, you plan to perform AIMS and PANSS testing only at weeks 4 and 8. In order to characterize the effect of your drug, more frequent testing would be necessary. Additionally, we have great concerns on your proposed change in the AIMS score descriptors. On face, we do not agree with this approach in the evaluation of your primary efficacy endpoint. Please also refer to our answer to question#10 regarding dose selection and the need for fixed-dose studies. Additional and more detailed comments on your phase 3 studies could be provided upon submission of your full protocols under the IND.*

**Neurocrine Response to FDA Preliminary Response on Question 11:**

1. The pathophysiology of Tardive Dyskinesia is the same regardless of underlying medical condition; all are due to dopamine antagonist exposure.
2. The Sponsor agrees that only stable psychiatric patients will be enrolled.
3. Sponsor will add additional AIMS and PANSS testing at week 2.
4. The AIMS scale has been preserved; the anchors of the original AIMS have been maintained (none, minimal, mild, moderate, severe) and the assessment is applied consistently for both placebo and active in a prospective manner.

**Discussion at Meeting:**

*The sponsor agreed not to include patients with GI disorders and metoclopramide-induced TD in their studies. We stated that, as described in the sponsor's briefing package, the phase 3 trial would include patients with schizophrenia with PANSS total scores  $\leq 80$ . We noted that symptom stability in patients with schizophrenia is usually assessed, among other parameters, as a PANSS total score  $\leq 70$ . The sponsor agreed to exclude patients with schizophrenia with PANSS total scores  $> 70$ . With regard to the use of central raters, we stated that we do not object the use of central raters, as long as that is pre specified in the protocol and SAP. Regarding the use of modified AIMS descriptors, the sponsor presented their rationale for their change, including videos of patients at different study visits as examples., We encouraged the sponsor to include their rationale and to pre-specify the rating methods to be used for their primary endpoint (i.e. AIMS descriptors, central vs. on-site raters, etc.) in their proposed phase 3 protocols.*

**Post meeting note:**

*Although we do not object to your use of central raters, we would expect the same rating method to be used at each study visit for the evaluation of the primary endpoint. We also note that, as currently written, your proposed 8-week phase 3 trial includes evaluation of the*

*primary endpoint (AIMS) only at baseline, week 4 and week 8. In order to characterize the effect of your drug, more frequent testing would be necessary.*

**Question 12:** Does the Division agree with the proposed primary and secondary endpoints and statistical analysis plan for the pivotal Phase 3 efficacy study?

**FDA Response to Question 12:**

*The change from baseline on the total score for the first 7 items of the AIMS would be acceptable as a primary endpoint for your pivotal trials. However, please refer to our response to question #11 regarding the use of modified AIMS score descriptors.*

(b) (4)

(b) (4)

**Neurocrine Response to FDA Preliminary Response on Question 12:**

See Question 11 for AIMS. We will analyze CGI as a continuous variable.

**Discussion at Meeting:**

*No further discussion.*

**Question 13:** Does the Division agree with the Sponsor's proposal of when suicidal ideation will be reported as an adverse event?

**FDA Response to Question 13:**

*No, we do not agree. We expect that patients would be assessed for suicidal ideation and behavior with an acceptable instrument (e.g. C-SSRS) at baseline and any worsening of the patient's score on the same instrument at any study visit would be reported as an adverse event.*

**Neurocrine Response to FDA Preliminary Response on Question 13:**

The Sponsor has proposed that all worsening of suicidal ideation (on the C-SSRS) is reported as an adverse event. We do not understand the nature of the preliminary written comment and request clarification.

**Discussion at Meeting:**

*We clarified that the baseline to which all subsequent C-SSRS scores should be compared for assessment of suicidal ideation/behavior as an adverse event should be based on a recent history prior to screening (e.g. 1 month). Using longer periods of time before screening or lifetime history of suicidal ideation/behavior for the baseline C-SSRS measurement would minimize the drug effect on this safety parameter and would not be acceptable.*

**Question 14:** Does the Division agree that the proposed open-label safety study is acceptable to assess the safety of chronic NBI-98854 use?

**FDA Response to Question 14:**

*On face, the proposed open-label studies appear acceptable to evaluate the safety of longer-term NBI-98854 use. However, to support an NDA submission, you would have to meet the ICH E1 guidelines for the number of subjects exposed to NBI-98854.*

**Neurocrine Response to FDA Preliminary Response on Question 14:**

See Question 15.

**2.3. Regulatory**

**Question 15:** Does the Division agree that the proposed number of subjects in the NBI-98854 safety database supplemented by an evaluation of safety data published from the Xenazine NDA, FDA AERS Database, and international safety data for tetrabenazine is sufficient to support a NDA submission?

**FDA Response to Question 15:**

*No, we do not agree. Your NDA submission would have to include safety data from a sufficient number of subjects exposed to NBI-98854 to meet ICH E1 guidelines.*

**Neurocrine Response to FDA's Preliminary Response to Question 15:**

We believe that we have proposed an adequate safety database for a serious disease with no available therapy. We would like to discuss this further with the Division.

**Discussion at Meeting:**

*We stated that the expected number of subjects exposed to NBI-98854 could be sufficient to file an NDA, given that a second phase 3 trial would increase the number of patients exposed to NBI-98854 and that there are publicly available sources of safety data for tetrabenazine.*

**Question 16:** Does the Division agree with the proposed strategy for the NBI-98854 Pediatric Study Plan submission?

**FDA Response to Question 16:**

 (b) (4)

**Discussion at Meeting:**

*No further discussion.*

**Additional Question:**

Do the existing clinical data support breakthrough therapy designation?

**Discussion at Meeting:**

*We stated that we could not address this question at this time, that the standards for breakthrough therapy designation were higher than for Fast Track designation and involved evaluation by several officials within CDER. We also stated that it was the sponsor's decision to proceed with a request for breakthrough therapy designation.*

### **3.0 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **3.1 DATA STANDARDS FOR STUDIES**

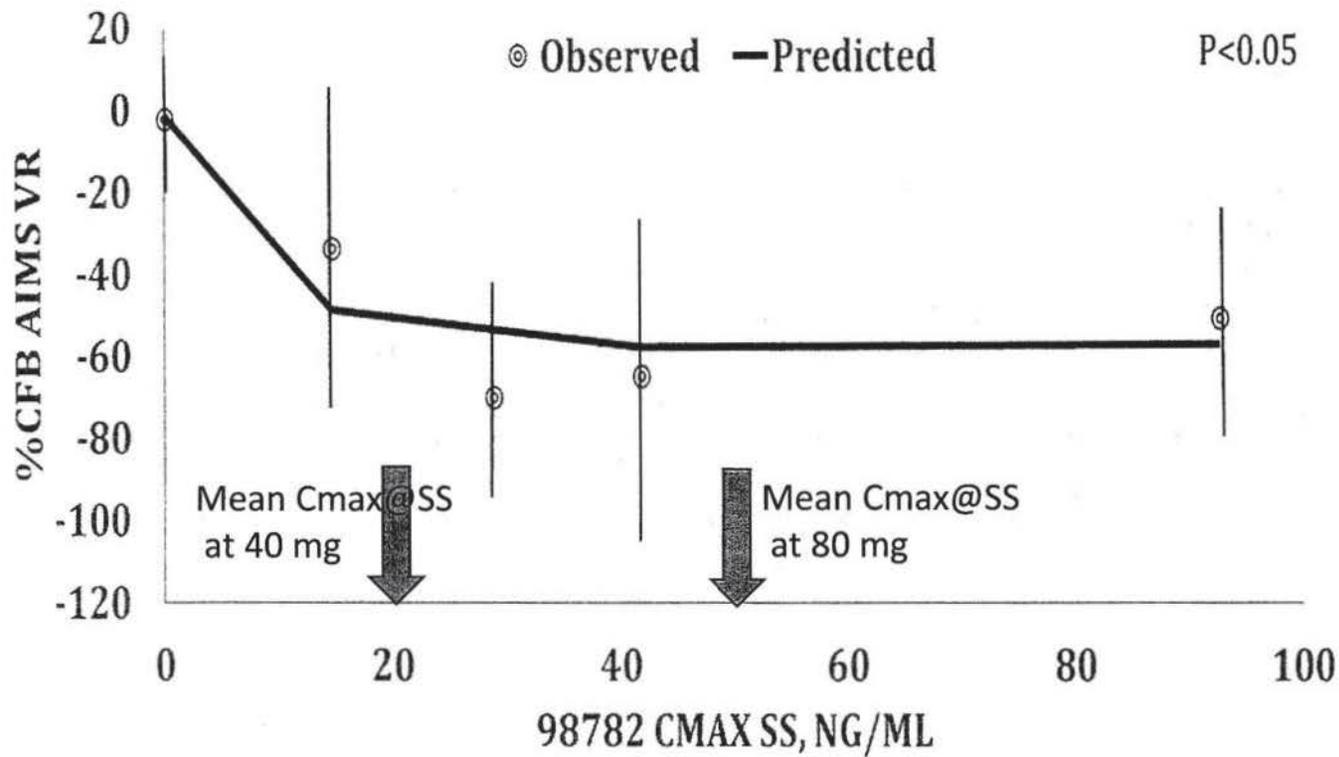
CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

### **3.2 LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review.

Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests \(http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm\)](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

4.0 ATTACHMENTS AND HANDOUTS



**AIMS Score Descriptors Comparison**

| Score | AIMS (NIMH 1976) | AIMS Score Descriptors for Studies NBI-98854-1001, -1101, and -1201   | AIMS Score Descriptors for Study NBI-98854-1202  |
|-------|------------------|---|--|
| 0     | None             | None  | None: No dyskinesia  |
| 1     | Minimal          | Minimal: given when there is some movement, but you are not sure that it is TD. May be at upper extreme of normal range | Minimal or slight dyskinesia: Low amplitude, present during some but not most of the exam                                  |
| 2     | Mild             | Mild: rated if movements are definitely TD, however slight  | Mild dyskinesia: Low amplitude and present during most of the exam (or moderate amplitude and present during some of exam) |
| 3     | Moderate         | Moderate: assigned when there is an increase in amplitude and frequency of movements                                    | Moderate dyskinesia: Moderate amplitude and present during most of exam  |
| 4     | Severe           | Severe: rated if movements are constant, very noticeable, unsightly. Sharp increase of amplitude and frequency          | Severe dyskinesia: Maximal amplitude and present during most of exam   |

| Facial and Oral Movements  | None         | Minimal | Mild | Moderate | Severe |
|--|--------------|---------|------|----------|--------|
| <b>1. Muscles of Facial Expression</b><br>e.g., movements of forehead, eyebrows, periorbital area, cheeks, include frowning, blinking, smiling, grimacing  | 0            | 1       | 2    | 3        | 4      |
| <b>2. Lips and perioral area</b><br>e.g., puckering, pouting, smacking   | 0            | 1       | 2    | 3        | 4      |
| <b>3. Jaw</b> e.g., biting, clenching, chewing, mouth opening, lateral movement  | 0            | 1       | 2    | 3        | 4      |
| <b>4. Tongue</b><br>Rate only increase in movement both in and out of mouth, NOT inability to sustain movement   | 0            | 1       | 2    | 3        | 4      |
| Extremity Movements  |              |         |      |          |        |
| <b>5. Upper (arms, wrists, hands, fingers)</b><br>Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e., repetitive, regular, rhythmic) | 0            | 1       | 2    | 3        | 4      |
| <b>6. Lower (legs, knees, ankles, toes)</b><br>e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot  | 0            | 1       | 2    | 3        | 4      |
| Trunk Movements  |              |         |      |          |        |
| <b>7. Neck, shoulders, hips</b><br>e.g., rocking, twisting, squirming, pelvic gyrations  | 0            | 1       | 2    | 3        | 4      |
| Global Judgments   |              |         |      |          |        |
| <b>8. Severity of abnormal movements overall</b>   | None, Normal | Minimal | Mild | Moderate | Severe |
| <b>9. Incapacitation due to abnormal movements</b>   | 0            | 1       | 2    | 3        | 4      |
| <b>10. Subject's awareness of abnormal movements (rate only Subject's report)</b> 0=No awareness, 1=Aware, no distress, 2=Aware, mild distress, 3=Aware, moderate distress, 4=Aware, severe distress   | 0            | 1       | 2    | 3        | 4      |
| Dental Status  |              |         |      |          |        |
| <b>11. Current problems with teeth and/or dentures</b>   |              |         |      | No       | Yes    |
| <b>12. Does the subject usually wear dentures?</b>   |              |         |      | No       | Yes    |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MITCHELL V Mathis  
07/30/2014

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



NDA 209241

**LATE-CYCLE MEETING MINUTES**

Neurocrine Biosciences, Inc.  
Attention: Kristine Kim, M.S.  
Director, Regulatory Affairs  
12780 El Camino Real  
San Diego, CA 92130

Dear Ms. Kim:

Please refer to your New Drug Application (NDA) dated August 11, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ingrezza (valbenazine) 40mg Capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 7, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mona Kalsi, Regulatory Project Manager at (240) 402-8977.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, MD  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** February 7, 2017  
09:00 AM to 10:30 AM (EST)

**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1315

**Application Number:** NDA 209241

**Product Name:** Ingrezza (valbenazine) 40mg Capsules

**Applicant Name:** Neurocrine Biosciences, Inc.

**Meeting Chair:** Mitchell V. Mathis, MD

**Meeting Recorder:** Mona Kalsi, PharmD

**FDA ATTENDEES**

|                             |   |
|-----------------------------|---|
| Ellis Unger, MD             | Director, Office of Drug Evaluation I                     |
| Mitchell Mathis, MD         | Director, Division of Psychiatry Products (DPP)           |
| Tiffany Farchione, MD       | Deputy Director, DPP                                      |
| Michael Davis, MD, PhD      | Medical Officer, DPP                                      |
| Marc Stone, MD              | Deputy Director for Safety, DPP                           |
| Brian Miller, MD, MBA, MPH  | Medical Officer, Safety Team, DPP                         |
| Hao Zhu, PhD                | Team Leader, Office of Clinical Pharmacology (OCP)        |
| Di Zhou, PhD                | Clinical Pharmacology Reviewer, OCP                       |
| Kevin Krudys, PhD           | Team Leader, Division of Pharmacometrics, OCP             |
| Gopichand Gottipati, PhD    | Reviewer, Division of Pharmacometrics, OCP                |
| Aisar Atrakchi, PhD         | Pharmacology/Toxicology Supervisor, DPP                   |
| Darren Fegley, PhD          | Pharmacology/Toxicology Reviewer, DPP                     |
| Peiling Yang, PhD           | Biometrics Team Leader, Office of Biometrics (OB)         |
| Thomas Birkner, PhD         | Biometrics Reviewer, OB                                   |
| Juliette Touré, PharmD, MBA | Senior Policy Advisor, DPP                                |
| Leah Hart, PharmD           | Risk Management Analyst, Division of Risk Management      |
| Peter Stein, MD             | Deputy Director, Office of New Drugs                      |
| Noah Nevo, PharmD, BCPP     | Safety Evaluator, Division of Pharmacovigilance I (DPV I) |
| Vicky Chan                  | Safety Evaluator, DPV I                                   |

**APPLICANT ATTENDEES**

|                            |   |
|----------------------------|---|
| Chris O'Brien, M.D.        | Chief Medical Officer                   |
| Grace Liang, M.D.          | Medical Director                        |
| Haig Bozigan, Ph.D.        | Chief Development Officer               |
| Gordon Loewen, Ph.D.       | Vice President, Preclinical Development |
| Malcolm Lloyd-Smith, M.Sc. | Chief Regulatory Officer                |

Kristine Kim, M.S. Director, Regulatory Affairs (b) (4)

## 1.0 BACKGROUND

NDA 209241 was submitted on August 11, 2016 for Valbenazine 40mg capsules.

Proposed indication: Tardive Dyskinesia

PDUFA goal date: April 11, 2017

FDA issued a Background Package in preparation for this meeting on January 30, 2017.

## 2.0 DISCUSSION

### 1. Introductory Comments

***Discussion:*** *The Division explained the purpose and objectives of the Late-Cycle Meeting and informed Neurocrine that the application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) therefore, the final regulatory decision for the application will not be addressed at the meeting.*

### 2. Discussion of Minor Review Issues

#### **Clinical Pharmacology:**

Based on our review thus far, we have identified the following issues:

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

***Discussion:*** *The Applicant indicated that the E-R analysis at Week 6 is just a snapshot of the entire data and reported that additional improvement can be seen beyond Week 6. The Division agreed with the Applicant that sufficient treatment duration is important to achieve adequate clinical outcomes. However, as shown in the clinical trials, patients receiving the 80 mg dose experienced further improvement as compared to patients receiving 40 mg, even after the plateau (over time) has been achieved at each dose level. Therefore, the Division recommended that a higher dose be assessed to explore whether a higher dose can result in further improvement in efficacy (considering the safety/tolerability profile, see response to Section 4 for more information). The Applicant responded that they are open to looking at higher doses.*

- It appears that the effect of CYP2D6 inhibition [either presence of strong CYP2D6 inhibitors or poor metabolizer (PM) status] has not been adequately characterized. We acknowledge your finding of a 2-fold higher exposure in PMs vs. non-PMs from your population PK analysis, but have the following concern:

- The dataset used for the population PK analyses consists of a total of only 16 PMs, of which 13 PMs are in studies with sparse sampling (n = 10 in NBI-98854-1304, n=3 in NBI-98854-1202) and only 2 PMs were administered the therapeutically recommended dose (80 mg). As noted previously in the pre-NDA meeting minutes (February 4, 2016, in response to Question 8), we expressed concern with accurately estimating the C<sub>max,ss</sub> using the sparse PK sampling scheme, especially when the doses were administered without regard to food. Although there was information about the specific use of CYP2D6 inhibitors (weak, moderate and strong), details pertinent to the time of administration and their dose were lacking.

In light of the above, there appears to be inconclusive evidence with regards to the precise magnitude of difference in exposures of NBI-98782 in PMs vs. non-PMs. This may impact labeling statements regarding dose adjustment as well as the estimate of QT prolongation in this population.

***Discussion:*** *The Applicant agreed with the Division's concerns about the small sample size of subjects who are CYP2D6 PMs in their population PK analyses dataset, but they pointed out that CYP2D6 was not the only metabolic pathway for NBI-98782. They indicated that other data from various early Phase 1 studies to support the 2-fold exposure increase in this group of subjects (PMs). In terms of food effect, the Applicant indicated that food increased the C<sub>max</sub> of parent drug ~50% but has minimal impact on C<sub>max</sub> of metabolite (<20%). In their opinion, the overall database was consistent within a reasonable range with their estimate. The Division expressed concerns regarding the precision of magnitude of change and discussed the potential impact on labeling. Whether the dose reduction language can be included in the label is highly dependent on the availability of the appropriate data and accuracy/reliability of the estimate. The Division agreed with Applicant's comment that although the Phase 2 and 3 trials consisted of several patients who were on concomitant CYP2D6 inhibitors, there was no obvious trend in the exposure differences in NBI-98782 between subjects who were on weak, moderate and strong inhibitors. The Division also indicated that it was important to predict the QT effect in CYP2D6 PMs especially if higher doses were to be explored. In addition, the Division raised the concern that sparse sampling may not have adequately characterized the PK profile, including C<sub>max</sub>. The Applicant stated that they would summarize the CYP2D6 PM subjects' information from early Phase 1 studies and send it to the Division with their justifications for review.*

- The change of valbenazine exposure in severely renal impairment patients has not been evaluated. We understand that valbenazine is not primarily cleared via the renal route. However, it has been shown that the CYP2D6-mediated clearance can be decreased in patients with severe renal impairment (Ref 1). Since CYP2D6 is involved in the metabolism of NBI-98782, it is unclear if the exposure will be affected in patients with severe renal impairment.

***Discussion:*** *The Applicant indicated that as discussed previously during the breakthrough therapy designation meeting held in May, 2015, they have planned to conduct a renal*

*impairment study. At this time, they have already engaged in doing this study. The Agency agreed with the Applicant's plan.*

- The inhibitory effect of valbenazine on CYP2D6 enzyme has not been fully assessed in the development program. The calculated  $[I]/K_i$  value suggests that an in vivo DDI study may be necessary.

***Discussion:*** *The Applicant indicated that, according to Drug Interaction guidance, if  $[I]/K_i > 0.1$ , a mechanistic static model analysis could be used to estimate the AUC. Their model predicted AUC only increased 3%; therefore, they did not conduct an in vivo study. The Agency agreed to further review the Applicant's rationale, but also expressed concerns regarding the concomitant use of valbenazine with other antipsychotics in patients, many of which are CYP2D6 substrates.*

- The Drug Interaction Guidance recommends evaluation of CYP enzyme induction potential for the major circulating moieties. According to the guidance, induction potential of NBI-136110 has not evaluated for CYP2B6.

***Discussion:*** *The Applicant agreed with the Agency's comments and indicated that NBI-136110 is the most abundant metabolite. The Applicant believed that this metabolite was indirectly assessed when assessing potential enzyme induction with the parent drug. They also tested NBI-136110 as a PXR activator in a reporter gene assay at clinically-relevant concentrations but it was not shown to be a PXR activator. The Applicant planned to submit their rationale to the Agency for further review.*

- The tested concentration range of the test compounds in study 08-98854-001-MT did not represent the therapeutically relevant concentrations, and clinical relevance of the findings cannot be inferred.

***Discussion:*** *The Applicant indicated that this study report is a summary of seven or eight different studies. The Agency stated that the concentrations used for the study 20  $\mu\text{M}$  is much higher than the therapeutic concentrations ( $C_{\text{max,ss}}$  is  $\sim 1.68 \mu\text{M}$  and  $0.16 \mu\text{M}$ , respectively, for NBI-98854 and NBI-98782). The high concentration could undermine the efflux transporter effect. The Applicant indicated that the concentration in GI tract could be even higher than 20  $\mu\text{M}$  and the concentration proposed by the agency might be too low. The Applicant would like to submit their rationale for further review.*

- The Drug Interaction Guidance recommends evaluation of investigational drugs as substrate for transporters BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3. These effects have not been evaluated in the current studies.

***Discussion:*** *The Applicant stated that they did not observe efflux effect for BCRP so they did not think valbenazine would be a substrate. They also indicated that, because the renal elimination pathway is minor, valbenazine was not likely to be the substrate of OAT1/3 and OCT2 per Drug Interaction guidance. For OATP1B1/3, the Applicant stated that using the*

*decision tree in Drug Interaction guidance, valbenazine does not have characteristics that would be suggestive of active uptake in the liver being important. This compound is highly permeable and not an anion at physiological pH. This evidence may rule out the necessity to evaluate valbenazine as OATP1B1/3 substrate. The agency requested the Applicant to send their detailed justification for review.*

- NBI-679006 appears to be an active metabolite, but it was not evaluated as a substrate or a perpetrator for major CYPs and transporters.

**Discussion:** *The Applicant indicated that, based on Figure 4 of the Drug Interaction guidance, if a metabolite presented at  $\geq 25\%$  of parent drug AUC, it is an active metabolite and should be assessed as any other active moiety. The Applicant stated that NBI-679006 contributed only about 1/20 to 1/30 the activity at VMAT2, thus they did not think it contributes significantly to overall activity. The Agency expressed concerns regarding the Applicant's calculation on VMAT2 inhibition potential, and pointed out that the Applicant's approach ( $C_{max}/K_i$ ) only calculated the inhibition potential at  $C_{max}$ . It did not represent the overall inhibition potential on VMAT2. The Agency recommended the Applicant to include the information of total concentration/exposure information, instead of  $C_{max}$ , to recalculate the relative potency, which was essentially the AUEC. The Applicant stated that the only source of exposure data they have for this metabolite is from the mass balance study, and they did not have its protein binding information. The Applicant will send the agency the data to support their view that NBI-679006 is not a significant contributor to VMAT2 activity.*

**Reference:**

Ref1: Yoshida K, Sun B, Zhang L, Zhao P, Abernethy DR, Nolin TD, Rostami-Hodjegan A, Zineh I, Huang SM. Systematic and quantitative assessment of the effect of chronic kidney disease on CYP2D6 and CYP3A4/5. Clin Pharmacol Ther. 2016 Jul;100(1):75-87.

**Clinical:**

- We note that there were no subjects of Asian race in the ITT analysis sets for both pivotal studies (1202 and 1304). We are not aware of any reason to believe that there would be differences in TD treatment response other than potential pharmacokinetic variability, but are interested in a comment from the Applicant.

**Discussion:** *The Applicant acknowledged the small number of Asians subjects who have participated in the valbenazine development program. The studies were not designed to exclude subjects of Asian races, and clinical sites were located throughout the United States as well as in Puerto Rico and Canada. The Applicant described some scientific literature suggesting Asians were less likely to develop tardive dyskinesia but acknowledged the existence of conflicting reports on this topic. The Applicant did not think there was any reason that Asian subjects would respond to treatments for tardive dyskinesia differently than other races; the Division generally agreed with this viewpoint other than potential differences in pharmacokinetic variability. Finally, the Applicant indicated they are currently planning to conduct a study in Japanese subjects.*

- In Study 1304, we were intrigued by the difference in PGIC score and responder-rate between valbenazine-treated subjects and placebo, as it seems counterintuitive that subjects who objectively have improvement in TD symptoms (as assessed by central raters) would have less appreciation for the benefit than subjects receiving placebo. We are interested in thoughts from the Applicant about this finding.

**Discussion:** *The Applicant agreed that this was an interesting finding but noted that the PGIC was not a validated instrument for use in this population. Furthermore, subjects with tardive dyskinesia are quite heterogeneous with regard to levels of insight into dyskinesic movements varying widely according to primary diagnosis. Thus, the PGIC was not an appropriate primary study endpoint. The Applicant described improvement in PGIC scores in subjects taking valbenazine over the course of the long-term extension period, and the Division indicated that subjects' knowledge that they were receiving active treatment during this period would confound the interpretation of these findings.*

- We are assessing the effect of valbenazine in various patient subgroups (age, TD duration, sex, race, ethnicity, BMI, diagnosis group, antipsychotic use, anticholinergic use). It appears that sex and the use of antipsychotic medications might impact the response to valbenazine (e.g., in Study 1304, women appear to have improved benefit from the valbenazine 40 mg dose than men, and the absence of antipsychotic use appears to be associated with an improved overall response to valbenazine). We would be interested in thoughts from the Applicant about possible subgroup effects.

**Discussion:** *The Applicant and the Division were in agreement that these subgroup analyses were exploratory and there were limited numbers of subjects in subgroups on which to base conclusions. The Applicant indicated that they had performed subgroup analyses and created forest plots for use during the previously-cancelled Advisory Committee meeting. They found the archetypal valbenazine responder to be Caucasian women with mood disorders who were no longer taking antipsychotic medications. However, the Applicant noted that, by far, the strongest variable associated with response was whether the subject received valbenazine 80 mg daily.*

(b) (4)

### 3. Information Requests

**Clinical:**

- None – we have submitted several Information Requests in the course of the review, and there are no outstanding requests to discuss at this time.

**Discussion:** *The Division expressed appreciation for rapid response to information requests throughout the review process. It was also noted that a CMC information request was sent the day prior to the meeting and that a comment from the Controlled Substance Staff may be forthcoming.*

*The Applicant confirmed that the SAP for Study 1202 was submitted. The Division noted that the 'ITT' analysis set in Study 1202 is a completer set and that a number of randomized subjects who discontinued during the DB blind phase are not included. The Division is interested in some additional analyses to explore the potential impact of excluding those patients from the primary efficacy analysis.*

- *Please provide the submission date(s) and serial number(s) of the SAP and potential SAP amendments for Study 1202.*
- *The primary analysis method (i.e., ANCOVA) requires the MCAR (missing completely at random) assumption in the presence of missing data. Please provide some sensible sensitivity/supportive analyses using varying assumptions to help us understand the impact of the exclusion of randomized subjects from the 'ITT' analysis set on the primary efficacy results/conclusions of your study.*

#### 4. Postmarketing Requirements/Postmarketing Commitments

##### **Clinical:**

- **Assessment of the efficacy and safety of a higher dose of valbenazine:** At the Type B End of Phase 2 Meeting on June 24, 2014, the Division recommended that a wider range of doses be studied to capture the minimal and maximal effective doses. Given the tolerability of the 80 mg dose in Study 1304 and the observation that the (dose)/exposure-response relationships for efficacy do not seem to plateau within the tested dose range of 80 mg, it seems reasonable to assess whether a higher dose would confer additional therapeutic benefit for patients with tardive dyskinesia (TD). We would like to discuss this possibility as well as potential study designs (e.g., dosage, duration, potential exclusion of CYP2D6 PMs, etc.).

**Discussion:** *The Division noted that, even while the mean change in AIMS total dyskinesia score improved in subjects receiving valbenazine 80 mg daily, a substantial number of subjects had residual TD symptoms (as indicated by scores greater than minimal or mild on at least one individual body area comprising the AIMS measure). The Applicant considered whether the goal of treatment would be to completely eliminate all dyskinetic movements vs. reduce the overall severity of tardive dyskinesia. The Applicant created shift tables to assess the changes in movement severity and found a majority of subjects responded to valbenazine. Regarding the possibility of assessing a higher dose of valbenazine, the Applicant noted that healthy subjects did not tolerate repeated doses of valbenazine  $\geq 100$  mg, with the caveat that these subjects were started on 100 mg rather than titrated to dose. The Division suggested the consideration of a study design in which non-responders to valbenazine 80 mg would be randomized to continue the 80 mg dose vs. increase to a higher dose, and the Applicant indicated they may consider this approach for the future.*

- **Additional evidence for treatment durability and persistence:** The long-term treatment periods in Studies 1304 and 1402 provide some evidence suggesting that continuing valbenazine treatment may maintain the reduction in TD symptoms, and stopping valbenazine treatment is associated with a recurrence of TD symptoms.

However, there was significant attrition over the course of the 48 week treatment, and the lack of a placebo control raise the possibility that subjects' knowledge as to whether they are receiving an active treatment might affect TD symptom severity. We would like to discuss the possibility of including a randomized withdrawal period in a post-marketing study.

***Discussion:*** *The Applicant indicated that they considered tardive dyskinesia to be a permanent, persistent disorder in the majority of patients. However, from analysis of valbenazine studies to date, they noted that a subset of patients who experienced clinical remission from tardive dyskinesia did not experience a return in dyskinesic movements following drug discontinuation. Exploratory analyses seemed to suggest that this subset of patients consisted of patients with mood disorders who were no longer taking antipsychotics. The Applicant is considering a randomized withdrawal study to further address this question in which subjects would be stratified based on continued antipsychotic usage. The Division was supportive of this line of inquiry and suggested a six week stabilization period should occur prior to randomization.*

**Clinical meaningfulness:** We are interested in whether the statistically significant improvement on the AIMS total dyskinesia translates into long-term functional improvements for subjects with TD. The results from the Tardive Dyskinesia Impact Scale (TDIS) and Tardive Dyskinesia Rating Scale (TDRS) showed numerical improvements associated with valbenazine treatment as well as placebo treatment. We are interested in the Applicant's thoughts about study designs that might answer this question.

***Discussion:*** *The Applicant also expressed interest in assessing functional improvements associated with reduction in tardive dyskinesia symptoms. However, this is difficult to accomplish given the functional heterogeneity in patients with tardive dyskinesia. The Applicant believes social isolation might be the functional impairment most widely associated across individuals with tardive dyskinesia. The Applicant is conducting a non-treatment study titled "RECONNECT" to further explore tardive dyskinesia-associated functional impairments and help develop future treatment studies.*

## 5. Major Labeling Issues

### **Clinical:**

- Because the AIMS scale used by central video raters used modified score descriptors, we think it is important to include the score descriptors in Section 14.1 when discussing the AIMS measure.

***Discussion:*** *The Applicant indicated that they did not believe this would be useful, because multiple AIMS score descriptors have been used in the literature, and the original AIMS measure did not include descriptors; the modified score descriptors would rather be included in future journal publications. The Division indicated that clinicians who use the AIMS in clinical practice may appreciate knowing the Applicant's modified score descriptors to help*

contextualize the study data [REDACTED] (b) (4)

- It is apparent that some of the MedDRA terms for AEs are too specific and do not accurately capture the adverse effects of the drug. We are regrouping the AEs and have found greater signals for somnolence and EPS.

**Discussion:** *The Applicant agreed that terms artificially split adverse events, and [REDACTED] (b) (4)*

- For safety analyses, the trial pooling strategy in your ISS cannot be utilized due to differences in trial duration and dosing regimens. Fixed dose, dose titration, and dose reduction studies with different exposure windows cannot be pooled as prospective, randomized controlled trials. Our safety analyses strategy to characterize the effects of the drug differs. First, we are individually analyzing the three controlled, randomized Phase 2/3 trials (Studies 1201, 1202, and 1304). Second, we are combining these three controlled trials with the open-label extension studies (Studies 1201, 1304, and 1402) and treating this database as a pooled prospective observational epidemiologic database. [REDACTED] (b) (4)

**Discussion:** *The Division described how directly pooling the three controlled studies with different randomization ratios would be both imprecise and inaccurate. Specifically, the Division pointed out that using a random effects model to account for differences in randomization would be more appropriate for pooling [REDACTED] (b) (4). The Division clarified that the adverse event incidence would likely not be significantly different from this analysis approach; term grouping would more significantly affect the adverse event incidence across studies.*

## 6. Review Plans

- Internal labeling discussions are ongoing.
- We plan to complete our review and take action by the April 11, 2017, PDUFA goal date.

**Discussion:** *No further discussion.*

### **Post meeting comment from Office of Pharmaceutical Quality**

*We determined that your stability data support a [REDACTED] (b) (4) month drug product expiry period. This is due to the limited stability data from the commercial drug product site (six months in bottles and three months in blisters). Further, only one of the three primary drug product batches manufactured at the [REDACTED] (b) (4) site used drug substance from the proposed commercial drug substance manufacturing site. We acknowledge that some of your statistical models used the [REDACTED] (b) (4) month [REDACTED] (b) (4) supportive data to demonstrate that the assay would not go below the acceptance criterion until [REDACTED] (b) (4) months. However these batches were not manufactured at the proposed [REDACTED] (b) (4) commercial site and some models found batches failing near the [REDACTED] (b) (4) month time point. It*

*was in the context of the totality of this information that the (b) (4) month expiry period was found acceptable; however, the expiry may be extended based on real-time data from the primary (b) (4) stability batches.*

## 7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL); therefore, this meeting did not address the final regulatory decision for the application.

***Discussion:*** *The Division indicated the review is currently on track for completion by the PDUFA date. Draft labeling will be sent to the Applicant by February 28, 2017. The Applicant enquired whether there was a possibility for a review decision prior to the PDUFA action date. The Division indicated this would depend on the progression of the remaining review.*

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/s/  
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MITCHELL V Mathis  
03/03/2017