CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208082Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 208082 SUPPL # HFD # 120

Trade Name Austedo

Generic Name deutetabenazine tablets

Applicant Name Teva Pharmaceuticals USA, Inc.

Approval Date, If Known 4/3/17 (PDUFA)

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

      YES ☑    NO ☐

   If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8 505(b)(2)

   b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

      YES ☑    NO ☐

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data.
c) Did the applicant request exclusivity?  

YES ☑  NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

d) Has pediatric exclusivity been granted for this Active Moiety?  

YES ☐  NO ☑

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  

YES ☐  NO ☑

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐  NO ☑
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES □ NO □

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.) IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES ☐    NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

       YES ☐    NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

       YES ☐    NO ☐

       (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

       YES ☐    NO ☐

If yes, explain:
(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES □  NO □

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES □  NO □

Investigation #2

YES □  NO □

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation
duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES □   NO □

Investigation #2

YES □   NO □

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES □   !   NO □

!   Explain:

Investigation #2

IND #

YES □   !   NO □

!   Explain:
(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES □  |  NO □

Explain:  |  Explain:

Investigation #2

YES □  |  NO □

Explain:  |  Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES □  NO □

If yes, explain:

Name of person completing form:  Stacy Metz, Pharm D
Title:  Senior Regulatory Project Manager
Date:  3/31/17
Name of Office/Division Director signing form: Eric Bastings, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
03/31/2017

ERIC P BASTINGS
04/01/2017
# Action Package Checklist

## Application Information

<table>
<thead>
<tr>
<th>NDA # 208082</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA #</td>
<td>BLA Supplement #</td>
<td></td>
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<tr>
<td>Proprietary Name: Austedo</td>
<td>Applicant: Teva Pharmaceuticals USA, Inc.</td>
<td></td>
</tr>
<tr>
<td>Established/Proper Name: deuterabenazine</td>
<td>Agent for Applicant (if applicable): Christine Schultes</td>
<td></td>
</tr>
<tr>
<td>Dosage Form: Oral Tablet</td>
<td>Division: DNP</td>
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<tr>
<td>RPM: Stacy Metz</td>
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</tbody>
</table>

- NDA Application Type:  
  - 505(b)(1)  
  - 505(b)(2)  
  - 505(b)(3)  
- Efficacy Supplement:  
  - 505(b)(1)  
  - 505(b)(2)  
- BLA Application Type:  
  - 351(k)  
  - 351(a)  
- Efficacy Supplement:  
  - 351(k)  
  - 351(a)  

For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  - No changes
  - New patent/exclusivity (notify CDER OND IO)
  - Date of check:

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.

### Actions

- Proposed action
- User Fee Goal Date is 4/3/17

<table>
<thead>
<tr>
<th>Actions</th>
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<tr>
<th>AP</th>
<th>TA</th>
<th>CR</th>
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- Previous actions (specify type and date for each action taken)

<table>
<thead>
<tr>
<th>Previous actions</th>
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</table>

If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

- Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm069965.pdf)). If not submitted, explain

<table>
<thead>
<tr>
<th>Received</th>
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<tbody>
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</table>

### Application Characteristics³

³ 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):**  
(Confirm chemical classification at time of approval)

- Fast Track  
- Rolling Review  
- Orphan drug designation  
- 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

<table>
<thead>
<tr>
<th>NDAs: Subpart H</th>
<th>BLAs: Subpart E</th>
<th>REMS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval based on animal studies</td>
<td>Approval based on animal studies</td>
<td>ETASU</td>
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</tbody>
</table>

- Submitted in response to a PMR  
- Submitted in response to a PMC  
- Submitted in response to a Pediatric Written Request

**Comments:**

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)  
  - Yes  
  - No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action  
    - Yes  
    - No
  - Indicate what types (if any) of information were issued  
    - None  
    - FDA Press Release  
    - FDA Talk Paper  
    - CDER Q&As  
    - Other Social Media (twitter,)

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?  
    - No  
    - Yes

- Patent Information (NDAs only)
  - Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.  
    - Verified  
    - Not applicable because drug is an old antibiotic.

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  
  - Included

- Documentation of consent/non-consent by officers/employees  
  - Included

Reference ID: 4080310
## Action Letters

- Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s) CR 5/27/16

## Labeling

<table>
<thead>
<tr>
<th>Description</th>
<th>Include Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Package Insert <em>(write submission/communication date at upper right of first page of PI)</em></td>
<td>Included</td>
</tr>
<tr>
<td>- Most recent draft labeling <em>(if it is division-proposed labeling, it should be in track-changes format)</em></td>
<td>X Included</td>
</tr>
<tr>
<td>- Original applicant-proposed labeling</td>
<td>X Included</td>
</tr>
<tr>
<td>Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <em>(write submission/communication date at upper right of first page of each piece)</em></td>
<td>Included</td>
</tr>
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<td>- Most-recent draft labeling <em>(if it is division-proposed labeling, it should be in track-changes format)</em></td>
<td>X Included</td>
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<tr>
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</tr>
<tr>
<td>Labels <em>(full color carton and immediate-container labels)</em> <em>(write submission/communication date on upper right of first page of each submission)</em></td>
<td>Included</td>
</tr>
<tr>
<td>- Most-recent draft labeling</td>
<td></td>
</tr>
</tbody>
</table>

## Proprietary Name

- Acceptability/non-acceptability letter(s) *(indicate date(s))*
- Review(s) *(indicate date(s))*

| RPM | None 8/6/15 |
| DMEDPA | None 10/30/15 |
| DMPP/PLT (DRISK) | None 7/12/16 |
| OPDP | None 6/6/16 |
| SEALD | None |
| CSS | None |
| Product Quality | None |
| Other | None |

| Labeling reviews *(indicate dates of reviews)* |  |

## Administrative / Regulatory Documents

- RPM Filing Review4/Memo of Filing Meeting *(indicate date of each review)*
- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/17/15 Filing Meeting</td>
<td></td>
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<tr>
<td>5/24/16 Filing Review at</td>
<td></td>
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<tr>
<td>Not a (b)(2) cleared 5/27/16</td>
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</tbody>
</table>

- NDAs only: Exclusivity Summary *(signed by Division Director)* | Included |

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4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
<table>
<thead>
<tr>
<th>Application Integrity Policy (AIP) Status and Related Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
</tr>
<tr>
<td>• Applicant is on the AIP</td>
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<tr>
<td>□ Yes  ✗ No</td>
</tr>
<tr>
<td>• This application is on the AIP</td>
</tr>
<tr>
<td>□ Yes  ✗ No</td>
</tr>
<tr>
<td>o If yes, Center Director’s Exception for Review memo (indicate date)</td>
</tr>
<tr>
<td>o If yes, OC clearance for approval (indicate date of clearance communication)</td>
</tr>
<tr>
<td>□ Not an AP action</td>
</tr>
<tr>
<td>❖ Pediatrics (approvals only)</td>
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<tr>
<td>• Date reviewed by PeRC</td>
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<tr>
<td>If PeRC review not necessary, explain: Orphan Designation</td>
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<tr>
<td>• Breakthrough Therapy Designation</td>
</tr>
<tr>
<td>❖ N/A</td>
</tr>
<tr>
<td>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</td>
</tr>
<tr>
<td>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)</td>
</tr>
<tr>
<td>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)</td>
</tr>
<tr>
<td>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</td>
</tr>
<tr>
<td>❖ 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.) (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)</td>
</tr>
<tr>
<td>❖ 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)</td>
</tr>
<tr>
<td>• Minutes of Meetings</td>
</tr>
<tr>
<td>□ N/A or no mtg 10/18/16</td>
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<tr>
<td>• If not the first review cycle, any end-of-review meeting (indicate date of mtg)</td>
</tr>
<tr>
<td>□ N/A or no mtg 10/18/16</td>
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<tr>
<td>• Pre-NDA/BLA meeting (indicate date of mtg)</td>
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<tr>
<td>□ No mtg 4/17/15</td>
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<tr>
<td>• EOP2 meeting (indicate date of mtg)</td>
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<tr>
<td>□ No mtg 12/26/12</td>
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<tr>
<td>• Mid-cycle Communication (indicate date of mtg)</td>
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<td>□ N/A 12/2/15</td>
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<tr>
<td>• Late-cycle Meeting (indicate date of mtg)</td>
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<tr>
<td>□ N/A 3/21/16</td>
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<tr>
<td>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)</td>
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<tr>
<td>Decisional and Summary Memos</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td><strong>Office Director Decisional Memo (indicate date for each review)</strong></td>
</tr>
<tr>
<td><strong>Division Director Summary Review (indicate date for each review)</strong></td>
</tr>
<tr>
<td><strong>Cross-Discipline Team Leader Review (indicate date for each review)</strong></td>
</tr>
<tr>
<td><strong>PMR/PMC Development Templates (indicate total number)</strong></td>
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</tbody>
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### Clinical

<table>
<thead>
<tr>
<th>Clinical Reviews</th>
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<tbody>
<tr>
<td><strong>Clinical Team Leader Review(s) (indicate date for each review)</strong></td>
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<tr>
<td><strong>Clinical review(s) (indicate date for each review)</strong></td>
</tr>
<tr>
<td><strong>Social scientist review(s) (if OTC drug) (indicate date for each review)</strong></td>
</tr>
<tr>
<td><strong>Financial Disclosure reviews(s) or location/date if addressed in another review OR</strong></td>
</tr>
<tr>
<td>If no financial disclosure information was required, check here □ and include a review/memo explaining why not (indicate date of review/memo)</td>
</tr>
</tbody>
</table>

| Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)^3 | □ None |

| Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) | □ N/A 7/30/15, 3/8/16 and |

### Risk Management

| REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) |
| REMS Memo(s) and letter(s) (indicate date(s)) |
| Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) | □ None 5/2/16 and 4/3/17 |

| OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) | □ None requested 2/22/16 |

### Clinical Microbiology

| Clinical Microbiology Team Leader Review(s) (indicate date for each review) | □ No separate review |
| Clinical Microbiology Review(s) (indicate date for each review) | □ None |

### Biostatistics

| Statistical Division Director Review(s) (indicate date for each review) | □ No separate review |
| Statistical Team Leader Review(s) (indicate date for each review) | □ No separate review |
| Statistical Review(s) (indicate date for each review) | □ None 2/19/16 |

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^3 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).
### Clinical Pharmacology

- Clinical Pharmacology Division Director Review(s) (indicate date for each review)  
  - No separate review
- Clinical Pharmacology Team Leader Review(s) (indicate date for each review)  
  - No separate review
- Clinical Pharmacology review(s) (indicate date for each review)  
  - None 4/13/16 and 2/23/17
- OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)  
  - None requested 4/6/16

### Nonclinical

- Pharmacology/Toxicology Discipline Reviews
  - ADP/T Review(s) (indicate date for each review)  
    - No separate review 5/24/16
  - Supervisory Review(s) (indicate date for each review)  
    - No separate review 3/31/16
  - Pharm/tox review(s), including referenced IND reviews (indicate date for each review)  
    - None 2/4/16 and 1/18/17
- Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)  
  - None
- Statistical review(s) of carcinogenicity studies (indicate date for each review)  
  - No carc
- ECAC/CAC report/memo of meeting  
  - None Included in P/T review, page
- OSI Nonclinical Inspection Review Summary (include copies of OSI letters)  
  - None requested

### Product Quality

- Product Quality Discipline Reviews
  - Tertiary review (indicate date for each review)  
    - None
  - Secondary review (e.g., Branch Chief) (indicate date for each review)  
    - None
  - Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)  
    - None 4/18/16, 5/24/16
- Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)  
  - None
- Environmental Assessment (check one) (original and supplemental applications)
  - Categorical Exclusion (indicate review date) (all original applications and all efficacy supplements that could increase the patient population)  
    - see CMC Review 3/7/17
  - Review & FONSI (indicate date of review)
  - Review & Environmental Impact Statement (indicate date of each review)
- Facilities Review/Inspection
  - Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)  
    - Acceptable

---

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

Reference ID: 4080310
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
<th>Status</th>
</tr>
</thead>
</table>
| ✗ For all 505(b)(2) applications:  
  • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)                                                                                           | ✗ No changes |
| • Finalize 505(b)(2) assessment                                                                                                                                                                                                  | ✗ Done  |
| ✗ For Breakthrough Therapy (BT) Designated drugs:  
  • Notify the CDER BT Program Manager                                                                                                                                                                                      | ✗ Done  |
| ✗ For products that need to be added to the flush list (generally opioids): Flush List  
  • Notify the Division of Online Communications, Office of Communications                                                                                       | ✗ Done  |
| ✗ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email                                                                                                                            | ✗ Done  |
| ✗ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter                                                                 | ✗ Done  |
| ✗ Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name | ✗ Done  |
| ✗ Ensure Pediatric Record is accurate                                                                                                                                                                                          | ✗ Done  |
| ✗ Send approval email within one business day to CDER-APPROVALS                                                                                                                                                              | ✗ Done  |
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
04/05/2017
-----Original Message-----
From: PeRC
Sent: Thursday, November 17, 2016 1:39 PM
To: Metz, Stacy
Subject: RE: NDA 208082 Resubmission to CR/Austedo (deuterated tetrabenazine) in Huntington's disease--Orphan Designation

Thanks Stayce-

No additional information is needed at this time.

Meshaun

-----Original Message-----
From: Metz, Stacy
Sent: Thursday, November 17, 2016 12:10 PM
To: PeRC
Subject: NDA 208082 Resubmission to CR/Austedo (deuterated tetrabenazine) in Huntington's disease--Orphan Designation
Importance: High

Hello.

DNP received an NDA resubmission to a CR for a Huntington's disease product on 10/3/16 with PDUFA of 4/3/16.

NDA 208082: will not trigger PREA because the application has an Orphan designation. I have attached the orphan designation letter.
EDR Location: \CDSESUB1\evsprod\NDA208082\208082.enx

Please let me know if you need anything else.
Thanks!
Stacy
DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5295
Silver Spring, MD 20993

NOV 05 2014

Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, D.C. 20005-5929

Attention: Kurt R. Karst
US Regulatory Representative

Re: Designation Request # 12-3832
Amendment dated: September 8, 2014
Amendment received: September 10, 2014

Dear Mr. Karst:

This letter responds to your amended request submitted on behalf of Auspex Pharmaceuticals for orphan-drug designation of d₈-tetraabenazine (also referred to as: SD-809 and deuterabenazine) for “treatment of chorea associated with Huntington’s disease.”

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of d₈-tetraabenazine (deuterabenazine) is granted for treatment of Huntington’s disease. Please note that the designation granted is broader than the indication proposed in your designation request. Please be advised that it is the active moiety or principal molecular structural features of the drug¹ and not the formulation of the drug that is designated.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug’s orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26

¹ The term “drug” in this letter includes drug and biological products.
If the same drug is approved for the same orphan indication before you obtain marketing approval of your drug, you will have to demonstrate that your drug is clinically superior to the already approved same drug in order to obtain orphan-drug exclusivity. Failure to demonstrate clinical superiority over the already approved same drug will result in your drug not receiving orphan-drug exclusivity. 21 CFR 316.34(c)

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30

Please notify this Office within 30 days of submitting a marketing application for the drug’s designated use. Once your marketing application is approved, please contact Stephanie Donahoe, RPh, MPH, at 301-796-8681 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact John D. Milto, MD, at 301-796-8687 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
03/31/2017

Reference ID: 4078400
NDA 208082

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Teva Pharmaceuticals, Inc.
3333 North Torrey Pines Court, Suite 400
La Jolla, CA 92037

ATTENTION: Christine Schulteis, PhD
Senior Director, Regulatory Affairs

Dear Dr. Schulteis:

Please refer to your New Drug Application (NDA) Class 2 Resubmission dated and received October 03, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Deutetrabenazine Tablets, 6mg, 9mg, and 12mg.

We also refer to your correspondence, dated and received October 17, 2016, requesting review of your proposed proprietary name, Austedo.

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

If any of the proposed product characteristics as stated in your October 17, 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:


Reference ID: 4040575
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ruth Maduro, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4232. For any other information regarding this application, contact Stacy Metz, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2139.

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

/s/

RUTH L MADURO
01/11/2017

DANIELLE M HARRIS on behalf of TODD D BRIDGES
01/12/2017
NDA 208082

MEETING MINUTES

Teva Pharmaceuticals, Inc.
Attention: Christine Schulteis, PhD
Global Regulatory Affairs
3333 North Torrey Pines Court
Suite 400
La Jolla, CA 92037

Dear Dr. Schulteis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Austedo (deutetrabenazine) Oral Tablets 6 mg, 9 mg, and 12 mg.

We also refer to the meeting between representatives of your firm and the FDA on September 20, 2016. The purpose of the meeting was to discuss the issues identified in the Complete Response letter, with particular focus on the issues identified with respect to clinical pharmacology and nonclinical data.

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 Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-2139.

Sincerely,

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 3999982
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: End of Review

Meeting Date and Time: September 20, 2016; 11:00 – 12:00 PM EST
Meeting Location: FDA White Oak: Bldg 22/Room 1309

Application Number: NDA 208082
Product Name: Austedo (deutetrabenazine) Oral Tablets
Indication: Treatment of chorea associated with Huntington’s disease
Sponsor/Applicant Name: Teva Pharmaceuticals, Inc.

Meeting Chair: Eric Bastings, MD
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES
Ellis Unger, MD, ODE I
Eric Bastings, MD, Deputy Director
Gerald Podskalny, DO, MPHIS, CDTL, Clinical Team Leader
Ken Bergmann, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Nonclinical Pharmacologist
Chris Toscano, PhD, Nonclinical Pharmacologist
Kristina Dimova, PhD, Clinical Pharmacology Reviewer
Stacy Metz, PharmD, Senior Regulatory Project Manager
Division of Psychiatry Products
Mitch Mathis, MD, Director
Tiffany Farchione, MD, Deputy Directory
Aisar Atrakchi, PhD, Pharmacology/Toxicology Supervisor (via phone)
Hao Zhu, PhD, Office of Clinical Pharmacology Team Leader (via phone)
Praveen Balimane, PhD, Office of Clinical Pharmacology Reviewer (via phone)
Martin Yoon, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES
Dennis Ahern, MS, Senior Director, Global Regulatory Affairs
Leonard Alansky, Associate Director, Regulatory Affairs CMC
Margaret Bradbury, PhD, Senior Director, Research and Development
Donna Cox, PhD, Director, Clinical Pharmacology
James Ottinger, Senior Vice President, Global Regulatory Affairs
Christine Schulteis, PhD, Senior Director, Global Regulatory Affairs

Reference ID: 3999982
David Stamler, MD, Vice President, Clinical Development, Hyperkinetic Movement Disorders  
Doron M Shinar, PhD DABT, Senior Director, Head of Nonclinical Safety  
Andreas Sommer, PhD, Vice President, Research

1.0 BACKGROUND

NDA 208082 was submitted on May 29, 2015, and a Complete Response Letter was received from FDA on May 27, 2016. The purpose of this Type A meeting is to discuss the issues identified in the Complete Response letter, with particular focus on the issues identified with respect to clinical pharmacology and nonclinical data. Specific objectives include:

- To discuss new data from bioanalytical characterization of M1 and M4 that demonstrate M1 and M4 are minor metabolites.
- To reach agreement with FDA that the bioanalytical results presented for M1 and M4, identifying them as minor, complete the characterization of the metabolites of SD-809 in humans.
- To confirm that no further nonclinical studies of M1 and M4 are needed, given the characterization of these metabolites as minor and also taking into account the results from the additional safety assessments that have been conducted with these metabolites.
- To reach agreement with FDA on the contents and timing of submission of a complete response to NDA 208082.

FDA sent Preliminary Comments to Teva Pharmaceuticals, Inc. on September 16, 2016.

2.0 DISCUSSION

2.1. Clinical Pharmacology Questions

**Question 1:**
Based on the totality of the data and updated analyses from Studies SD-809-C-12 and AUS-SD-809-CTP-07, Part 2, which are to be included in the Complete Response submission, Teva has demonstrated that:

- M1 represents ≤10% of total circulating drug material and, therefore, is a minor metabolite of SD-809;
- Nonclinical investigations and assessments confirm no safety concerns associated with M1;
- Thus, Teva has concluded that no additional nonclinical studies for M1 are required.

Pending review and acceptance of the complete response and the new analyses defining M1 as minor, does FDA agree that no further studies of M1 are required?
Teva submitted a response document on September 19, 2016, discussing Questions 1 and 3. See Teva’s September 19, 2016, Pre Meeting Response under Question 1.

**FDA Response to Question 1:**

**Nonclinical**

If M1 is determined to be a major circulating metabolite in humans, you will either need to perform a carcinogenicity assessment of M1 in a single species or demonstrate adequate exposure to M1 at the doses of TBZ administered in the 6-month carcinogenicity study in transgenic mice (cf. Xenazine labeling).

**Clinical Pharmacology Response to Question 1:**

Per the analysis presented in this briefing document, the plasma concentrations for M1 and M4, obtained using validated bioanalytical methods, were used to calculate the respective Area Under the Concentration-time (AUC) curves from time 0, extrapolated to infinity (AUCinf). The AUCinf values for M1 and M4 were subsequently expressed as a percentage of the AUCinf for total drug-related material that were previously quantified from samples for the same 216-hour post-dose time period (Ref: Study Report SD-809-C-12, Listing 16.2.6.2). In this case, the use of AUCinf is not acceptable for the following reasons. Based on SD-809-C-12 study results, the elimination half-life of total plasma radioactivity could only be calculated in 1 subject [Ref: Clinical Study Report SD-809-C-12 Amendment 01 Version 2.0 (06 March 2015), Page 66 of 287]. Consequently, in 5 out of the 6 subjects, you were unable to obtain an adequate estimate of the AUC0-inf for total plasma radioactivity. It is not clear how the AUCinf values presented in the briefing document were estimated. Therefore, we suggest calculating the percentage of total drug-related material based on AUC0-last (for total plasma radioactivity and for M1/M4) instead of the AUCinf.

**Teva’s September 19, 2016, Pre Meeting Response**

In response to the FDA comment, “It is not clear how the AUCinf values presented in the briefing document were estimated,” Teva would like to clarify that the AUCinf values reported for total drug-related material in plasma were reported in the original SD-809-C-12 Clinical Study Report (CSR) (NDA 208082, Sequence 0003, Listing 16.2.6.2).

AUCinf is the appropriate metric when comparing the relative overall systemic exposure of a metabolite to total drug-related material, given the differences in bioanalytical ranges applied to the different analytes. AUClast underestimates the contribution of longer-lived circulating metabolites to the AUC of total drug-related material.

Teva acknowledges the statement made on page 66 of the SD-809-C-12 CSR, which indicated that the elimination half-life of total plasma radioactivity could only be calculated in one subject, leading to one AUCinf brought forward from the listings to the summary tables. The exclusion of the other AUCinf values was based on the criteria that were applied to the acceptance of elimination rate constants by the vendor [Ref: Clinical Study Report SD-809-C-12 Amendment 01 Version 2.0 (06 March 2015), Page 66 of 287].

In preparation of the briefing document, Teva had re-evaluated the criteria for acceptance of the elimination rate constants and %AUCextrap to determine which subjects were suitable for calculation of the percentage of total drug-related material for M1. Based on AUCextrap and the totality of the data, Teva had accepted AUCinf for 5 of the 6 subjects. In light of FDA’s comment above, Teva has revisited the criteria for accepting elimination rate constants in the original CSR. Teva believes that...
r2 > 0.75 and %AUCextrap less than 25% are the most relevant to the current analysis of total drug-related material; whereas the ratio of the duration of time used to derive the regression constant/half-life is minimally applicable to a composite analyte, such as total plasma radioactivity.

Upon this current re-evaluation, Teva deems 4 of the 5 remaining subjects described in the briefing document as acceptable, as their r2 for elimination rate constants were greater than 0.75, there were suitable sampling intervals relative to the regressions (unity or greater), and AUCextrap values were ranged from 8.4% to 16.3% (Table 1).

In a single subject (S005; Table 1), the r2 for elimination rate constant was less than 0.75; this AUCinf could be considered not evaluable. Nonetheless, if this one subject is removed from the data set, the impact on the average for the percentage of total drug-related material for M1 is inconsequential. Therefore Teva asserts that the AUCinf as described in the briefing document was adequately characterized.

Given that the elimination rate constant can be reliably estimated from 4 of 6 subjects in the mass-balance study, a ratio of M1:total drug-related material based on AUCinf (9.1% or 9.2%) is acceptable. The calculation of M1 as a percentage of total drug-related material using AUClast provides an average of 10.6% (range of 8.5% to 11.8%). All of these values are close to the 10% threshold recommended in the guidance. Based on the suitability of AUCinf, Teva concludes that the data in the briefing document lead to the conclusion that M1 is a minor metabolite.

### Table 1: Evaluation of Elimination Rate Constants, AUCinf of Total Drug-Related Material, and M1 Percentage of Total Drug-Related Material in Study SD-809-C-12, SD-809-Treated Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>$r^2$ (elimination rate constant of TDRM)$^a$</th>
<th>Duration of time used for regression constant/derived half-life$^b$</th>
<th>AUC% extrap</th>
<th>M1</th>
<th>Acceptance Based on Teva Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S001</td>
<td>0.9945</td>
<td>1.35</td>
<td>11.8%</td>
<td>9.2%</td>
<td>Acceptable</td>
</tr>
<tr>
<td>S002</td>
<td>0.7883</td>
<td>1.36</td>
<td>16.3%</td>
<td>10.0%</td>
<td>Acceptable</td>
</tr>
<tr>
<td>S003</td>
<td>0.9939</td>
<td>3.20</td>
<td>8.4%</td>
<td>10.2%</td>
<td>Acceptable</td>
</tr>
<tr>
<td>S004</td>
<td>0.7356</td>
<td>0.34</td>
<td>47.0%</td>
<td>Did not calculate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not included in briefing document analysis (AUC$_{extrap}$ &gt;25%)</td>
</tr>
<tr>
<td>S005</td>
<td>0.3550</td>
<td>0.53</td>
<td>24.9%</td>
<td>8.6%</td>
<td>Could consider excluding from analysis ($r^2$&lt;0.75)</td>
</tr>
<tr>
<td>S006</td>
<td>0.8404</td>
<td>1.30</td>
<td>15.4%</td>
<td>7.3%</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Average (S001, 002, 003, 005, 006)</td>
<td></td>
<td></td>
<td>9.1%</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Average (S001, 002, 003, 006)</td>
<td></td>
<td></td>
<td>9.2%</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: AUC, area under concentration-time curve; TDRM, total drug-related material.
Teva acceptance criteria applied to total drug-related material: $r^2 > 0.75$, duration of time used for
regression constant/derived half-life > 1; $\text{AUC}_{\text{extrap}} < 25\%$
Vendor acceptance criteria: $r^2 > 0.90$, Duration of time used for regression constant/derived half-life > 2;
$\text{AUC}_{\text{extrap}}$ not described
a: Source: Study SD-809-C-12 Clinical Study Report, Listing 16.2.6.2.
b: Derived from the elimination beginning and end and half-life, both provided in Study SD-809-C-12
Clinical Study Report, Listing 16.2.6.2.

Regardless of whether M1 is described as more or less than 10% of total drug-related material, it
is understood that the 10% value listed in the FDA Guidance on “Safety Testing of Drug
Metabolites,” was not intended to represent a rigid threshold. Importantly, metabolites on
the borderline of 10% should be considered on a case-by-case basis, taking into account the totality
of available safety information.

In the case of M1, a substantial body of in silico, in vitro, and in vivo safety data has been
assembled and described in the briefing document, indicating that M1 does not exhibit safety
signals of concern. As noted in the briefing document:

- M1 is not genotoxic (no mutagenicity, no chromosomal aberrational activity). This
  observation is as expected, since oxidation of the isobutyl substituent to a carboxylic
  acid does not introduce a carcinogenic motif.
- M1 differs from the dihydrotetabenazine metabolites of SD-809 (and tetrabenazine) by
  replacement of a terminal methyl group by a carboxylic acid function, a structural
  change associated with significantly increased polar surface area and decreased LogP (2
  changes known to decrease biological activity).
- (Q)SAR confirms M1 is negative for mutagenicity predictions.
- M1 is not pharmacologically active.
- M1 is negative when examined in-silico ([Q]SAR) for alerting pharmacological
  or toxicological structures associated with risk for carcinogenicity.
- Short-term studies with isolated M1 indicate that it is well tolerated in rats at
  exposure levels exceeding the maximal clinical exposure.
- M1 embryofetal developmental toxicity was adequately tested, as it is present at
  high levels in rabbits, which are one of the two species tested with tetrabenazine.

In summary, Teva is confident in the final characterization of the amount of M1 as a percentage
of total drug-related material. Based on the favorable clinical and nonclinical safety profile and
the demonstration above that M1 is a minor metabolite of SD-809 and tetrabenazine, the safety
assessment of M1 is sufficient for the complete response.

Meeting Discussion:
The sponsor discussed the criteria for acceptance of the elimination rate constants and the
$\%\text{AUC}_{\text{extrap}}$ (e.g., $\%\text{AUC}_{\text{extrap}}$ less than 25%) of the total radioactivity, and the calculation of M1
as a percentage of total drug-related material using the data from Study SD-809-C-12. The
Agency reiterated that this will be a review issue and recommended that the sponsor submit all supporting information/justification in the NDA resubmission.

The Division stated that a determination as to whether or not a carcinogenicity study is needed cannot be made until the Sponsor provides definitive data identifying M1 as either a major or minor metabolite. The Sponsor asked whether a carcinogenicity waiver request should be submitted with the NDA. The Division stated that justification, with all supportive data, for not conducting a carcinogenicity study should be submitted, but that a formal waiver request was not necessary. The Division did note that some of the Sponsor’s arguments against the need for a carcinogenicity study of M1, as described in the meeting package, are not particularly compelling, e.g., the lack of toxicity in oral toxicity or reproductive and developmental toxicology studies, or the negative genotoxicity studies.

**Question 2:**
Based on the totality of the data and updated analyses from Studies SD-809-C-12 and AUS-SD-809-CTP-07, Part 2, which are to be included in the Complete Response submission, Teva has demonstrated that:

- M4 represents ≤10% of total circulating drug material and, therefore, is a minor metabolite of SD-809;
- Nonclinical investigations and assessments confirm no safety concerns associated with M4;
- Thus, Teva has concluded that no additional nonclinical studies for M4 are required.

Pending review and acceptance of the complete response and the new analyses defining M4 as minor, does FDA agree that no further studies of M4 are required?

**FDA Response to Question 2:**
On face, it appears that the additional nonclinical data may demonstrate sufficient exposure to M4 in the pivotal nonclinical studies. However, the adequacy of the data will be a matter of review.
Also see the Clinical Pharmacology Response to Question 1.

**Meeting Discussion:**
No further discussion at the meeting.

**Question 3:**
Given the additional data to be submitted for M1 and M4 in the Complete Response submission, together with the data already submitted and reviewed in NDA 208082, Teva's position is that all the major metabolites of SD-809 have been identified and that all major circulating human metabolites have been either been adequately bridged to Xenazine and/or adequately assessed in nonclinical studies. Does FDA agree?
FDA Response to Question 3:
See responses to Questions 1 and 2.

Teva’s September 19, 2016, Pre Meeting Response
To be discussed in the context of Question 1 above.

Meeting Discussion:
See meeting discussion under Question 1.

2.2. Regulatory Question

Question 4:
Does FDA agree that submission of the proposed sections will be sufficient to address the comments provided in the Complete Response Letter (dated May 27, 2016) and will be acceptable as a Complete Response submission for NDA 208082?

FDA Response to Question 4:
The adequacy of your NDA resubmission is a matter of review. The resubmission needs to address the issues included in the Complete Response Letter, and those described in our responses to Questions 1 and 2.

Meeting Discussion:
No further discussion at the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Teva submitted a clarification question to CSS on August 31, 2016. At the time of the meeting that question was pending.

Clarification Question for CSS
Specifically, the team (at TEVA) would like further information on the statement highlighted in yellow below. We have investigated several of the scales listed in the CRL in First-HD and have not identified a rebound effect unique to SD-809. Any additional information that the review team could provide regarding the data assessed as suggesting a rebound effect would be of great assistance in assuring we can assess any effects correctly.

FDA Response
The change in rating scales scores following withdrawal of study medication in study # SD-809-C-15 (First HD) seems to indicate a possibility of the rebound, which was not captured in its entirety because the follow-up period after discontinuing study drug only lasted 1 week. It seems patients experienced rapid worsening of TMS, BARS, BBT and UPDRS dysarthria/speech question scores during the first week after drug discontinuation. This could indicate rebound and
CSS recommended an extension of the follow-up period to clarify if the observed change in scores after discontinuation was indeed a rebound.

4.0 ACTION ITEMS
There are no action items.

5.0 ATTACHMENTS AND HANDOUTS
There are no attachments or handouts.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY M METZ
10/17/2016

ERIC P BASTINGS
10/18/2016
Dear Dr. Schulteis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AUSTEDO (deutetrabenazine) Oral Tablets 6 mg, 9 mg, and 12 mg.

We also refer to the teleconference between representatives of your firm and the FDA on November 3, 2015. 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 Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Gerald D. Podskalny, DO, MSPH
Clinical Team Lead
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
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

Nonclinical

- Based on the data you have provided, there is uncertainty regarding the adequacy of the nonclinical assessment of major circulating human metabolites of SD-809.
  - The data are inconsistent regarding whether or not M1 is a major metabolite in humans following oral administration of SD-809.
  - M4 appears to be a major human metabolite following oral administration of SD-809 and tetrabenazine.

Neither M1 nor M4 is listed as a major human metabolite in the labeling for the RLD.

Meeting Discussion:

The Division expressed concern regarding the inconsistencies in the data on circulating levels of SD-809 metabolites resulting, in part, from differences in the methods used for quantitation (i.e., semi-quantitative vs quantitative). The semi-quantitative method failed to identify 9-O-desmethyl-β-DHTBZ, a known major human metabolite of tetrabenazine (TBZ), as a major metabolite (i.e., >10% of total drug-related exposure) in humans following administration of TBZ (study SD-809-C-12). Because only semi-quantitative data are available for certain metabolites (e.g., M1), it is unclear if all major human metabolites have been identified and, therefore, if all major human metabolites have been adequately assessed in the appropriate nonclinical studies.

- The specification limits for impurities [144x180] are below the qualification threshold; however, you have not provided information regarding the genotoxic potential of these impurities (cf. ICH M7, May 2015).

Meeting Discussion:

The Sponsor committed to performing QSAR assessment of these impurities.
Clinical Pharmacology

- The Clinical Pharmacology review issues regarding metabolites have been communicated to Teva during the 25 Sept 2015 teleconference and in the 09 Oct 2015 Memorandum. The drug interaction potential strategy for M4 proposed in Teva’s Response to FDA Telecon Request for Information Regarding Metabolites (20 Oct 2015) is acceptable, providing the reports summarizing the results of the proposed in vitro studies are submitted to the NDA no later than Jan 15, 2016.

**Meeting Discussion:**

*The Sponsor might not be able to provide the results of the vitro studies by January 15, 2016. The FDA needs to review the full reports of these studies as part of the NDA review, not just a summary of the results. January 15, 2016, is late in the review cycle, which leaves little time to review this information before primary reviews are completed.*

- Based on the results of Studies AUS-SD-809-CTP-06 and SD-809-C-08 and on simulation and modeling, the dose of SD-809 should be adjusted, e.g. capped at 18 mg BID (36 mg daily) in patients taking strong CYP2D6 inhibitors or who are poor metabolizers of SD-809.

**Meeting Discussion:**

*The Sponsor noted that no adjustment in SD-809 dosing is needed in patients taking strong CYP2D6 inhibitors, or patients who are poor metabolizers of SD-809 based on the overlapping ranges in predicted total (α+β)-HTBZ exposures. In addition, the dose of SD-809 for each patient can be titrated based on efficacy of chorea control and tolerability.*

The FDA Clinical Pharmacology reviewers found that all four CYP2D6 PMs in study AUS-SD-809-CTP-06 were actually intermediate metabolizers. In addition, results from the DDI study, SD-809-C-08 show a 3-fold increase in total (α+β)-HTBZ exposures when paroxetine was co-administered with SD-809. In the Phase 3 study, patients taking strong CYP2D6 inhibitors were limited to a maximum dose of SD-809 of 18 mg BID (36 mg daily).

The Sponsor used data from the Phase 3 study to conduct additional simulations, which show subjects with impaired CYP2D6 function, SD-809 at 48 mg/day (100% of the maximum recommended daily dose) is predicted to yield median AUC0-24 values that fall within the exposure range of tetrabenazine 50 mg/day in subjects with impaired CYP2D6 function.

*The Office of Clinical Pharmacology will continue its ongoing review if this issue.*
Your strategy to bridge to the RLD is being discussed further by various offices in the FDA. We will provide an update when the Division receives additional information.

**Meeting Discussion:**

*At this time, the Division has no additional information regarding internal discussions about the pharmacokinetic bridging strategy submitted in the NDA.*

**Biopharmaceutics**

- In the assessment of the formulation of your proposed product, FDA has identified the presence of excipients: The 7.5 mg and 15 mg tablets that were used in pharmacokinetic studies are uncoated tablets whereas the proposed commercial formulation has a coating. In order to bridge these two formulations, provide comparative dissolution data and similarity f2 values for each strength of the uncoated tablets (7.5, 15 mg) versus each strength of the coated final formulation (6, 9, and 12 mg). Provide the complete dissolution profile data (individual, mean, SD, profiles) at the following sampling time points: 0.5 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, and 6 hr.
Meeting Discussion:

The Sponsor is committed to submitting the comparative dissolution data for the uncoated tablets (7.5 and 15 mg) and the coated tablets (6, 9, and 12 mg), by including the recommended time points.

3.0 INFORMATION REQUESTS

There are no outstanding information requests.

Meeting Discussion:

No further discussion at the meeting.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We are not planning to have a REMS for SD-809, but our review is still ongoing.

Meeting Discussion:

No further discussion at the meeting.

5.0 ADVISORY COMMITTEE MEETING

There is no Advisory Committee Meeting Planned.

Meeting Discussion:

No further discussion at the meeting.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Late Cycle Meeting (with Sponsor): February 25, 2016

- Face-to-face (or teleconference if requested by Sponsor)
- Duration: 1 hour

Action Goal date: May 29, 2016

Meeting Discussion:

No further discussion at the meeting.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERALD D PODSKALNY
12/02/2015
Dear Mr. Moran:

Please refer to your New Drug Application (NDA) dated and received May 29, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Deutetrabenazine Tablets, 6 mg, 9 mg, and 12 mg.

We also refer to your correspondence, dated and received May 29, 2015, requesting review of your proposed proprietary name, Austedo.

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

If any of the proposed product characteristics as stated in your May 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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  

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Stacy Metz, Regulatory Project Manager in the Office of New Drugs, at 301-796-2139.

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

/s/

TODD D BRIDGES
07/02/2015
Dear Mr. Moran:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SD-809 (deutetrabenazine) tablets.

We also refer to the meeting between representatives of your firm and the FDA on March 19, 2015. The purpose of the meeting was to discuss the top-line results from Study SD-809-C-15 (First-HD), a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that provides pivotal evidence of clinical benefit of SD-809 in subjects with chorea associated with Huntington’s disease (HD).

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 Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology 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: Pre-NDA

Meeting Date and Time: March 19, 2015
3:00 – 4:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1315
Silver Spring, Maryland 20903
Application Number: IND 112975
Product Name: SD-809
Indication: Treatment of chorea associated with Huntington’s disease (HD).
Sponsor/Applicant Name: Auspex Pharmaceuticals
Meeting Chair: Billy Dunn, MD, Director
Meeting Recorder: Stacy Metz, PharmD

FDA ATTENDEES

Billy Dunn, MD, Director, Division of Neurology Products (DNP)
Eric Bastings, MD, Deputy Director, DNP
Gerald Podskalny, DO, Clinical Team Leader, DNP
Susanne Goldstein, MD, Clinical Reviewer, DNP
J. Edward Fisher, PhD, Nonclinical Pharmacologist, DNP
Martha Heimann, PhD, CMC Team Leader
Angela Men, PhD, Clinical Pharmacology Team Leader
Kristina Dimova, PhD, Clinical Pharmacology Reviewer
Tristan Massie, PhD, Statistical Reviewer
John Milto, MD, Orphan Products
Katharine Chowdhury, MS, Orphan Products
Stacy Metz, PharmD, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Margaret Bradbury, PhD, Senior Director, Research and Development
Matthew Moran, MS, MBA, Vice President, Regulatory Affairs

Reference ID: 3733887
1.0 BACKGROUND

The purpose of this meeting was to discuss the main results from Study SD-809-C-15 (First-HD), a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that provides pivotal evidence of clinical benefit of SD-809 in subjects with chorea associated with HD. Auspex believes that the results of this study support review of a 505(b)(2) New Drug Application (NDA), with tetrabenazine (NDA 021894) as the reference listed drug. Auspex presented preliminary results of the Phase 3, open-label, long-term safety study of SD-809 (ARC-Switch), which provided additional safety data for SD-809 and information on overnight conversion of patients from tetrabenazine to SD-809 therapy.

In addition, Auspex presented an overview of nonclinical and clinical data demonstrating that the metabolic pathway of SD-809 is not changed by deuterium substitution and that plasma exposures to the major metabolites of SD-809 are comparable to those of the listed drug, allowing reference to the extensive safety database for tetrabenazine in the 505(b)(2) application.

The objectives and expected outcomes of the meeting were:

1. To reach agreement that the Phase 1 and Phase 3 study results and the safety database for SD-809 are sufficient to support review of the planned 505(b)(2) NDA.
2. To reach agreement that the characterization of SD-809 metabolism and demonstration of comparable exposure between SD-809 and tetrabenazine and relevant circulating metabolites is sufficient to support review of the planned 505(b)(2) NDA.
3. To reach agreement that the nonclinical development program for SD-809 is sufficient to support review of the planned 505(b)(2) NDA.
4. To reach agreement on the placement of integrated summaries of efficacy and safety in the NDA.

2.0 DISCUSSION

2.1. Clinical Pharmacology Questions

Question 1:

Does FDA agree that the available Phase 1 data are sufficient to support that systemic exposure to SD-809 and its major circulating metabolites are comparable to those for tetrabenazine within its approved dose range, thus allowing tetrabenazine (NDA 021894) to serve as the listed drug for a 505(b)(2) NDA for SD-809?
FDA Response to Question 1:

On face, the Phase 1 data appear adequate to support a 505(b)(2) NDA submission with tetrabenazine as the listed drug; however, the final decision is a matter for review.

We note that, in Study AUS-SD-809-CTP-07, you compared SD-809 to a generic form of tetrabenazine that is available in Australia. Please note that if you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you choose to rely on FDA’s finding of safety and/or effectiveness for a marketed, listed drug(s) and intend to support the scientific appropriateness of such reliance through a comparative BA study, you should use the specified listed drug(s), rather than a bioequivalent ANDA product or a non-US approved version of the product, in your bridging study.

Please clarify whether the alcohol dumping potential has been assessed for the ER formulation of SD-809.

Sponsor’s Pre-Meeting Comment:
A study was completed and will be provided in the NDA. Alcohol had no impact on the SD-809 drug product formulation.

Sponsor’s Pre-Meeting Comment:
Auspex acknowledges that this 505(b)(2) application is intended to bridge to listed drug (Xenazine) approved in the US. Despite repeated attempts to obtain the listed drug, Xenazine, to perform Phase 1 studies, Auspex was unsuccessful.

Instead, dose selection in Phase 3 was informed by Phase 1 studies in which SD-809 tablets were directly compared with immediate-release, tetrabenazine sourced in Australia. The Australian tetrabenazine tablets were qualitatively identical and behave pharmacokinetically the same as the listed drug, Xenazine. The table below describes the comparable pharmacokinetics between the listed drug, Xenazine, as presented in the Summary Basis of Approval to the Australian source of tetrabenazine used in the Phase 1 studies.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Xenazine 50 mg (listed drug) (NDA 107,018)</th>
<th>Xenazine 25 mg (listed drug) (NDA 107,018) Dose normalized</th>
<th>Australian Tetrabenazine 25 mg (CTP-07- Part 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=25)</td>
<td>(N=25)</td>
<td>(N=24)</td>
</tr>
<tr>
<td>α-HTBZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>77.3 (34%)</td>
<td>38.7 (34%)</td>
<td>42.4 (29%)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, hr</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;, ng·hr/mL</td>
<td>422 (53%)</td>
<td>211 (53%)</td>
<td>179 (53%)</td>
</tr>
<tr>
<td>β-HTBZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>42.9 (56%)</td>
<td>21.5 (56%)</td>
<td>22.9 (46%)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, hr</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;inf&lt;/sub&gt;, ng·hr/mL</td>
<td>184 (95%)</td>
<td>92 (95%)</td>
<td>80.7 (107%)</td>
</tr>
</tbody>
</table>

Data for C<sub>max</sub> and AUC presented as mean (coefficient of variation); data for t<sub>max</sub> presented as median (range).

Based on an exposure analysis of the Phase 1 studies, the exposure (AUC) for the total (α+β)-dihydrotetrabenazine (HTBZ) metabolites from 6 mg to 48 mg of SD-809 was comparable to exposure from 12.5 mg to 100 mg of tetrabenazine. The exposure-based bridging strategy derived from the Phase 1 program based on Australian tetrabenazine was confirmed in ARC-Switch, in which the listed drug, Xenazine, was used. In ARC-Switch, an open-label, Phase 3 trial, Auspex compared the safety and efficacy of 6 mg to 48 mg SD-809 with 12.5 mg to 100 mg of the listed drug, Xenazine. Subjects were switched overnight from their existing, stable dose of Xenazine to approximately half the milligram dose of SD-809. At the first critical postdose efficacy assessment at Week 1, chorea control was maintained and there were no adverse events related to loss of chorea control, indicating comparable pharmacologic response between the listed drug, Xenazine, and SD-809. In addition, a comparison of dose-normalized trough concentrations between the listed drug and SD-809 demonstrated comparable exposures of total (α+β)-HTBZ. Does FDA agree that the data derived from this approach will provide an adequate bridge to allow referencing to US-approved Xenazine as the listed drug.

**Meeting Discussion:**

The following two figures were provided by the sponsor and discussed at the meeting.
Figure 1 depicts a nonparametric model of the steady-state pharmacokinetic profile showing the results of SD-809 taken twice daily and generic tetrabenazine taken three times daily. However, this approach based on simulations alone does not directly bridge SD-809 to Xenazine.

In Figure 2, the sponsor compared dose-normalized plasma trough concentrations from healthy volunteers who took Australian-sourced tetrabenazine while on steady-state dosing in Study AUS-SD-809-CTP-07 Part 2 to a subset of patients with HD enrolled in the ARC-HD-Switch study while on steady-state dosing with Xenazine (prior to switching) or at steady state after switching to SD-809. The sponsor argued that because there is significant overlap in \((\alpha+\beta)\)-
HTBZ concentrations following SD-809 and Xenazine administration in the model, there is comparable exposure across a clinically relevant range of doses between Xenazine and SD-809.

The Agency indicated that, for bridging to Xenazine, Cmax levels after Xenazine or SD-809 administration need to be compared in addition to plasma trough concentrations after steady-state dosing with Xenazine or SD-809. The sponsor stated that in the ARC-HD-Switch study 12 patients (referred to as the “Rich” cohort in the protocol) underwent serial PK sampling through 6 hours post-dose and therefore plasma levels covering the Tmax of ($\alpha+\beta$)-HTBZ after administration of Xenazine (1-1.5 h) and SD-809 (3.5-4 h) are available. The sponsor was asked to provide this information as soon as possible after this meeting.

The following are the general comments 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).

- Submit a model development decision tree and/or table that provide an overview of modeling steps.

- 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.

Abbreviations: HTBZ, dihydrotetrazenazine.
Concentrations are plotted against actual times. Nominal times are shown in Table 1.
(L/h) and not as THETA (1). Also, provide in the summary of the report a description of the clinical application of modeling results.

- For examples of where program code and data should be located in the NDA, 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.

Sponsor’s Pre-Meeting Comment:

Auspex plans to comply with the standards described above.

Postmeeting Comment:

The bridging strategy outlined by the sponsor in Clinical Information Amendment 0047 (March 27, 2015) appears reasonable. However, the acceptability of the data itself will be a matter for review.

Question 2:

As previously requested by FDA Auspex has demonstrated that all of the circulating human metabolites of SD-809 are also metabolites of tetrabenazine. Furthermore, plasma concentrations of the major metabolites of SD-809 are within the range of concentrations of the corresponding metabolites of tetrabenazine at therapeutically equivalent doses. Does FDA agree that the available studies of SD-809 metabolism are sufficient to support review of a 505(b)(2) NDA for SD-809 with tetrabenazine (NDA 021894) as the listed drug?

FDA Response to Question 2:

On face, the available studies of SD-809 metabolism appear adequate to support a 505(b)(2) NDA submission with tetrabenazine as the listed drug; however, the final decision will be a matter for review.

Meeting Discussion:

No further discussion at the meeting.

2.2. Nonclinical Question

Question 3:

Auspex has completed the nonclinical program for SD-809, including toxicology studies as previously discussed with FDA (pre-IND and End-of-Phase 2 Meeting), and has demonstrated
that the metabolites of SD-809 are also metabolites of tetrabenazine. Does FDA agree that the available nonclinical studies are sufficient to support review of a 505(b)(2) NDA with tetrabenazine (NDA 021894) as the listed drug?

**FDA Response to Question 3:**

Based on the information provided, the nonclinical studies appear sufficient to support an NDA. However, it is not clear from your summary if impurity was adequately tested in the embryofetal development study, in addition to the 3-month toxicology study and in vivo mouse micronucleus assay. The adequacy of the studies will be a matter of review.

**Sponsor’s Pre-Meeting Comment:**

Auspex confirms that the dose formulations used in the embryofetal development study employed the same vehicle and were generated under the same acidic conditions as those in the 3-month toxicology and in vivo micronucleus assay. Thus, the 10 mg/kg/day maternal NOAEL in the embryofetal development study provided a safety factor of 2.3-fold for the , the same safety factor calculated for the 90-day rat toxicology study. The safety factor for in the mouse in vivo micronucleus study was 9.6-fold.

**Meeting Discussion:**

No further discussion at the meeting.

### 2.3. Clinical Questions

**Question 4:**

Auspex believes that the Phase 3 randomized, controlled trial outlined above (First-HD) provides sufficient evidence to assess the benefit and risks for SD-809 as treatment for subjects with chorea associated with HD. Does FDA agree that the results from this single pivotal study are sufficient for review of a 505(b)(2) NDA with tetrabenazine (NDA 021894) as the listed drug?

**FDA Response to Question 4:**

Yes, assuming an acceptable bridge to the reference listed drug (RLD) is provided in your application. Please also see our response to Questions 1 and 2 regarding submission and review of a 505(b)(2) NDA.

**Sponsor’s Pre-Meeting Comment:**

Please refer to the response to question 1 above.

**Meeting Discussion:**

The sponsor agreed to provide detailed information on the bridging strategy including:
Pharmacokinetic data from the SWITCH study
Pharmacokinetic data comparing generic tetrabenazine used in the studies to Xenazine, the RLD
Specific information from the RLD on which reliance is planned

Auspex used the generic tetrabenazine product available in Australia because efforts to obtain the RLD (Xenazine) from the NDA holder for PK comparison were unsuccessful. However, information from a PK study that directly compares the Australian generic tetrabenazine to Xenazine in the same study is not available. The sponsor was asked to provide detailed information on its efforts/difficulties in obtaining Xenazine for use in clinical trials.

**Question 5:**

Based on the dose-conversion algorithm in ARC-Switch, in which the SD-809 daily dose was administered at approximately half the milligram dose of the prior tetrabenazine daily dose (e.g., 50 mg tetrabenazine → 24 mg SD-809), 37 subjects were switched overnight from tetrabenazine to SD-809 therapy and evaluated for safety, tolerability, and adequacy of chorea control. Auspex believes that these data are sufficient to guide clinicians on safely switching patients from stable tetrabenazine dosing to SD-809.

Does FDA agree that the results of this study are sufficient to support review of the safety of overnight dose conversion from tetrabenazine to SD-809?

**FDA Response to Question 5:**

In your briefing package, you have presented preliminary results for the ARC-Switch study. We are unable to comment on whether the results of ARC-Switch provide sufficient information to inform providers about safely switch patients from stable tetrabenazine dosing to SD-809 based on this preliminary information.

**Sponsor’s Pre-Meeting Comment:**

*In the development program for the listed drug, Xenazine, withdrawal of drug led to return to baseline in chorea within 3 days. In the pivotal trial of the listed drug, Xenazine, the return to baseline was documented at the critical visit occurring 1 week after drug withdrawal. The objective of the ARC-Switch study was to assess safety and maintenance of chorea control after an overnight switch from a stable dose of the listed drug, Xenazine to SD-809. If chorea was not maintained following the withdrawal of the listed drug, Xenazine, and the switch to SD-809, chorea scores would be expected to increase by Day 3, which would be assessable at the critical Week 1 visit.*

*The Switch data will allow assessment of chorea control following the conversion from Xenazine to SD-809. We have presented data for 36 to 37 subjects completing the Week 1 and 4 assessments. At the critical Week 1 visit, the mean Total Maximal Chorea score was unchanged from baseline, indicating maintenance of chorea control, and there were no adverse events.*
related to loss of chorea control observed. Auspex believes that these data are adequate to characterize the safety of switching patients from the listed drug, Xenazine to SD-809 and to provide sufficient information to guide prescribers.

Auspex plans to provide complete analysis of safety and efficacy data, which were not included in the briefing book, with the existing visit cut-off date of 07 November 2014, including individual subject data listings.

Meeting Discussion:

The approach outlined by the sponsor in the pre-meeting comment is acceptable. However, the acceptability of the data itself will be a matter for review.

Question 6:

In addition to the exposure to SD-809 outlined above, the NDA will also reference the extensive safety database for tetrabenazine (NDA 021894). Does FDA agree that these combined data provide sufficient safety information for review of the 505(b)(2) NDA with tetrabenazine (NDA 021894) as the listed drug?

FDA Response to Question 6:

As noted in your briefing packet, 117 subjects with HD have been exposed to SD-809; however, only 18 subjects have been exposed for at least 6 months and 3 subjects for at least one year (Section 10.3.1 Table 17). In order to have sufficient exposure data, you plan to rely on the safety database for tetrabenazine. This plan is reasonable as long as you are able to adequately bridge to the data for the RLD (Xenazine). Please also refer to our responses to Question 1, 2 and 4.

Sponsor’s Pre-Meeting Comment:

Please refer to the response to Question 1.

Meeting Discussion:

FDA stated that the sponsor’s plan to rely on the FDA’s finding of safety for Xenazine depends on the sponsor’s ability to successfully bridge to Xenazine.

Postmeeting Comment

To add clarity to our preliminary response, you cannot rely on proprietary datasets (or information) contained in the Xenazine NDA. This includes FDA reviews of proprietary information submitted to the NDA or IND for Xenazine.

2.4. Regulatory Questions

Question 7:
Auspex plans to submit the narrative portions of the ISE and ISS, summarizing SD-809 efficacy and safety, within Module 2. The appendices, tables, figures, listings, and datasets will be provided in Section 5.3.5.3. Does FDA agree that this approach is acceptable?

**FDA Response to Question 7:**

Yes, provided the text portion of the ISS and ISE contain functioning hyperlinks to the information referenced in the appendices, tables, figures, listings, and datasets. All appendices must have a hyperlinked table of contents that uses logical names that describe its contents. If an appendix contains subsections, the TOC for the appendix should contain hyperlinks or bookmarks to each subsection. Create a Master TOC that lists the order and title of each of the appendices. The Master TOC should contain functioning hyperlinks or bookmarks that bring the reader to the location of each appendix listed. The ISS and ISE need to be clearly labeled and navigable.

Due to the flexible dosing design of your pivotal trial, First-HD, you need to include a table of adverse events for actual dose received by the study period (i.e., titration versus maintenance) for all subjects and a separate table for subjects who had a dose reduction anytime during the trial.

**Sponsor’s Pre-Meeting Comment:**

*Auspex plans to include the required information in the format requested.*

**Meeting Discussion:**

There was no further discussion at the meeting.

**Question 8:**

Given demonstration of robust efficacy, improvement in function, and a favorable safety profile that represents substantial improvement over the available therapy, Auspex believes that SD-809 provides a significant benefit for the treatment of the serious condition of chorea associated with HD. Auspex plans to request Priority Review as part of the 505(b)(2) NDA for SD-809. Does FDA agree with the rationale for requesting Priority Review?

**FDA Response to Question 8:**

A decision on whether to grant Priority Review to an application is made at the time of an NDA submission.

**Sponsor’s Pre-Meeting Comment:**

*Auspex would like to discuss priority review at the face-to-face meeting.*

**Meeting Discussion:**

FDA reiterated that review status is determined at the time of NDA submission.
The sponsor asked about the status of the Breakthrough Designation application. FDA stated that Breakthrough Designation applications are reviewed separately from meeting requests and the determination regarding Breakthrough Designation will be communicated in a separate letter.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  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. Based on the safety profile observed in the Phase 3 program, Auspex does not believe a REMS is necessary, rather a risk management plan will be included in the NDA.
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 that a complete application will be submitted. Therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting was held on February 12, 2015. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

**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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**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 [PLLR Requirements for Prescribing Information](#) websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

**Sponsor’s Pre-Meeting Comment:**
Auspex plans to provide labeling in PLR labeling format, in accordance with FDA regulations and guidance documents.

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.

Sponsor’s Pre-Meeting Comment:

The in vitro pharmacology of SD-809 is identical to Xenazine. Therefore, no additional mechanisms exist to impact the abuse potential of SD-809. Auspex plans to reference the known lack of abuse potential of Xenazine through the 505(b)(2) application. Reference is made to page 8 of the Clinical Pharmacology (part 1) Summary Basis of Approval for Xenazine memo, which outlines the abuse potential data. In addition, Auspex will conduct a literature search and review postmarketing safety data for Xenazine for evidence of abuse potential.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”
<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sponsor’s Pre-Meeting Comment:**

*Auspex plans to include the requested information in the format requested.*

## 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at [http://www.regulations.gov](http://www.regulations.gov)).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies
described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<table>
<thead>
<tr>
<th>Source of information (e.g., published literature, name of listed drug)</th>
<th>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Example: Published literature</td>
<td>Nonclinical toxicology</td>
</tr>
</tbody>
</table>

Reference ID: 3733887
2. Example: NDA XXXXXX “TRADENAME”  
   Previous finding of effectiveness for indication X

3. Example: NDA YYYYYY “TRADENAME”  
   Previous finding of safety for Carcinogenicity, labeling section XXX

4. Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Sponsor’s Pre-Meeting Comment:

Auspex plans to include the required information in the format requested.

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.

**Sponsor’s Pre-Meeting Comment:**

*Auspex will provide the information requested by the Office of Scientific Investigations (I through III).*
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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
├── m5
│   └── datasets
│       └── bimo
└── site-level
```

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.

¹ 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

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

5.0 ACTION ITEMS
There were no action items.

6.0 ATTACHMENTS AND HANDOUTS
The following two figures were provided by the sponsor and discussed at the meeting.

![Graph showing plasma concentration over time](image)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn

04/17/2015
Dear Mr. Lowenthal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SD-809 (d₆-tetrabenazine).

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2012. The purpose of the meeting was to discuss the proposed development plan intended to support a 505(b)(2) NDA for SD-809 and to discuss the results of the completed Phase 1 clinical trials.

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 Nicole L. Bradley, PharmD, Regulatory Project Manager, at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Attachments
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2 (clinical/nonclinical only)
Meeting Date and Time: December 5, 2012, at 2:00 – 3:00 PM EST
Meeting Location: FDA White Oak Campus; Building 22, Room 1309
Application Number: IND 112975
Product Name: SD-809 (d₆-tetabenazine)
Indication: Huntington’s Disease
Sponsor/Applicant Name: Auspex Pharmaceuticals
Meeting Chair: Russell Katz, MD
Meeting Recorder: Nicole Bradley, PharmD

FDA ATTENDEES

Office of Drug Evaluation I
Robert Temple, MD, Deputy Director

Division of Neurology Products
Russell Katz, MD, Director
Eric Bastings, MD, Deputy Director
Dave Podskalny, DO, MS, Clinical Team Leader
Anne Constantino, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
J Edward Fisher, PhD, Nonclinical Reviewer
Nicole Bradley, PharmD, Regulatory Project Manager
Taura Holmes, PharmD, Regulatory Project Manager

Division of Clinical Pharmacology I
Michael Pacanowski, Pharmacology Team Leader
Jeffrey Kraft, PhD, Pharmacology reviewer

Division of Clinical Pharmacology I
Angela Men, PhD, Clinical Pharmacology Team Leader
Hristina Dimova, PhD, Clinical Pharmacology Reviewer

Division of Biometrics I
Kun Jin, PhD, Biostatistics Team Leader
SPONSOR ATTENDEES
Andreas Sommer, Ph.D., COO, Auspex Pharm., Inc.
David Stamler, MD, CMO, Auspex Pharm., Inc.
Margaret Bradbury, Ph.D., Sr. Dir. R&D, Auspex Pharm., Inc.
Lawrence C. Fritz, Ph.D., President and CEO, Auspex Pharm., Inc.
1.0 BACKGROUND

We note a CMC only End of Phase 2 meeting was held between Auspex Pharmaceuticals and the Office of New Drug Quality Assessment on November 13, 2012.

Auspex Pharmaceuticals submitted a clinical/nonclinical End of Phase 2 meeting request to the Division of Neurology Products for SD-809 (d6-tetrabenazine) on September 19, 2012. The meeting request was granted by the Division on September 26, 2012. The purpose of this meeting was to discuss the proposed development plan intended to support a 505(b)(2) NDA for SD-809 and to discuss the results of the completed Phase 1 clinical trials.

The official meeting minutes for the December 5, 2012, End of Phase 2 meeting between Auspex Pharmaceuticals and the Division of Neurology products are provided below, in the following format:

- FDA’s preliminary responses, dated December 4, 2012, denoted in black bold font
- Sponsor’s pre-meeting comments to FDA’s preliminary responses, dated December 5, 2012, denoted in blue font
- Meeting discussion, denoted in black italic font

2.0 DISCUSSION

2.1. Nonclinical Development Plan

Question 1:

1(a) Does the Agency agree that the completed nonclinical studies with SD-809, in combination with the planned reproductive toxicology study are adequate to support submission and approval of a 505(b)(2) NDA for SD-809?

FDA Preliminary Response to Question 1(a):
On face, the completed and planned nonclinical studies are adequate to support the NDA for SD-809, provided that clinical exposures to the parent compound and any major circulating metabolites fall within the range of those for the RLD, as previously discussed. Also, see preliminary response to Question 1(b).

Sponsor’s Pre-meeting Response:
Auspex has no comments. See response to question 4.

Meeting Discussion:
None.
1(b) Does the Agency agree that the proposed specifications for [redacted] in DS and [redacted] in DP) are acceptable without additional nonclinical studies?

**FDA Preliminary Response to Question 1(b):**
To support the proposed specifications, it would be necessary to qualify the impurity by providing evidence that it has been adequately tested in nonclinical studies or is present as a circulating metabolite in humans at levels substantially higher than would result from its presence in the drug product at the proposed specification limit.

**Sponsor’s Pre-meeting Response:**
Auspeix would like to discuss the limits for the two degradants and rationale for qualification of these substances. One of these degradants [redacted] is qualified by animal toxicology studies. The [redacted] is considered qualified [redacted]. See Attached 1 to this response that includes a summary of data and rationale for the qualification of these two degradants.

**Meeting Discussion:**
The Division indicated that a theoretical argument and in vitro data alone would not suffice as support for the proposed specification, but that in vivo data such as plasma concentrations of the impurity could provide the information needed to qualify the impurity as noted in the preliminary response to this question. The sponsor acknowledged the need for in vivo data and asked if measurement of gastric fluid levels would be an acceptable alternative. The Division stated that such an approach would need to be justified. The sponsor asked whether the information supporting the specification for the impurity would be needed prior to the Phase 3 clinical trials. The Division replied that while this is generally the case, the timing would depend in part on the size and duration of the proposed clinical studies and that they would advise further in the minutes.

**Post-meeting Comment**
After the meeting, it was determined by the Division based on a review of the proposed clinical studies that the information needed to support the impurity specifications would not be required prior to initiation of the Phase 3 trials but should be provided as soon as possible.

2.2. **Clinical Development Plan**

**Question 2:**
Does the Agency agree that repeating a food effect study with the commercial image tablet of SD-809 [redacted] is not required for NDA submission given the ongoing SD-809-C-11 study and the fact that the product will be labeled to be taken immediately after a meal?

**FDA Preliminary Response to Question 2:**
Yes.
Sponsor’s Pre-meeting Response:
Auspex has no comments.

Meeting Discussion:
None.

Question 3:
Does the Agency agree that the design of the SD-809-C-11 study is adequate to support dosing in the pivotal trials as well as appropriate descriptive labeling of the pharmacokinetics of SD-809 and NDA submission?

FDA Preliminary Response to Question 3:
Yes, however you need to conduct an in vitro alcohol dumping study for SD-809.

Sponsor’s Pre-meeting Response:
Auspex has no comment, but wants to confirm this study is needed for the 505(b)(2) NDA and not for the pivotal trials.

Meeting Discussion:
The current pivotal study protocol (SD-809-C-09) allows the use of alcohol with caution. Since SD-809 is an [b][4] tablet and alcohol may alter the PK/PD of SD-809, we recommend that you conduct an in-vitro alcohol dumping study before you initiate pivotal trials, otherwise patients should not be allowed to consume alcohol for the duration of the proposed pivotal studies.

Question 4:

4(a) Does the Agency agree there is no significant increase clinical risk from this metabolic shift away from O-demethylation and towards more oxidative mechanisms?
4(b) Does the Agency agree there are no further human clinical metabolism or nonclinical studies necessary for the initiation of the pivotal trial?
4(c) Does the Agency agree there are no further human clinical metabolism or nonclinical studies that will be required for the submission of a 505(b)(2) NDA for SD-809?

FDA Preliminary Response to Question 4(a)(b)(c):

• In the Clinical Summary of your submission (section 2.7, page 43) you claim that the identity of M4 is under investigation. Please provide the results of this investigation.

Sponsor’s Pre-meeting Response:
Auspex confirms that we will attempt to identify this metabolite (M4) and provide the results prior to NDA submission.

Meeting Discussion:
The Xenazine label describes α-HTBZ, β-HTBZ, 9-desmethyl-β-DHTBZ and sulfate conjugates of desmethyl-HTBZ as the only major circulating metabolites in human plasma after administration of tetrabenazine, M4 is not listed as a major metabolite. The sponsor clarified that the samples from the mass balance comparison study (SD-809-C-12) were analyzed by the same bioanalytical CRO that analyzed the samples from the Xenazine mass balance study. The CRO reported that they have failed to detect M4 at the time of the Xenazine mass balance analysis, however the current results show that this metabolite is present after tetrabenazine administration as well.

• In the Clinical Summary of your submission (section 2.7, page 43) you also claim that “the radioactivity ascribed to the active metabolites d6-α- and β-HTBZ (M6 and M5, respectively) were increased between 3.2 and 6.0-fold as compared to those from tetrabenazine, consistent with the increased exposure to deuterated HTBZ metabolites measured in a previous study of powder in capsule formulations (Section 2.7.2.2.1)”. However, the results from Study AUS-SD-809-CTP-06 (Table 2.7-1, Section 2.7.2.2.1, page 6) show that α- and β-HTBZ exposures (AUC_{inf}) were increased between 2.0 and 2.3-fold as compared to those from tetrabenazine. Please explain this discrepancy.

Sponsor’s Pre-meeting Response:
The deuterium effect shown by comparison of the radioactivity ascribed to d6-α- and β-HTBZ is difficult to compare to prior pharmacokinetic studies given the small sample size, the parallel groups and the different approach to quantification (AUC versus time-proportional pooling). Thus, it is difficult to conclude that there are true inter study differences. Auspex places more weight on the data from the AUS-SD-809-CTP-06 and AUS-SD-809-CTP-07 studies, which are larger, randomized, cross-over pharmacokinetic studies. Auspex will further evaluate these apparent differences and provide potential explanations for the findings in the IND when we file the final metabolism study report.

Meeting Discussion:
None.

• Per your mass balance study results, there is a 3-fold exposure increase of M1 following the administration of SD-809 compared to that of tetrabenazine. The dose of SD-809 is about half of tetrabenazine. Therefore, there is an uncertainty on whether the total amount of M1 at steady state is...
comparable to that of tetrabenazine. You need to provide evidence to justify your claim that the actual exposures to the SD-809 metabolites (Table 2.7-24) at steady state will be similar for both tetrabenazine and SD-809 and are not expected to represent an increased safety risk for patients after dose adjustment. If there is a significant increase of M1 exposure observed following SD-809 administration, the DDI potential of the metabolite M1 needs to be assessed. Please refer to the FDA Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

**Sponsor’s Pre-meeting Response:**
Auspex notes that data provided in the meeting package were preliminary derived from a single pooled sample per cohort. Auspex can now present data from the individual subjects based on time-proportional pooling (‘updated results’) that are provided in the attached document (See Attachment 2). These data demonstrate that M1 is not present as a major metabolite of SD-809. These results show that M1 for SD-809 is approximately 2-fold higher than observed for tetrabenazine. Given this Auspex believes there is no safety risk given that SD-809 is given at approximately half the dose of tetrabenazine. Auspex therefore believes that no further justification for M1 exposure needs to be demonstrated.

**Meeting Discussion:**
The Division expressed concern about the variability in the individual results of SD-809 metabolites (Attachment 2, Table 2). The sponsor clarified that this variability is similar to that observed for tetrabenazine.

**Question 5:**

5(a) Does the Agency agree with the overall study design, including the target population to be studied, for the pivotal trial?

**FDA Preliminary Response to Question 5(a):**
(i) The randomized withdrawal study design and the target population is an acceptable design for demonstrating efficacy. However, despite the controlled nature of the randomized withdrawal phase, that phase does not provide controlled safety data, due to the fact that treated patients have been shown to be tolerant of the drug. Your clinical trials program must provide adequate safety information for SD-809 (b)(4) to describe in labeling because, by design, the PK profile of the active metabolites of SD-809 (b)(4) will differ from Xenazine.

**Sponsor’s Pre-meeting Response:**
Auspex confirms that the SD-809-C-09 study will support efficacy of SD-809 Reference ID: 3235634
in Huntington’s patients with chorea, but that additional safety data may be needed to support labeling.

Meeting Discussion:
The sponsor proposed adding a placebo arm to the naïve patient study 2:1 ratio (n=30 SD-809, n=15 placebo) to provide information to describe the frequency of adverse events (AEs). The Division expressed concern that because the trial is small, it would only be able to describe the frequency of the most common adverse events. They also proposed that they would consider conducting a study that compares AEs in patients on SD-809 and placebo. Although the trial they are proposing (to provide controlled safety data) is acceptable, a relatively small number of dropouts may have a large effect on the percentage of the AEs. Higher plasma concentration in poor metabolizers may influence the incidence of events, therefore the sponsor may wish to stratify randomization by CYP2D6 genotype. Prospective blinded genotyping would help insure that poor metabolizers would be adequately represented in a trial of tetrabenazine naïve patients. The sponsor should consider adding a third arm, (Xenazine comparator), in addition to the placebo group.

(ii) Patients with liver impairment, including patients with mild elevations of transaminases, need to be excluded in the proposed pivotal trial (SD-809-C-09).

Sponsor’s Pre-meeting Response:
Auspex notes that the SD-809-C-09 includes an entry criterion, which excludes subjects with more than a 2.5-fold increase in transaminases over the upper limit of normal. Auspex believes that increases below 2.5 ULN do not pose a significant risk to patients and Auspex is unaware of any evidence that mild transaminase elevations are associated with impaired metabolism of either tetrabenazine or SD-809.

Meeting Discussion:
The Division agrees to the sponsor’s proposal and clarified that “mild hepatic impairment” refers to Child-Pugh criteria not patients who only have elevated transaminases.

The Division clarified that patients with hepatic impairment defined as Child-Pugh score of 5 points or higher must be excluded from the pivotal trials.

(iii) Doses above 24 mg/day in patients taking potent CYP2D6 inhibitors/poor CYP2D6 metabolizers should be justified. Data from Study SD-800-C-08 demonstrated that the AUC of total d6-(α+β)-HTBZ was increased 3-fold after
co-administration of SD-809 with a potent CYP2D6 inhibitor and the half-life of d6-(α+β)-HTBZ was increased 166%.

**Sponsor’s Pre-meeting Response:**
As can be predicted by the deuterium kinetic isotope effect, the drug interaction with strong CYP2D6 inhibitors is less with SD-809 than with tetrabenazine. Based on the data from SD-809-C-08 study, combined with all available pk data from both SD-809 and tetrabenazine, pk modeling predicts that the dose of SD-809 which will result in exposures greater than those observed with tetrabenazine 50mg in poor metabolizers is >36mg/day. Although it is possible that poor metabolizers who receive doses greater than 36mg/day could have higher exposures, there is significant overlap in the predicted exposures across the dose levels of 36-48mg. Since patients in the study will be titrated based on tolerability and chorea control, Auspex in believes it is justifiable to dose poor metabolizers up to 48mg SD-809 in the controlled setting of a clinical study (see Attachment 3).

**Meeting Discussion:**
The Division agreed that unblinding of CYP2D6 genotype data at doses of SD-809 above 36 mg daily is acceptable. Additionally, subjects that have already demonstrated tolerability of tetrabenazine at or above 50 mg daily need not have genotype information unblinded.

The Division agreed that unblinding in the naïve trial (SD-809-C-15) may introduce potential bias and agreed that an analysis on the effects of CYP2D6 genotype and clinical outcome may be conducted at the completion of the trial.

See also meeting discussion under Question (5g).

(iv) A PK sample needs to be collected in case of a SAE

**Sponsor’s Pre-meeting Response:**
Auspex confirms that this will be implemented in SD-809-C-09.

**Meeting Discussion:**
None.

**Potential Clinical Hold Issues**
- Your protocol does not clearly specify trial entry criteria and informed consent procedures to identify patients with diminished capacity due to cognitive impairment in Huntington’s disease. The current inclusion criteria will permit patients with a TFC score of ≥ 5 to enter the trial and patients with moderate to severe dementia and impaired judgment will be eligible to enter the trial. You
must propose standardized criteria to identify patients with diminished decision-making capacity due to Huntington’s disease. The “opinion of the investigator” is not sufficient to determine a patient’s ability for capacity to provide a valid consent. The Secretary’s Advisory Committee on Human Research Protections (SACHRP-2008) advises, “Capacity assessment should be conducted by someone other than principal investigator or others involved with research”.

- Any patient that scores in the dementia range on a standard clinical test (e.g., MMSE) must have a legally authorized representative (LAR) sign consent. Any patients with a cognitive testing result that does not meet criteria for dementia but they have a psychiatric illness or impaired judgment that the investigator suspects may impair the patients capacity to provide informed consent, must also have a legally authorized representative provide consent.

*Sponsor’s Pre-meeting Response:*
Auspex agrees to perform an MMSE at Screening in order to determine whether the patient has the capacity to provide informed consent. We propose that subjects with an MMSE \( < 20 \) at screening must have a legally authorized representative provide informed consent. Given that the MMSE is an objective measure of cognition, we believe it may be administered by the study staff.

*Meeting Discussion:*
The sponsor initially proposed requiring all patients with an MMSE score of 20 or less to have a Legally Authorized Representative (LAR) sign consent. The Division believes that all patients with an MMSE score below 28 should either have an independent evaluation by a qualified mental health provider for determination of capacity for medical research decision making or have a LAR sign consent.

The sponsor believes that MMSE is not a sensitive scale for detecting dementia or a useful scale for determining capacity. The sponsor proposed using the Total Functional Scale and the MoCA to determine capacity along with the judgment of the site investigator. The Division is open to using other methods (besides the MMSE) to screen patients for dementia; however, the sponsor should provide justification to support the procedures they select for determining that patients retain mental capacity for research participation in the protocol.

- We strongly recommend consent from patients include a research advanced directive at the time of trial entry for all long-term clinical trials. In the event that a patient loses the capacity to provide consent during the course of the trial, it would allow the patient to continue trial participation.

*Sponsor’s Pre-meeting Response:*
Auspex appreciates the advice of the Agency to obtain a research advanced directive for long term studies. We believe the SD-809-C-15 (12 weeks
treatment) and SD-809-C-09 (9 weeks treatment) do not fall into this category. For the planned long term safety study (SD-809-C-14) with SD-809, Auspex will include a research advanced directive in the consenting process.

**Meeting Discussion:**
None.

- To avoid an unreasonable and significant risk of illness or injury to human subjects by insuring the safety of patients with cognitive impairment, you must require trial participants with disabilities (physical, cognitive, or psychiatric) to have a capable live-in caregiver to observe the patients once they have entered the trial. Patients will be exposed to an increased risk for suicidality, depression, falls, and other known adverse reactions associated with tetrabenazine treatment.

**Sponsor’s Pre-meeting Response:**
In order to protect the safety of cognitively impaired subjects, Auspex agrees to require a capable live-in caregiver for subjects likely to be disabled by HD (stage II or higher), as indicated by a TFC score of < 10. Subjects with TFC scores of 11 or higher are less likely to be cognitively or physically disabled and, therefore, should not be required to have a live-in caregiver. Nonetheless, such subjects will be still be required to have a reliable caregiver who will observe the patient on a daily basis, oversee study drug administration, assure attendance at study visits and participate in evaluations, as required.

**Meeting Discussion:**
The Division recognized this may require a judgment on the part of the responsible investigator; however our primary concern is patient safety and accurate adverse event reporting by patients with impaired cognitive function.

- You must use a validated clinical questionnaire to screen for dysphagia prior to study entry. The UPDRS dysphagia and dysarthria scores do not adequately evaluate dysphagia in patients with Huntington’s disease. The ability to swallow an intact tablet is important for your ?(89) formulation because patients cannot crush, split, or dissolve the tablets.

**Sponsor’s Pre-meeting Response:**
Auspex agrees to use a validated questionnaire to screen for dysphagia in the patient studies. Auspex is considering using the Swallowing Disturbance Questionnaire (Movement Disorders, 2007; 22:1917) and would appreciate feedback from the Agency on its acceptability.

**Meeting Discussion:**
The sponsor should include a justification for the questionnaire they select for use in the trial.

- Your protocol must be revised to include a method to monitor for treatment compliance. You should propose minimum standards for compliance and provide analyses of efficacy and adverse events (number and percentages) for patients who met a reasonable standard of medication compliance.

**Sponsor’s Pre-meeting Response:**
Auspex plans to assess medication compliance by pill count at post-baseline visits. Compliance of 80% or higher will be used as a criterion for defining the per protocol population.

**Meeting Discussion:**
None.

5(b) Does the Agency agree with the primary endpoint and the primary efficacy analysis as specified in the protocol?

**FDA Preliminary Response to Question 5(b):**
Yes, the primary endpoint of an increase in the Total Maximum Chorea Score following randomized withdrawal is acceptable. However, your protocol does not address the issue of whether the increase in chorea (treatment failure) may be due to rebound (withdrawal emergent) when SD-809 is abruptly withdrawn. You should taper the dose over a longer period during the randomized withdrawal.

**Sponsor’s Pre-meeting Response:**
Based on data from the tetrabenazine 13 week parallel group study and the randomized withdrawal study, Auspex does not believe there is evidence for rebound when tetrabenazine is discontinued abruptly. Furthermore, our understanding from the Xenazine label is that there is no known withdrawal or discontinuation syndrome associated with abrupt discontinuation of tetrabenazine. Thus, Auspex does not believe tapering SD-809 is necessary.

**Meeting Discussion:**
The Division acknowledged that the Xenazine label does not require a slower tapering off of the medication, however there is concern that a withdrawal emergent effect could affect the primary endpoint.
5(c) Does the FDA agree with the key secondary endpoint and the definition of a treatment failure?

**FDA Preliminary Response to Question 5(c):**
Please explicitly state the definition of a “treatment failure” and clearly distinguish it from the definition of a “treatment success”. If you intend to describe the results of the key secondary endpoint in labeling, the results must not provide information that is similar to the information captured by the primary efficacy endpoint. We typically require replication (in a second independent trial) of the results supporting a new or comparative claim in order to describe it in labeling. The analysis of multiple secondary endpoints must include a plan to control for inflation of the type 1 error rate.

**Sponsor’s Pre-meeting Response:**
Regarding endpoints, the primary efficacy measure (change from baseline in total chorea score) is a physician assessed, quantitative variable. In contrast, the key secondary endpoint is based on a patient global measure of overall HD symptoms that is assessed by the subject. (With respect to your overall Huntington’s disease symptoms, how would you describe yourself now compared to your last study visit). Thus, Auspex believes that the key secondary endpoint does not replicate the primary endpoint.

In addition, Auspex will explicitly define a treatment failure in the protocol.

**Meeting Discussion:**
The sponsor will direct patient/caregivers to rate changes in overall function when responding to the global rating items. The sponsor believes the patient/caregiver global rating will not replicate the primary endpoint.

5(d) Are the proposed power calculations and associated statistical assumptions specified in the protocol acceptable?

**FDA Preliminary Response to Question 5(d):**
This will be discussed at the meeting.

**Sponsor’s Pre-meeting Response:**
None.

**Meeting Discussion:**
None.
5(e) Does the Agency agree with the overall approach toward dose conversion and titration and the single dose conversion scheme as outlined in the SD-809-C-09 protocol?

FDA Preliminary Response to Question 5(e):
In general, the plan for dose conversion is acceptable. However, dose titration after the initial conversion should be guided by control of chorea and the emergence of adverse reactions including drug induced Parkinsonism.

Sponsor’s Pre-meeting Response:
We agree that dose titration must be guided by chorea control and assessment of adverse events.

Meeting Discussion:
None.

5(f) Does the Agency agree that assessment of chorea prior to dose conversion and during the titration period are sufficient to evaluate the adequacy of chorea control during the switch?

FDA Preliminary Response to Question 5(f):
Yes, the assessment of chorea prior to and during dose conversion is acceptable. However, during the titration and maintenance phase, assessment of chorea by telephone will not evaluate patients for the severity of their chorea in patients who may have decreased awareness of their chorea. You should also revise your protocol to evaluate patients for developing signs and symptoms of drug induced Parkinsonism. Disability caused by drug induced Parkinsonism due to SD-809 may diminish a potential benefit associated with reduced chorea. You should provide an analysis of motor function that includes at least postural stability, gait, and voluntary motor performance. In addition, you must monitor patients for orthostatic changes in vital signs (pulse and BP) in the supine and standing position at baseline and during all face-to-face visits.

Sponsor’s Pre-meeting Response:
Auspex believes that caregiver involvement in telephone evaluations will allow an assessment of chorea and adverse events sufficient for the purpose of dose adjustment. In each case, telephone evaluations are followed by in clinic evaluation. Auspex also believes that drug induced Parkinsonism and postural stability are reliably assessed by the motor subscale of the UHDRS. SD-809 was not associated with orthostatic blood pressure changes in Phase 1 studies to date. In response to the Agency request, we would propose assessing orthostatic vital signs at baseline and once during titration and maintenance.
**Meeting Discussion:**

*The sponsor believes that requiring additional in-person visits may not be practical for patients with Huntington’s disease. However, the sponsor will make patients and caregivers aware of phone visits and remind them of scheduled telephone visits during in-person visits. In addition, investigators will seek information from caregivers before making the decision to increase the dose of study medication by phone. Patients who miss their telephone visit will not receive study medication for the next week of the trial until the telephone visit is complete.*

**5(g)** Does the Agency agree that these data can be analyzed after completion of the study to evaluate the influence of genotype on the clinical outcomes of patients titrated to their optimal dose?

**FDA Preliminary Response to Question 5(g):**
No. Blood samples for CYP2D6 genotyping should be collected at screening. Patients receiving SD-809 doses equivalent to 50 mg daily of Xenazine (i.e., >24 mg daily) who are being considered for further dose escalation should have CYP2D6 genotyping performed in a manner consistent with the Xenazine labeling. Additional dose increases in patients identified as poor metabolizers and those who are receiving CYP2D6 inhibiting drugs should be at the physicians discretion based on metabolic status, tolerability, and response. Otherwise, it is acceptable to evaluate the influence of genotype on clinical outcomes after completion of the study.

**Sponsor’s Pre-meeting Response:**
Auspex agrees to unblind genotype at estimated exposures greater than observed with 50 mg of tetrabenazine in poor metabolizers. As indicated in the response to Question 4 and the information in attachment 3, genotyping should be unblinded at doses greater than 36 mg SD-809.

**Meeting Discussion:**

*Please see meeting discussion under question 5(a)(iii).*

**5(h)** Does the agency agree that the pharmacokinetic blood sampling strategy proposed in the pivotal study will support the requirements for population pharmacokinetics?

**FDA Preliminary Response to Question 5(h):**
Yes.

**Sponsor’s Pre-meeting Response:**
None.

**Meeting Discussion:**
None.

5(i) Does FDA have any other comments on the proposed SD-809-C-09 protocol that may impact its acceptability as a single pivotal trial to support approval of SD-809 as part of a 505(b)(2) NDA?

**FDA Preliminary Response to Question 5(i):**
A single trial may be adequate to support the efficacy portion of an application, however, it is a matter for review. Please refer to comments regarding the need for adequate safety information.

**Sponsor’s Pre-meeting Response:**
Auspex agrees.

**Meeting Discussion:**
None.

Question 6:

6(a) Does the Agency agree with the proposed naïve patient study design, including the target population to be studied and adoption of the Xenazine titration frequency, for this trial?

**FDA Preliminary Response to Question 6(a):**
The proposed naïve patient study (SD-809-C-15) design will not provide controlled safety information that could be described in labeling.

**Sponsor’s Pre-meeting Response:**
See 6b.

**Meeting Discussion:**
None.

6(b) Does the Agency agree that the safety data from this open-label trial (SD-809-C-15) can be included in the SD-809 product labeling as frequency (%) of adverse events observed in order to provide specific SD-809 safety data and guidance for prescribers treating naïve patients?

**FDA Preliminary Response to Question 6(b):**
Please see our response to Question 6(a). The design of a long-term safety trial (SD-809-C-14) was not included in the meeting package, therefore we are unable.
to comment on the design or the potential of the information from the trial to support statements in labeling. In general, adverse event data from controlled trials that included blinded treatment assignments are included in labeling. Open label data would attribute all adverse events observed in the trial to SD-809.

**Sponsor’s Pre-meeting Response:**
Auspex would like to discuss whether inclusion of a placebo control group (e.g., 30 active: 15 placebo) in a double blind, randomized, placebo controlled investigation would allow inclusion of adverse event frequency in the product label.

**Meeting Discussion:**
None.

**Question 7:**
Does the FDA agree that the clinical development plan as outlined in this package is adequate to support an indication of chorea associated with HD, including both patients switching from tetrabenazine to SD-809 (based on SD-809-C-09) as well as naïve patients titrated onto SD-809 (based on SD-809-C-15)?

**FDA Preliminary Response to Question 7:**
Please see our previous comments regarding the design of SD-809-C-09 and SD809-C-15. In study SD-809-C-15, blood samples for CYP2D6 genotyping should be collected from all subjects at screening, consistent with study SD-809-C-09. CYP2D6 genotyping should be performed prospectively in subjects receiving doses equivalent to 50 mg tetrabenazine who are being considered for further dose escalation, as recommended under Question 5(g).

**Sponsor’s Pre-meeting Response:**
Auspex agrees to unblind genotype at estimated exposures greater than observed with 50 mg of tetrabenazine in poor metabolizers. As indicated in the response to Question 4 and the information in attachment 3, genotype should be unblinded at doses greater than 36 mg SD-809.

Auspex would like further clarification as to whether conducting the Switch and Naïve studies will support the proposed indication, given the protocol modifications proposed above.

**Meeting Discussion:**
Please see meeting discussion under question 5(a)(iii).
**Question 8:**
Given the indistinguishable pharmacology between SD-809 and tetrabenazine, as well as the planned human clinical safety data available at the time of submission, does the Agency agree that the planned exposure is adequate for submission of a 505(b)(2) NDA for review with the Reference Listed Drug being Xenazine (tetrabenazine)?

**FDA Preliminary Response to Question 8:**
The design of your planned long-term study SD-809-C-14 is not included in the EOP2 meeting package. You have not adequately described the size and duration of exposure for patients included in the long-term safety database. In addition, the controlled safety information generated by the current protocols will not be adequate. The adequacy of the safety database and the ability to rely on the Agency’s determination that tetrabenazine is safe will depend on how similar SD-809 [b] is to Xenazine with respect to the levels of the active metabolites and on the condition that there are no new significant metabolites that are unique to SD-809.

**Sponsor’s Pre-meeting Response:**
Auspex expects to have >100 patient exposures, at least 50 of which would have 6 months exposure or more at the time of NDA submission.

**Meeting Discussion:**
None.
4.0 PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 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. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

5.0 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

6.0 ATTACHMENTS AND HANDOUTS

The following attachments, provided by the sponsor and presented during the meeting, are appended to this document.

Attachment 1: Related substances justification of [REDACTED]
Attachment 2: Metabolic profile update
Attachment 3: Simulated pharmacokinetic parameters
ATTACHMENT 1: Related substances justification

Related Substance Limits of [REDACTED] in SD-809 [REDACTED]

Conclusions:

- [REDACTED]: No further study needed; exists as an isomer of SD-809, rats in toxicology studies expected to have experienced at least [REDACTED] % [REDACTED] after dosing.
- [REDACTED]: Qualified at [REDACTED] % of a maximum daily dose of 48 mg SD-809 [REDACTED]

Note: Specifications will be evaluated and modified prior to NDA submission based on manufacturing experience and stability as more data is acquired.
Isomerization of SD-809

Therefore, is anticipated to be present in gastric fluid at quantities exceeding those in current drug product batches and at quantities exceeding the proposed specification limit of .
ATTACHMENT 2: Metabolic profile update

The EOP2 package presented preliminary results from the comparative human mass balance recovery and metabolite profile study of radiolabeled SD-809 and tetrabenazine (Auspex study SD-809-C-12), with preliminary major metabolite levels based on a single pooled sample per cohort based on time proportional pooling (2-12 hours post dose). Data are now available from individual subjects (Table 1).

Table 1: Comparison of Metabolites M1-M6 of SD-809 and Tetrabenazine, updated results

<table>
<thead>
<tr>
<th>Metabolite Number and Identification</th>
<th>SD-809, n = 6*</th>
<th>Tetrabenazine, n = 6*</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1, Acid Metabolite of HTBZ</td>
<td>8.6 (4.5)</td>
<td>4.2 (2.0)</td>
</tr>
<tr>
<td>M2, Sulphate of O-desmethyl HTBZ</td>
<td>2.5 (1.1)</td>
<td>6.4 (2.9)</td>
</tr>
<tr>
<td>M3, Sulphate of O-desmethyl HTBZ</td>
<td>4.0 (1.5)</td>
<td>16.4 (5.6)</td>
</tr>
<tr>
<td>M4, +16 amu Metabolite</td>
<td>12.9 (3.2)</td>
<td>15.6 (4.9)</td>
</tr>
<tr>
<td>M5, β-HTBZ</td>
<td>8.3 (4.2)</td>
<td>1.8 (1.5)</td>
</tr>
<tr>
<td>M6, α-HTBZ</td>
<td>13.0 (4.6)</td>
<td>4.0 (1.4)</td>
</tr>
</tbody>
</table>

*: For individual subject data, see Tables 2 and 3

As shown above, the major human metabolites of SD-809 are M4 (+16 amu) and M6 (d₆-α-HTBZ).

M6: M6 is the active SD-809 active metabolite d₆-α-HTBZ (Table 1). The increase in d₆-α-HTBZ as a metabolite of SD-809 relative to tetrabenazine is an expected consequence of deuterium substitution.

M4: M4 is a major metabolite of SD-809 as well as tetrabenazine (Table 1). The % sample radioactivity ascribed to M4 in the SD-809 and tetrabenazine cohorts is similar.

M1: M1, currently defined as a carboxylic acid of HTBZ, is not a major metabolite of either SD-809 or tetrabenazine; in the preliminary results M1 was defined as a major metabolite of SD-809 (Table 2).

Doses of SD-809 in patient trials will be reduced by approximately 50% relative to tetrabenazine in order to provide similar systemic exposure to (α+β)-HTBZ. Thus, when the plasma concentrations of the d₆-HTBZ metabolites are optimized through SD-809 dose reduction, the systemic exposure to M1 as a metabolite of SD-809 is unlikely to exceed that already experienced by patients administered tetrabenazine.
Table 2 - M1-M6 metabolites of SD-809 (Subjects S001-S006), updated individual and preliminary results:

<table>
<thead>
<tr>
<th>Identification</th>
<th>Metabolite Number</th>
<th>S001</th>
<th>S002</th>
<th>S003</th>
<th>S004</th>
<th>S005</th>
<th>S006</th>
<th>Average (SD), n = 6</th>
<th>Preliminary, cohort pool in EOP2 package</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Metabolite of HTBZ</td>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.6 (4.5)</td>
<td>12.7</td>
</tr>
<tr>
<td>Sulphate of O-desmethyl HTBZ</td>
<td>M2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5 (1.1)</td>
<td>4.9</td>
</tr>
<tr>
<td>Sulphate of O-desmethyl HTBZ</td>
<td>M3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0 (1.5)</td>
<td>4.5</td>
</tr>
<tr>
<td>+ 16 amu Metabolite</td>
<td>M4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.9 (3.2)</td>
<td>19.9</td>
</tr>
<tr>
<td>β-HTBZ</td>
<td>M5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.3 (4.2)</td>
<td>13.3</td>
</tr>
<tr>
<td>α-HTBZ</td>
<td>M6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.0 (4.6)</td>
<td>15.9</td>
</tr>
</tbody>
</table>

Table 3 - M1 through M6 metabolites of Tetrabenazine (Subjects S007-S012), updated individual and preliminary results

<table>
<thead>
<tr>
<th>Identification</th>
<th>Metabolite Number</th>
<th>S007</th>
<th>S008</th>
<th>S009</th>
<th>S010</th>
<th>S011</th>
<th>S012</th>
<th>Average (SD), n = 6</th>
<th>Preliminary, cohort pool in EOP2 package</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Metabolite of HTBZ</td>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.2 (2.0)</td>
<td>4</td>
</tr>
<tr>
<td>Sulphate of O-desmethyl HTBZ</td>
<td>M2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.4 (2.9)</td>
<td>18.7</td>
</tr>
<tr>
<td>Sulphate of O-desmethyl HTBZ</td>
<td>M3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.4 (5.6)</td>
<td>15.4</td>
</tr>
<tr>
<td>+ 16 amu Metabolite</td>
<td>M4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.6 (4.9)</td>
<td>11.7</td>
</tr>
<tr>
<td>β-HTBZ</td>
<td>M5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8 (1.51)</td>
<td>2.2</td>
</tr>
<tr>
<td>α-HTBZ</td>
<td>M6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0 (1.4)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

It was noted that although M2 was a major tetrabenazine metabolite in preliminary analysis, it was not a major metabolite when individual data were analyzed due to improved chromatic resolution of the peak associated with M2.
ATTACHMENT 3: Simulated pharmacokinetic parameters

Simulated Pharmacokinetic Parameters ($\text{AUC}_{0-24}$, $\text{C}_{\text{max}}$) of total-(α+β)-HTBZ from Tetrabenazine (up to 50 mg/day) and SD-809 (up to 48 mg/day) in CYP2D6Poor Metabolizers

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Treatment</th>
<th>Total daily dose</th>
<th>Regimens</th>
<th>Median Values [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC$_{0-24SS}$ (h.ng/mL)</td>
</tr>
<tr>
<td>1</td>
<td>TBZ</td>
<td>25 mg</td>
<td>12.5 mg BID</td>
<td>1510 [819-2943]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>12 mg</td>
<td>6 mg BID</td>
<td>1061 [635-2034]</td>
</tr>
<tr>
<td>2</td>
<td>TBZ</td>
<td>37.5 mg</td>
<td>12.5 mg TID, 25/12.5, 12.5/25</td>
<td>2750 [1499-5326]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>18 mg</td>
<td>12/6 mg</td>
<td>1740 [1058-3105]</td>
</tr>
<tr>
<td>3</td>
<td>TBZ</td>
<td>50 mg</td>
<td>25 mg BID, 25/12.5/12.5, 12.5/25/12.5</td>
<td>4200 [2296-8155]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>24 mg</td>
<td>12 mg BID</td>
<td>2435 [1451-4723]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>30 mg</td>
<td>18/12 mg</td>
<td>3222 [1942-5775]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>36 mg</td>
<td>18 mg BID</td>
<td>3962 [2348-7735]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>42 mg</td>
<td>24/18 mg</td>
<td>4839 [2897-8695]</td>
</tr>
<tr>
<td></td>
<td>SD-809</td>
<td>48 mg</td>
<td>24 mg BID</td>
<td>5607 [3305-10980]</td>
</tr>
</tbody>
</table>
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/s/

RUSSELL G KATZ
12/26/2012
LATE-CYCLE COMMUNICATION
DOCUMENTS
Dear Dr. Schulteis:

Please refer to your New Drug Application (NDA) dated May 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for AUSTEDO (deutetrabenazine) Oral Tablets 6 mg, 9 mg, and 12 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 25, 2016.

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 Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-2139.

Sincerely,

[See appended electronic signature page]

Gerald D. Podskalny, DO, MSPH
Clinical Team Lead
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 25, 2016; 11:00-12:00 PM EST
Meeting Location: FDA White Oak: Bldg 22/Room 1309

Application Number: NDA 208082
Product Name: AUSTEDO (deutetrabenazine) Oral Tablets
Applicant Name: Teva Pharmaceuticals

Meeting Chair: Dave Podskalny, DO, MPHS, CDTL
Meeting Recorder: Stacy Metz, PharmD, RPM

FDA ATTENDEES
Ellis Unger, MD, ODE I (signatory)
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Dave Podskalny, MO, MPHS, CDTL (Clinical Team Lead)
Ken Bergmann, MD, Clinical Reviewer
Martha Heimann, PhD, CMC Team Lead
Lois Freed, PhD, Supervisory Pharmacologist
Chris Toscano, PhD, Nonclinical Reviewer
Angela Men, PhD, Clin Pharm Lead
Kristina Dimova, PhD, Clinical Pharmacology Reviewer
Xiaofeng Wang, PhD, Clinical Pharmacology Staff
Xiangmin Zhang, PhD, Statistical Reviewer
Naomi Lowy, MD, Medical Officer
Justine Harris, PhD, DMEPA Reviewer
LaShawn Dianat, PharmD, RPM DNP
Stacy Metz, PharmD, RPM DNP

EASTERN RESEARCH GROUP ATTENDEES
Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES
Dennis Ahern, MS, Senior Director, Global Regulatory Affairs
Len Alansky, Associate Director, CMC Regulatory Affairs
Margaret Bradbury, PhD, Senior Director, Research and Development
1.0 BACKGROUND

NDA 208082 was submitted on May 29, 2015 for AUSTEDO (deutetrabenazine) Oral Tablets

Proposed indication(s): Treatment of chorea associated with Huntington’s disease

PDUFA goal date: May 29, 2016

FDA issued a Background Package in preparation for this meeting on February 19, 2016.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (Gerald Podskalny, DO, MPH, CDIL/Stacy Metz, PharmD, RPM) --Welcome, Introductions, Ground rules, Objectives of the meeting

Meeting Discussion:

No further discussion at the meeting.

2. Discussion of Substantive Review Issues – 30 minutes (if needed)

Each issue will be introduced by FDA and followed by a discussion.

Clinical Pharmacology

- Metabolite Profiling and Identification results of the mass balance study SD-809-C-12 are inconclusive.
- The daily dose of SD-809 should not exceed 36 mg in patients taking strong CYP2D6 inhibitors and in patients who are CYP2D6 poor metabolizers.
Nonclinical

- TK analysis of SD-809 metabolites in nonclinical studies are limited to quantitation of the primary metabolites of SD-809 in plasma at steady-state. Therefore, if additional major human metabolites are identified, there are insufficient data to determine if they have been adequately tested in the appropriate nonclinical studies.

Meeting Discussion:

The division stated that the currently available data are not adequate to determine if all major circulating metabolites in humans have been adequately assessed in the appropriate nonclinical studies.

The available human experience with SD-809 or tetrabenazine may provide adequate information on the general toxicology of any major metabolites. However, previous human experience cannot address potential drug-related effects on reproductive and developmental toxicology or on carcinogenic potential. For each major human metabolite, you will need to provide plasma exposure data to bridge to the appropriate nonclinical studies of the RLD, as described in labeling.

3. Additional Applicant Data – 15 minutes (Applicant)

- Additional data or analyses (and proposed timelines) the applicant may wish to submit in response to FDA concerns/issues.

Meeting Discussion:

Differences between the results of Study SD-809-C-12 ([14C]-human ADME and mass balance study) and the study performed with tetrabenazine for the original Xenazine NDA were discussed.

The Clinical Pharmacology reviewer discussed the Agency’s opinion that the metabolite profiling and identification results of the mass balance study SD-809-C-12 are inconclusive.

- The results of the sponsor’s mass balance study regarding M1 as a major human metabolite (MHM; >10% total drug-related exposure), are inconclusive. The sponsor needs to assess levels of M1 using a validated assay.

- The ratios between deuterated and nondeuterated α-HTBZ and β-HTBZ metabolite exposures are two times higher in Study SD-809-C-12 than in the other Phase 1 studies.

- The plasma samples chosen for metabolite profiling (2, 2.5, 6, and 12 h) might not reflect the true relative exposure (AUC) of each analyte, and could be responsible for the
discrepancy between the original data for Xenazine (NDA 21894) and the SD-809-C-12 study results.

- In the mass-balance and metabolite identification study conducted with TBZ (NDA 21894), a total of 13 plasma samples, covering most of the concentration-time profile, including the time points where the max concentration of radioactivity in plasma was observed, were used for plasma pooling for metabolite profiling and identification.

The Clinical Pharmacology review team encouraged the sponsor to validate assays and quantify the M1 and M4 metabolites. Exposure at steady state (AUC) should be provided for M1 or M4 in animals and humans. Metabolite assessment in animals based on normalized peak height is not acceptable. The Clinical Pharmacology review team proposed that evaluating systemic exposure to the deuterated metabolites M1 and M4 from existing clinical study samples may provide the needed information. In addition, as the sponsor is unable to reference the activity of the metabolites M1 and M4 from past experience with Xenazine, M1 and M4 need to be evaluated in in vitro studies (VMAT2 and off-target binding).

The sponsor expressed concern regarding the stability of M1 and M4 in plasma samples, including those in which steady-state exposure had been achieved for α-HTBZ and β-HTBZ.

The sponsor suggested the clinical experience with tetrabenazine and the safety profile of SD-809 in the placebo-controlled and long-term safety studies in Huntington’s disease (SD-809-C-15 and SD-809-C-16) provides evidence for the safety of SD-809 and its metabolites. However, the review team noted, the clinical safety database would not provide information needed to address reproductive toxicity or carcinogenicity.

The sponsor can rely on information contained in the Xenazine label. However, the sponsor may not rely on proprietary information contained in the publically available versions of FDA reviews or on what was formerly known the “Summary Basis of Approval”.

4. Review Plans – 5 minutes
   The review goal date is March 29, 2016.

Meeting Discussion:
No further discussion at the meeting.
5. Wrap-up and Action Items – 5 minutes (Chair will summarize any outstanding action items)

- The sponsor acknowledged the need to limit the dose to 36 mg/day in patients with CYP2D6 impairment.

- The pharmacokinetic bridging strategy to the listed drug (Xenazine) was acceptable to the Agency.

- The Sponsor will submit a proposal to the Agency to address the concerns regarding the M1 and M4 metabolites. The Agency will provide comment to the sponsor regarding their proposal and the review timeline for the submission of new information.

*This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.*
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/s/

GERALD D PODSKALNY
03/21/2016