CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206500Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206500 SUPPL # HFD #

Trade Name Varubi

Generic Name rolapitant

Applicant Name Tesaro, Inc.

Approval Date, If Known September 1, 2015

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)(1)

c) 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:

d) 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

e) 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: Mary Chung
Title: Regulatory Project Manager
Date: 08/21/15

Name of Office/Division Director signing form: Donna Griebel
Title: Division Director/ Division of Gastroenterology and Inborn Errors Products

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/

MARY H CHUNG
08/31/2015

DONNA J GRIEBEL
08/31/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206500 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Varubi Established/Proper Name: rolapitant Dosage Form: tablets		Applicant: Tesaro, Inc. Agent for Applicant (if applicable):
RPM: Mary Chung		Division: Division of Gastroenterology and Inborn Errors Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
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 draft[2] 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 September 1, 2015 • User Fee Goal Date is September 5, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ 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/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[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): New Molecular Entity
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

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
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes *Sponsor requests 5 year NCE exclusivity*
❖ 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

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action and date Approval on September 1, 2015 Letter
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 9/1/15
• Original applicant-proposed labeling	☒ Included 9/5/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included 9/1/15
• Original applicant-proposed labeling	☒ Included 10/7/14
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 8/31/15, 6/19/15
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters: 3/31/15, 11/21/14 Reviews: 3/30/15, 11/18/14
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 11/18/14 DMEPA: ☐ None 7/7/15, 4/30/15 DMPP/PLT (DRISK): ☐ None 5/8/15 OPDP: ☐ None 5/8/15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None DPMH Maternal: 5/5/15
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/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	11/4/14 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC April 29, 2015 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• 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)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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 previous action letters, as these are located elsewhere in package)*	9/1/15; 8/27/15; 8/19/15; 8/18/15; 8/13/15, 8/12/15, 8/7/15, 8/6/15, 7/31/15, 7/30/15, 7/20/15, 7/8/15, 7/6/15, 7/2/15 , 5/20/15, 5/12/15, 5/1/15, 4/21/15, 4/15/15, 4/3/15, 3/26/15, 3/18/15, 3/17/15, 3/11/15, 3/9/15, 2/25/15, 2/10/15, 2/6/15 , 2/3/15, 1/21/15, 12/23/14, 12/3/14, 11/18/14 , 11/13/14
❖ 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)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 7/2/14
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A 2/12/15
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A 6/3/15
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	CMC only EOP2: 1/28/13

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 9/1/15
Division Director Summary Review *(indicate date for each review)*	☐ None 9/1/15
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None
PMR/PMC Development Templates *(indicate total number)*	☐ None 9/1/15
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	☐ None 9/1/15, 5/12/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See clinical review 5/12/15 page 15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DPMH Pediatrics: 5/5/15 QT IRT: 10/23/14 SEALD: 5/12/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ N/A 5/5/15
❖ 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)*	REMS not necessary review: ☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 5/4/15
Clinical Microbiology ☒ None	
❖ 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 ☐ None	
❖ 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 5/26/15

Clinical Pharmacology ☐ None	
❖ 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 5/5/15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review 3/9/15
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3/19/15
❖ 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 198
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ 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 5/4/15
❖ 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)*	5/4/15
☐ 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 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ 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/

MARY H CHUNG
09/03/2015

Chung, Mary

From: Chung, Mary
Sent: Tuesday, September 01, 2015 1:21 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Label Comment

Hello Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to labeling submission (carton container and PI/PPI) dated August 31, 2015.

(b) (4)

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
09/01/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, August 27, 2015 6:41 PM
To: Jennifer Jackson (jjackson@tesarobio.com)
Cc: GRossi@tesarobio.com; Chung, Mary
Subject: NDA 206500 rolapitant - carton/container label

Hello Jennifer,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to carton/container labels submitted on August 18, 2015, and August 5, 2015.

The container/carton labels provided on August 18, 2015 are not acceptable.

The carton/container labels provided on August 5, 2015, is the version that addresses our carton/container labeling comments provided. The August 5, 2015 carton/container labeling includes the trade name, USAN drug name (rolapitant) and USAN drug substance name (rolapitant hydrochloride) as well as the equivalency statement in parenthesis.

Please resubmit carton/container labeling that is consistent with our comments provided, which is the version submitted on August 5, 2015.

Please submit this by August 28, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/28/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, August 27, 2015 5:59 PM
To: Jennifer Jackson (jjackson@tesarobio.com)
Cc: GRossi@tesarobio.com; Chung, Mary
Subject: NDA 206500 rolapitant - PI and PPI
Attachments: NDA 206500 rolapitant FDA proposed PI clean copy 8-27-15.doc; NDA 206500 rolapitant FDA proposed PI clean copy 8-27-15.pdf; NDA 206500 rolapitant FDA proposed PI tracked changes 8-27-15.doc; NDA 206500 rolapitant FDA proposed PI tracked changes 8-27-15.pdf; NDA 206500 rolapitant FDA proposed PPI clean copy 8-27-15.doc; NDA 206500 rolapitant FDA proposed PPI clean copy 8-27-15.pdf; NDA 206500 rolapitant FDA proposed PPI tracked changes 8-27-15.doc; NDA 206500 rolapitant FDA proposed PPI tracked changes 8-27-15.pdf

Good afternoon,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

On August 18, 2015, we received your proposed labeling submission to this application (PI and PPI), and have proposed revisions that are included as an enclosure (PI and PPI). We request that you resubmit labeling that addresses these issues by August 28, 2015.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

---

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

/s/

MARY H CHUNG
08/27/2015

Chung, Mary

From: Chung, Mary
Sent: Wednesday, August 19, 2015 12:26 PM
To: Jennifer Jackson (jjackson@tesarobio.com)
Cc: GRossi@tesarobio.com; Chung, Mary
Subject: NDA 206500 rolapitant- Clinical Information Request

Good afternoon,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information.

- Please provide a complete patient narrative for patient 020-00537 in Study 51 who met criteria for Hy's Law. Specifically, we are interested in the following:
    1. Did this patient have any symptoms associated with the increased liver enzymes?
    2. What were the patient's concomitant medications?
    3. Was the patient jaundiced?

We request to receive this information to the NDA by August 21, 2015, or before if possible.
It would be appreciated if you could please confirm receipt of this message.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/19/2015

Chung, Mary

From: Chung, Mary
Sent: Tuesday, August 18, 2015 3:58 PM
To: Jennifer Jackson (jjackson@tesarobio.com)
Cc: GRossi@tesarobio.com; Chung, Mary
Subject: NDA 206500 rolapitant - Clinical Information Request

Good afternoon,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

> Reference is made to section 14, "Multiple-Cycle Extension" section of the PI. Please provide three bar graphs showing the results cycles 2 through 6 of studies 1, 2, and 3 for the proportion of patients with no vomiting/retching and no nausea that interfered with normal day activities. The graphs should include the number of patients in each treatment cycle and the confidence interval by study.

We request to receive this information to the NDA by August 20, 2015.
It would be appreciated if you could please confirm receipt of this message.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/18/2015

Chung, Mary

From: Chung, Mary
Sent: Tuesday, August 18, 2015 3:59 PM
To: Jennifer Jackson (jjackson@tesarobio.com)
Cc: GRossi@tesarobio.com; Chung, Mary
Subject: NDA 206500 rolapitant - Clinical Information Request

Good afternoon,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information.

For patients in Studies 32, 33, and 34, please provide TEAE data by age using the following cut point: < 65 and ≥ 65.

We request to receive this information to the NDA by August 20, 2015.
It would be appreciated if you could please confirm receipt of this message.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/18/2015

Chung, Mary

From: Gabriela Rossi <GRossi@tesarobio.com>
Sent: Thursday, August 13, 2015 1:16 PM
To: Chung, Mary
Subject: RE: NDA 206500 rolapitant PMR and PMC
Attachments: emfinfo.txt

Hello Mary,

I confirm Tesaro's agreement with the proposed list of PMR and PMC and associated timelines below.

Regards,

Gabriela

From: Chung, Mary [mailto:Mary.Chung@fda.hhs.gov]
Sent: Thursday, August 13, 2015 8:56 AM
To: Gabriela Rossi
Cc: Chung, Mary
Subject: NDA 206500 rolapitant PMR and PMC

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We also refer to our proposed list of Post Marketing Requirements (PMR) and Post Marketing Commitments (PMC) for this application transmitted to you on July 31, 2015, and your responses and comments provided on August 5, 2015. Please see below current list of proposed PMRs and PMCs for this application. Please confirm your agreement with these requirements and commitments, including agreement with the proposed milestone dates.

We request that you provide your response by August 14, 2015. Thank you.

GLP toxicology study in juvenile rats
Final Report Submission: 1/30/2017

A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of rolapitant in pediatric patients ages 0-17 years old
Final Protocol Submission: 2/28/2017
Study/Trial Completion: 7/31/2020
Final Report Submission: 11/30/2020

A study to evaluate the efficacy and safety of a single oral dose of rolapitant in pediatric patients aged 0-17 years old
Final Protocol Submission: 11/30/2020
Study/Trial Completion: 04/30/2026
Final Report Submission: 08/30/2026

In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant
Final Protocol Submission: 12/31/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 06/30/2016

In vitro studies to evaluate the inhibitory potential of rolapitant on renal transporters i.e. organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3)

Final Protocol Submission: 12/31/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 06/30/2016

In vitro study to evaluate the inhibitory potential of rolapitant on OATP1B1, and OATP1B3. The in vitro study results will determine the need for subsequent clinical assessments of drug interactions (b) (4)

Final Protocol Submission: 2/28/2016
Study/Trial Completion: 06/30/2016
Final Report Submission: 08/31/2016

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/17/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, August 13, 2015 8:55 AM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- PMC

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to our July 31, 2015 correspondence on the proposed PMRs/PMCs for this application. You indicated in your response on August 5, 2015, for PMC *"In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant,"* (b) (4) You also proposed to modify the milestone dates of this PMC.

(b) (4)
l.

You need to submit the protocol to fulfill this PMC indicated as a PMC protocol, according to the timelines agreed upon for this PMC.

(b) (4)

We propose to keep our July 31, 2015 proposed timelines for this PMC.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/13/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, August 13, 2015 8:56 AM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant PMR and PMC

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We also refer to our proposed list of Post Marketing Requirements (PMR) and Post Marketing Commitments (PMC) for this application transmitted to you on July 31, 2015, and your responses and comments provided on August 5, 2015. Please see below current list of proposed PMRs and PMCs for this application. Please confirm your agreement with these requirements and commitments, including agreement with the proposed milestone dates.

We request that you provide your response by August 14, 2015. Thank you.

GLP toxicology study in juvenile rats
Final Report Submission: 1/30/2017

A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of rolapitant in pediatric patients ages 0-17 years old
Final Protocol Submission: 2/28/2017
Study/Trial Completion: 7/31/2020
Final Report Submission: 11/30/2020

A study to evaluate the efficacy and safety of a single oral dose of rolapitant in pediatric patients aged 0-17 years old
Final Protocol Submission: 11/30/2020
Study/Trial Completion: 04/30/2026
Final Report Submission: 08/30/2026

In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant
Final Protocol Submission: 12/31/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 06/30/2016

In vitro studies to evaluate the inhibitory potential of rolapitant on renal transporters i.e. organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3)

Final Protocol Submission: 12/31/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 06/30/2016

In vitro study to evaluate the inhibitory potential of rolapitant on OATP1B1, and OATP1B3. The in vitro study results will determine the need for subsequent clinical assessments of drug interactions (b) (4).

Final Protocol Submission: 2/28/2016
Study/Trial Completion: 06/30/2016
Final Report Submission: 08/31/2016

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/13/2015

Chung, Mary

From: Chung, Mary
Sent: Wednesday, August 12, 2015 6:55 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- FDA comments on PI & PPI
Attachments: NDA 206500 rolapitant FDA proposed PI 8-12-15 clean copy.doc; NDA 206500 rolapitant FDA proposed PI 8-12-15 clean copy.pdf; NDA 206500 rolapitant FDA proposed PI 8-12-15 tracked changes.doc; NDA 206500 rolapitant FDA proposed PI 8-12-15 tracked changes.pdf; NDA 206500 rolapitant FDA proposed PPI 8-12-15 clean copy.doc; NDA 206500 rolapitant FDA proposed PPI 8-12-15 clean copy.pdf; NDA 206500 rolapitant FDA proposed PPI 8-12-15 tracked changes.doc; NDA 206500 rolapitant FDA proposed PPI 8-12-15 tracked changes.pdf

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

On July 29, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (for both PI and PPI). We request that you resubmit labeling that addresses these issues by August 17, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

---

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

/s/

MARY H CHUNG
08/12/2015

Chung, Mary

From: Chung, Mary
Sent: Friday, August 07, 2015 9:34 AM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant - Clinical Information Request

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

Please provide any available update on the pregnancy outcome of Patient 00306, Study P04852.

We request to receive a response to this request by Monday August 10, 2015 .

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/07/2015

Chung, Mary

From: Chung, Mary
Sent: Wednesday, March 11, 2015 8:27 AM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Please confirm whether you have submitted a 4-month safety update report for NDA 206500 in accordance with 21 CFR 314.50(d)(5)(vi)(b). If this has not been submitted you should submit the 4-month safety update report according to 21 CFR 314.50(d)(5)(vi)(b) to the NDA.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/06/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, March 26, 2015 1:44 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Information Request: Pediatric/Pediatric Plan

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to Section 1.9 Pediatric Administrative Information. This section requires the following additional information:

> Section 1.9.2.3 Certification: The sponsor should certify that all statements made in their request for deferral of pediatric studies are true and correct, and that the information included is believed to adequately support the Request for a Deferral of Pediatric Studies. In this section, the applicant should also certify that the clinical studies of NDA 206500 in pediatric patients will be conducted with due diligence at the earliest possible time.

Please submit this information to the NDA as an amendment to Section 1.9 by April 3, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/06/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, August 06, 2015 5:47 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Clinical Information Request

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

Can you please provide the numbers and proportions of patients in each treatment group (phase 3 studies only) who were dosed rolapitant at a 14 day interval by completing the following simple table

Rolapitant Phase 3 Patients

	Received rolapitant at a 14 day interval during any phase 3 study	Received rolapitant during any phase 3 study
Number of patients		

We request a response to the above will be provided as soon as possible. Thank you.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
08/06/2015

Chung, Mary

From: Chung, Mary
Sent: Friday, July 31, 2015 11:28 AM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- PMR/PMC

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Please see below the current list of Post Marketing Requirements (PMR) and Post Marketing Commitments (PMC) for this application. Please confirm your agreement with these requirements and commitments, including agreement with the proposed milestone dates.
We request that you provide your response by August 4, 2015.

Post Marketing Requirements

GLP toxicology study in juvenile rats

Final Report Submission: 11/30/2016

A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of rolapitant in pediatric patients ages 0-17 years old

Final Protocol Submission: 2/28/2017
Study/Trial Completion: 1/31/2020
Final Report Submission: 11/30/2020

A study to evaluate the efficacy and safety of a single oral dose of rolapitant in pediatric patients ages 0-17 years old

Final Protocol Submission: 08/30/2019
Study/Trial Completion: 08/30/2025
Final Report Submission: 08/30/2026

Post Marketing Commitments

In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant

Final Protocol Submission: 12/31/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 06/30/2016

In vitro studies to evaluate the inhibitory potential of rolapitant on renal transporters i.e. organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3)

Final Protocol Submission: 12/31/2015
Study/Trial Completion: 04/30/2016
Final Report Submission: 06/30/2016

In vitro study to evaluate the inhibitory potential of rolapitant on OATP1B1, and OATP1B3. The in vitro study results will determine the need for subsequent clinical assessments of drug interactions (b) (4)

Final Protocol Submission:	2/28/2016
Study/Trial Completion:	06/30/2016
Final Report Submission:	08/31/2016

Would appreciate confirmation of receipt of this correspondence.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
07/31/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, July 30, 2015 12:51 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant Container/Carton Label

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to your July 13, 2015 container/carton label submission. We have the below comments and recommendations.

Regarding 2-tablet immediate container labels:

1. Display the required statement "See package insert for dosage information" per 21 CFR 201.55

(b) (4)

Please resubmit labeling that addresses these comments by August 7, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
07/30/2015

Chung, Mary

From: Chung, Mary
Sent: Monday, July 20, 2015 7:05 PM
To: Gabriela Rossi
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- FDA comments on PI and PPI
Attachments: NDA 206500 rolapitant FDA proposed PI 7-20-15 Clean Copy.doc; NDA 206500 rolapitant FDA proposed PI 7-20-15 Clean Copy.pdf; NDA 206500 rolapitant FDA proposed PI 7-20-15 tracked changes.doc; NDA 206500 rolapitant FDA proposed PI 7-20-15 tracked changes.pdf; NDA 206500 rolapitant PPI FDA proposed 7-20-15 clean copy.docx; NDA 206500 rolapitant PPI FDA proposed 7-20-15 clean copy.pdf; NDA 206500 rolapitant PPI FDA proposed 7-20-15 tracked changes.docx; NDA 206500 rolapitant PPI FDA proposed 7-20-15 tracked changes.pdf

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

On July 13, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (for both PI and PPI). We request that you resubmit labeling that addresses these issues by July 27, 2015, or before.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

---

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

/s/

MARY H CHUNG
07/20/2015

Chung, Mary

From: Chung, Mary
Sent: Wednesday, July 08, 2015 2:57 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Clinical Information Request

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to your May 20, 2015 response to our May 12, 2015 Information Request regarding safety analyses for chemotherapeutic agents that are substrates of BCRP or CYP2D6 used in Pooling Group 1 by drug.

We have the following request for additional information:

- Posterior Reversible Encephalopathy Syndrome was seen in two rolapitant patients and no placebo patients. Each of the rolapitant patients was taking a concomitant BCRP receptor substrate—one was taking 5-FU and another was taking irenotecan.
    - Please provide information regarding the background rate of this syndrome in the general population, the expected rate in the cancer population, and the rate expected with 5-FU exposure and with irinotecan exposure.
    - Please provide information to explain how the concomitant use of rolapitant with the BCRP substrates 5-FU and irinotecan would not be expected to contribute to increased risk of this syndrome.
    - In addition, please provide narratives for these two patients that may help identify other contributing factors.

We request to receive your response to this information request by July 17, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
07/08/2015

Chung, Mary

From: Chung, Mary
Sent: Monday, July 06, 2015 7:44 AM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Carton/Container FDA comments
Attachments: NDA 206500 rolapitant carton container FDA comments 7-6-15.pdf

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to your June 19, 2015 container/carton label submission. We have the attached comments and recommendations.

Please resubmit labeling that addresses these comments by July 17, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

Regarding twinned blister and twinned blister strip

1. (b) (4)

2. On the other side of each twinned blister also display the lot# and expiration date as follows:

Exp:
Lot:

Regarding carton labels

1. The drug product name should be displayed on the carton label consistently as shown below:

Varubi
(rolapitant) tablets
90 mg*
*(equivalent to 100 mg rolapitant hydrochloride)

(b) (4)

7. To ensure that the patients understand both tablets constitute a complete dose and should be taken at the same time, we recommend you revise the usual dosage statement from [redacted] (b) (4)

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

/s/

MARY H CHUNG
07/06/2015

Chung, Mary

From: Chung, Mary
Sent: Thursday, July 02, 2015 4:40 PM
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- FDA comments on PI
Attachments: NDA 206500 rolapitant FDA Proposed PI 7-2-15 tracked changes.pdf; NDA 206500 rolapitant FDA Proposed PI 7-2-15 tracked changes.doc; NDA 206500 rolapitant FDA Proposed PI 7-2-15 Clean Copy.pdf; NDA 206500 rolapitant FDA Proposed PI 7-2-15 Clean Copy.doc

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

On June 12, 2015, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (for both PI and PPI). We request that you resubmit labeling that addresses these issues by July 14, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

---

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

/s/

MARY H CHUNG
07/02/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Carton/Container FDA comments
Date:	Wednesday, May 20, 2015 10:32:35 AM
Attachments:	NDA 206500 rolapitant FDA Container Carton Comments 5-20-15.pdf

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to your March 26, 2015 container/carton label submission. We have the attached comments and recommendations.

Please resubmit labeling that addresses these comments by June 20, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

Regarding twinned blister and twinned blister strip

(b) (4)

2. On the other side of each twinned blister also display the lot# and expiration date as follows:

Exp:
Lot:

Regarding carton labels

1. The drug product name should be displayed on the carton label as shown below:

Varubi
(rolapitant) tablets
90 mg*
*(equivalent to 100 mg rolapitant hydrochloride)

2. Display total number of tablets per carton e.g. "2 tablets"

3. Revise to storage statement as shown below:

Store at 20º to 25ºC (68º to 77ºF); excursions are permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]

4. (b) (4)

5. Submit container carton labels for (b) (4) (b) (4)

6. (b) (4)

7. (b) (4)

(b) (4)

8. (b) (4)

9.

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

/s/

MARY H CHUNG
05/20/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- FDA comments on PI & PPI
Date:	Wednesday, May 20, 2015 4:50:30 PM
Attachments:	N 206500 rolapitant FDA Proposed PI 5-20-15 Clean Copy.pdf N 206500 rolapitant FDA Proposed PI 5-20-15 Clean Copy.docx NDA 206500 rolapitant FDA Proposed PI 5-20-15 Tracked Changes.pdf NDA 206500 rolapitant FDA Proposed PI 5-20-15 Tracked Changes.doc NDA 206500 rolapitant FDA Proposed PPI 5-20-15 Clean Copy.pdf NDA 206500 rolapitant FDA Proposed PPI 5-20-15 Clean Copy.docx NDA 206500 rolapitant FDA Proposed PPI 5-20-15 Tracked Changes.pdf

---

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

On October 7, 2014 and December 9, 2014, we received your proposed labeling submission to this application, and have proposed revisions that are included as an enclosure (for both PI and PPI). We request that you resubmit labeling that addresses these issues by June 12, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

have received this document in error, please notify us immediately by telephone at (301) 796-0260. Thank you.

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

---

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

/s/

MARY H CHUNG
05/20/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant
Date:	Wednesday, March 18, 2015 5:48:00 PM

Dear Gabriela,
During the teleconference on March 19, 2015 for NDA 206500 rolapitant, we intend to indicate the below message regarding the limitations of the phase 2 study (TS- P04351) (b) (4) (b) (4)

Unblinded interim analysis

An unblinded interim analysis was conducted by sponsor personnel for planning future studies. It is not clear that adequate procedures were in place to ensure that results of the analysis were not revealed to persons connected with the study. This is especially problematic since the study did not use an independent third party or an independent data monitoring committee (IDMC). 21 CFR 314.126(b)(5) states in part that sponsors of well-controlled studies should take adequate measures to minimize bias with respect to the analysis of the data. Since your study data may have been compromised through the unblinded interim analysis, we do not feel that the phase 2 trial meets our usual requirements for being an adequate and well-controlled study.

References:

1. CFR Sec. 314.126 Adequate and well-controlled studies
2. ICHE6 Guidance for Industry, Good Clinical Practice: Consolidated Guidance, Section 5.5
3. Guidance for Clinical Trial Sponsors "Establishment and Operation of Clinical Trial Data Monitoring Committees", Section 4.2

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
05/18/2015

From: Chung, Mary
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant - Information Request - Clinical
Date: Tuesday, May 12, 2015 8:15:34 AM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

1. Please provide an analysis comparing the rate of rescue medication use vs. responder rates based only on VAS <25 and VAS<5

   Please complete the following table, or similar, for Studies 32, 33, and 34, and for the HEC studies combined.

Proportion of patients using Rescue Medication

	VAS<5 N= % (n)	VAS<25 N= % (n)	Overall N= % (n)
Rolapitant			
Control			
Total			

2. Please provide the incidence of TEAEs by Cycle. Please complete the table below or a similar table for Rolapitant and Control Patients.

Incidence of TEAEs by Cycle, Pooling Group 1

	Cycle 1 N= % (n)	Cycle 2 N= % (n)	Cycle 3 N= % (n)	Cycle 4 N= % (n)	Cycle 5 N= % (n)	Cycle 6 N= % (n)
Subjects with ≥1 TEAE						
Subjects with ≥1 TEAE of CTCAE Grade ≥3						
Subjects with ≥1 TESAE						
Subjects with an TEAE leading to study drug discontinuation						
Subjects with TEAE resulting in death						

3. Given that the cycle lengths varied (and therefore, the interval of time between rolapitant dosing), please provide an assessment of TEAEs by rolapitant dosing interval. Please use cutoffs of 2 weeks, 3 weeks, and 4 weeks. Please provide information for both rolapitant and control patients in Pooling Group 1.

4. Please provide an assessment of patients in each treatment group (Pooling Group 1) with the following:
   a. AST >3xULN
   b. AST 5xULN
   c. AST >10xULN
   d. Tbili >2xULN

We request that you provide a response to this request by Thursday May 14, 2015, or before as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
05/12/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Clinical Information Request
Date:	Tuesday, May 12, 2015 3:12:11 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

> Please provide safety analyses for chemotherapeutic agents that are substrates of BCRP or CYP2D6 used in Pooling Group 1 by drug. The safety analyses should include total TEAE, TESAEs, and a breakdown of these events by SOC and PT.

We request that a response to this information request would be provided by Wednesday May 20, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
05/12/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant
Date:	Friday, May 01, 2015 4:28:07 PM
Attachments:	NDA 206500 rolapitant - 5-1-2015.pdf

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

Additional reference is made to your 12/9/14 and 4/8/15 responses to FDA Information Requests dated 4/3/15 and 12/3/14.

We have the attached comments regarding your responses.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

Attachment: 5/01/15 NDA 206500 rolapitant Correspondence

We have concerns regarding the ability of the phase-2 study results (P04351) to support rolapitant's efficacy for the delayed phase based on our assessment of your responses, which indicate the statistically significant result of the delayed phase reported in the NDA submission is sensitive to the removal of a single subject.

We note that for the delayed phase, the number of patients in the rolapitant 200 mg treatment group reported in the original NDA submission received on 09/05/2014 (see Table 1) was based on one less patient (n=88) when compared to results reported by the response documents (Table 2) received on 12/09/2014, based on 89 patients in the rolapitant 200 mg treatment group.

Table 1 (Applicant's) Summary of Complete Response by treatment group using data in Cycle 1

Time Interval[a]	Placebo (E)		SCH 619734 10 mg (A)		SCH 619734 25 mg (B)		SCH 619734 100 mg (C)		SCH 619734 200 mg (D)	
	Response Rates[b]									
	n	%	n	%	n	%	n	%	n	%
0–120 hr[c]	(b) (4)									
0–24 hr[d]										
>24–120 hr[d]	90	48.9	91	50.5	88	54.5	91	58.2	88	63.6

a: Overall (0-120 hr), acute (0-24 hr), and delayed (>24-120 hr) phases; b: Response rates are raw percentages.
c: Primary efficacy endpoint; d: Key secondary efficacy endpoint.

Table 2 Complete Response in the Acute, Delayed and Overall Phases of CINV – Phase 2 Study TS-P04351 (HEC)

CINV Phase Treatment	N	n (%)	95% CI for %[1]	Between-Group P-Value[2]
Overall Phase (0-120 hrs)	(b) (4)			
Placebo				
SCH619734 10 mg				
SCH619734 25 mg				
SCH619734 100 mg				
SCH619734 200 mg				
Acute Phase (0-<24 hrs)				
Placebo				
SCH619734 10 mg				
SCH619734 25 mg				
SCH619734 100 mg				
SCH619734 200 mg				
Delayed Phase (24-120 hrs)				
Placebo	90	44 (48.9)	(38.2, 59.7)	
SCH619734 10 mg	91	46 (50.5)	(39.9, 61.2)	0.814
SCH619734 25 mg	91	48 (52.7)	(42.0, 63.3)	0.592
SCH619734 100 mg	91	53 (58.2)	(47.4, 68.5)	0.199
SCH619734 200 mg	89	56 (62.9)	(52.0, 72.9)	0.056

[1] Exact 95% confidence interval for the response rate;
[2] P-value for the between-group comparison is from the Cochran-Mantel-Haenszel test stratified by gender.

We applied the logistic regression SAS code received on 04/08/2015 to analyze the complete response rate for the delayed phase using the dataset (response dataset) received on 12/09/2014. The efficacy analysis results for the delayed phase are presented in Table 3.

Table 3 (Reviewer's) Efficacy comparison assessed by the complete response in the delayed phase using applicant's logistic regression code and response dataset

Treatment Group	N	Number (%) of Patients Responding	Rolapitant versus Control[a]	
			% Difference	P-value
Control Regimen	91	44 (48.4%)	NA	
Rolapitant Regimen	90	56 (62.2%)	13.8	0.056

[a]: Analysis via applicant's Logistic regression SAS codes stratified by gender and CEC.

Table 3 indicates that when using your logistic regression codes with the statement code "where complete response for delayed phase not equal to missing" and the response dataset, the delayed complete response rate for the rolapitant 200 mg treatment group is not significantly higher than that of the control group (62.2% vs. 48.4%; p = 0.056). Comparing Table 1 and Table 3, we note that two more non-responder patients are included in the rolapitant 200 mg treatment group compared to the original study report, and one more non-responder patient is included in the control group compared to the original study report.

In order to explore the impact of the one patient difference reported between the original study report and the response document, we also applied your logistic regression SAS codes with the statement code "where complete response for delayed phase not equal to missing" to the response dataset by removing one non-responder patient from the rolapitant 200 mg treatment group and one non-responder patient from the control group to analyze the complete response rate for the delayed phase. In this way, there would be 89 patients in the rolapitant 200 mg treatment group and 90 in the control group, just as in Table 2. Table 4 presents the results.

Table 4 Efficacy comparison assessed by the complete response in the delayed phase using applicant's logistic regression code and response dataset by removing one non-responder from both rolapitant regimen and control regimen

Treatment Group	n	Number (%) of Patients Responding	Rolapitant versus Control[a]	
			% Difference	P-value
Control Regimen	90	44 (48.9%)	NA	
Rolapitant Regimen	89	56 (62.9%)	14.0	0.054

[a]: Analysis via applicant's logistic regression SAS codes stratified by gender and CEC.

Table 4 indicates that using response document data (i.e., removing one non-responder patient from both rolapitant and control from response dataset) and the applicant's Logistics regression codes with statement code "where complete response for delayed phase not equal to missing", the complete response rate in the delayed phase for the rolapitant 200 mg treatment group is still not significantly higher than that of the control group (62.9% vs. 48.9%; p = 0.054).

Finally, we also applied your logistic regression SAS codes with the statement code "where complete response for delayed phase not equal to missing" to the original dataset submitted in the NDA to analyze the complete response rate for the delayed phase. Table 5 presents these results.

Table 5 Efficacy comparison assessed by the complete response in the delayed phase using applicant's logistic regression code and original dataset

Treatment Group	n	Number (%) of Patients Responding	Rolapitant versus Control[a] % Difference	P-value
Control Regimen	90	44 (48.9%)	NA	
Rolapitant Regimen	88	56 (63.6%)	14.7	0.042*

[a]: Analysis via applicant's Logistic regression SAS codes stratified by gender and CEC.

Table 5 indicates that when using your logistic regression codes with the statement code "where complete response for delayed phase not equal to missing" and the original dataset received on 09/05/2014, the complete response rate in the delayed phase for the rolapitant 200 mg treatment group becomes significantly higher than that of the control group (63.6% vs. 48.9%; p = 0.042), generating results similar to those reported in the original study report.

Conclusion

Based upon the above findings, the significant results for the delayed phase reported in the original study report are not reliable. Accordingly, the complete response rate for the delayed phase for the rolapitant 200 mg treatment group should not be deemed to be significantly higher than that of the control group. (b) (4)

(b) (4)

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

/s/

MARY H CHUNG
05/01/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Clinical Information Request
Date:	Wednesday, April 15, 2015 1:36:15 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

> Please provide comparative adverse event data for patients treated with concomitant Breast-Cancer-Resistance-Protein (BCRP) transporter drugs with a narrow therapeutic index such as methotrexate, topotecan, and irinotecan. Rolapitant is known to be a moderate inhibitor of this transporter and concomitant use with rolapitant can increase the plasma concentrations of BCRP substrates.

We request you provide your response to the above by April 22, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
04/15/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Information Request/ Biostatistics
Date:	Friday, April 03, 2015 11:26:03 AM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

> For Study P04351, please submit your SAS programs and the associated data sets that you used to perform the efficacy analyses based upon complete response rates for the delayed, acute, and overall phases stated in section 9.7.1.3 Efficacy Analyses.

Please provide this information to the application by April 9, 2015, or before if possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
04/03/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA206500

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

TESARO, Inc.
1000 Winter Street, Suite 3300
Waltham, MA 02451

ATTENTION: Gabriela Rossi
Director, Regulatory Affairs

Dear Ms. Rossi:

Please refer to your New Drug Application (NDA) dated and received September 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rolapitant Tablets, 90 mg.

We also refer to your correspondence, dated and received January 14, 2015, requesting review of your proposed proprietary name, Varubi, and amendment dated and received March 27, 2015.

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

If any of the proposed product characteristics as stated in your above submissions 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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Mary Chung, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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
03/31/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Information Request (Label)
Date:	Tuesday, March 17, 2015 12:02:53 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

Please submit copies of immediate container closure and carton labels for all drug product packaging configurations you intend to market.

Please submit this to the application as soon as possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
03/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA206500

MID-CYCLE COMMUNICATION

TESARO, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Rossi:

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

We also refer to the teleconference between representatives of your firm and the FDA on February 12, 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 me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 12, 2015 3:00- 4:00 PM EST

Application Number: NDA 206500
Product Name: rolapitant hydrochloride
Indication: Prevention of chemotherapy induced nausea and vomiting
Applicant Name: TESARO, Inc.

Meeting Chair: Ruyi He, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Dragos Roman, M.D.	Deputy Director (acting)
Joyce Korvick, M.D., M.P.H.	Deputy Director for Safety
Joette Meyer, PharmD.	Associate Director for Labeling (acting)
Ruyi He, M.D.	Medical Team Lead
Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Tracy Behrsing, Ph.D.	Pharmacology Reviewer
Aisha Peterson, M.D.	Medical Reviewer
Mary Chung, PharmD.	Regulatory Project Manager

Office of Clinical Pharmacology

Sue-Chih Lee, Ph.D.	Team Lead
Insook Kim, Ph.D.	Clinical Pharmacology Reviewer
Jee Eun Lee, Ph.D.	Pharmacometrics Reviewer

Office of Pharmaceutical Quality

Marie Kowblansky, Ph.D.	CMC Team Lead
Akm Khairuzzaman, Ph.D.	CMC Reviewer
Sharmista Chatterjee	CMC Reviewer
Tien Mien Chen	Biopharmaceutics Reviewer
Peng Duan	Biopharmaceutics Reviewer

Division of Biometrics III

Mike Welch, Ph.D.	Deputy Director

Yeh-Fong Chen, Ph.D. Statistics Team Lead
Wen Jen Chen, Ph.D. Statistics Reviewer

Office of Compliance/ Office of Scientific Investigations
Susan Leibenhaut, M.D. Scientific Investigator

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Eastern Research Group
Marc Goldstein, Easter Research Group

APPLICANT ATTENDEES
Mary Lynne Hedley, Ph.D., President and Chief Scientific Officer
Tanya Lewis, Regulatory Affairs Vice President
Gabriela Rossi, Regulatory Affairs Director
Thomas Perrone, Ph.D., Regulatory Affairs Director (CMC)
Robert Martell, M.D., Ph.D., Chief Medical Officer
Allen Poma, M.D., Senior Medical Director
Sujata Arora, Biostatistics Consultant
(b) (4)
Vikram Kansra, Ph.D., Vice President, Clinical Pharmacology
Zhi-Yi Zhang, Ph.D., Director, DMPK
Xiaodong Wang, Ph.D., Director, Clinical Pharmacology
Jennifer Christensen, Director, Program Development
Hajira Koeller, Ph.D., Associate Director Clinical Scientist
Simona Cipra, Vice President, Clinical Operations
Heidi Kempinski, Vice President, Pharmaceutical Development and Manufacturing Operations
George Wu, Ph.D., Vice President, Pharmaceutical Sciences

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

Clinical/ Biostatistics

The Division is concerned that the data submitted in the rolapitant NDA (b) (4)

(b) (4)

Please see attached comments from Biostatistics regarding the limitations of the phase 2 study (TS-P04351) (b) (4)

Additional Clinical Comments:

(b) (4)

CMC

See "Information Requests" listed below (issued February 6, 2015).

Clinical Pharmacology

The significant inhibitory effect of rolapitant on CYP2D6 activity is observed at 7 days after single dose administration of rolapitant. Although the [I]/Ki values for rolapitant declined over the 7-day study period, the extent of inhibition was not reduced suggesting the in-vitro data does not predict the duration of inhibitory effects. Therefore, an in-vivo study may be necessary to evaluate the duration of the inhibition of CYP2D6 activity.

3.0 INFORMATION REQUESTS

CMC

a. Your proposed new dissolution QC method (Method-3) consists of USP II (Paddle) with 50 rpm in acetate buffer, pH 4.0 and the proposed acceptance criterion is Q= (b) (4) % at 30 min. However, the complete dissolution profile data

using this final new dissolution method (Method-3) for the registration lots (KXWB, KXVY, and KXVZ) could not be located in the NDA.

To obtain the complete dissolution profile data, an additional sampling time point at 20 minutes (i.e., at 15, 20, 30, 45, and 60 minutes) should be collected in order to set the final dissolution acceptance criterion. Provide the complete dissolution data (including individual; n=12, mean, and standard deviation) and mean dissolution profiles for the above three lots for review.

Discussion Summary:
Sponsor indicated the requested information was submitted previously to the IND. FDA requested the information be resubmitted to the NDA for review and sponsor agreed.

b. Also, we remind you that in the 74-Day letter (Product Quality, Item #6), you were requested to submit the following information for review.

(b) (4)

The proposed dissolution method (Method-3) with sampling time points at 15, 20, 30, 45, and 60 minutes should be employed. The similarity factor (f2) should be calculated to demonstrate similarity between the comparative dissolution profiles if f2 >50.

Discussion Summary:
Sponsor indicated this information was previously submitted in December 2014.

c. (b) (4)

d.

e. (b) (4)

Additional CMC Comments

Sponsor indicated they would like to discuss process validation related updates. FDA indicated proposed manufacturing changes cannot be discussed until they are submitted to the NDA (with a detailed description of the changes, including evaluation of the effect of these changes on the drug substance properties) and evaluated by the FDA.

4.0 MAJOR SAFETY CONCERNS/ RISK MANAGEMENT

At this stage, we do not believe that a REMs is necessary to ensure benefits of this product outweigh the risks.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an AC meeting

6.0 LATE-CYCLE MEETING/ OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is June 2, 2015. In addition, please note the following projected milestone dates:

PDUFA Action Date September 5, 2015

Additional Biostatistics Comments:

FDA summarized the following concerns regarding the limitations of the phase 2 study (TS-P04351) (b) (4)

1. Interim analysis planned but no data monitoring committee implemented

   In section 9.7.3 "Interim Analysis" of the protocol, we noted that the phase-2 trial was an exploratory dose finding study with an interim analysis to plan the direction of future CINV phase-3 trials. In addition, we also noted that no Data Monitoring Committee was implemented as a fire wall to protect study integrity. Because the study data were unblinded to conduct the interim analysis, we have concerns regarding the quality of the phase 2 study. (b) (4)

2. Small number of patients enrolled compared to failed phase-3 trials

   For the phase-2 study, about 90 patients were enrolled in each arm. However, for the two other HEC phase-3 trials, more than 260 patients were enrolled in each arm. In addition, for the phase-3 MEC study, 666 patients were enrolled in each arm, which is over seven times larger than that of the phase-2 trial. (b) (4)

   Due to much smaller sample size used in the phase-2 exploratory trial and our concern regarding data quality, the results of the phase-2 trial may not be able to outweigh the findings from the more reliable phase-3 trials.

3. Unstable efficacy results and the pre-planned multiplicity procedure

   Based on your multiplicity adjustment method specified in the phase-2 trial protocol, the logistic regression model with two covariates of gender and concomitant emetogenic chemotherapy (CEC) was used to analyze the first key secondary endpoint (i.e., CR in the delayed phase) before testing the second key secondary endpoint (i.e., CR in the acute phase). (b) (4)

(b) (4)

phase-2 trial). The result of the phase-2 study for the delayed phase appears to be extremely sensitive to this CEC covariate. In addition, when the gender covariate is removed from the logistic regression model, the p-value becomes (b) (4) It appears that primary results in this phase-2 study were not statistically persuasive.

If the patient populations are similar among the phase-2 and phase-3 trials, the evidence from the phase-2 trial also need to be considered with the same statistical methods as applied in the phase-3 trials (b) (4) For the phase-3 trial, the Cochran-Mantel-Haenszel test (CMH) stratified by gender was pre-specified to analyze data for the delayed phase, acute phase, and overall phase, in that order. (b) (4)

(b) (4)

Finally, we noted that the populations for the phase-2 and phase-3 trials were very similar (according to the medical division's evaluation). (b) (4)

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

/s/

MARY H CHUNG
03/13/2015

From: Chung, Mary
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Clinical Information Request
Date: Monday, March 09, 2015 7:04:34 AM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

> Reference is made to your February 20, 2015 response to our Information Request dated February 11, 2015. The information you presented was for the pooled HEC populations from studies 32, 33, and 34 (according to ASCO 2011 guidelines).
>
> Please also provide the primary and key secondary endpoints for the HEC and MEC populations for study 34 alone (according to ASCO 2011guidelines) by filling in the following tables.

Study 34, Emetogenicity Categorization according to ASCO 2011 Guidelines, MITT

	Rolapitant (N)	Placebo (N)
HEC		
MEC		
Total		

Study 34, Complete Response Assessment, HEC Patients, MITT

Phase	Rolapitant (n/N)	Placebo (n/N)	Odds Ratio (95% CI)	p-value*
Delayed				
Acute				
Overall				

*Method of p-value calculation

Study 34, Complete Response Assessment, MEC Patients, MITT

Phase	Rolapitant (n/N)	Placebo (n/N)	Odds Ratio (95% CI)	p-value*
Delayed				
Acute				
Overall				

*Method of p-value calculation

We request to receive your response to the above by March 13, 2015, or before if possible.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
03/09/2015

From: Chung, Mary
To: GRossi@tesarobio.com
Cc: Chung, Mary
Subject: NDA 206500 rolapitant- Information Request
Date: Wednesday, February 25, 2015 1:38:48 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information:

> The Pregnancy and Lactation Rule (PLLR) published December 4, 2014 ((79 FR 72063). The PLLR implementation date is June 30, 2015; however, we encourage you to comply with PLLR with your current submission. See Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).
>
> Please revise the current sections of 8.1 (b) (4) in the Use in Specific Populations section of the prescribing information, as recommended in the guidance, and submit for our review.

We request you provide your response to the above by March 11, 2015, or before if possible.

Regards,
Mary
Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
02/25/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Clinical Information Request
Date:	Tuesday, February 10, 2015 8:45:00 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information.

> Please reassign patients in Study 34 to HEC or MEC according to the ASCO 2011 guidelines which presented changes in the emetogenicity category (from MEC to HEC) for anthracyclines (including doxorubicin, epirubicin, idarubicin and daunorubicin) administered in combination with cyclophosphamide (Basch E, Prestrud A, Hesketh P, et al. Antiemetics; American Society of Clinical Oncology Clinical Practice Guideline Update. JCO. 2011. Vol 29:4189-4198).

Once reassigned, please provide primary and secondary endpoint calculations by emetogenicity category (HEC and MEC).

We request you provide your response to the above by Friday February 20, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
02/11/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Clinical Information Request
Date:	Tuesday, February 03, 2015 4:36:20 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information.

> During review of the pregnancy data from the clinical development program, there were two patients, and possibly a third patient, noted to be pregnant while taking rolapitant. Details on the outcomes of these pregnancies are missing from the NDA submission. Please provide follow-up information for these three patients to include study drug and dose assigned, duration of study drug treatment, estimated duration of fetal exposure, pregnancy outcome, gestational age at delivery or termination, pregnancy complications, infant outcomes, and fetal malformations.
>
> The study and subject numbers are listed below:
> - Study P04852 (subject 1/000306): a 26 year old woman with a positive HCG on day 22 of the study. At the time of the report, the clinical database had not been unblinded. It was unknown if the subject was on placebo or active drug.
> - Study P04937 (subject 016-1284): patient had a positive HCG.
> - Study P04937 (subject 032-1314): patient had a positive HCG.

We request you provide your response to the above by Friday February 6, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
02/03/2015

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant- Clinical Information Request
Date:	Wednesday, January 21, 2015 5:23:14 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information.

1. Please provide enrollment data for each study by country and by region for Studies 51, 32, 33, and 34.
2. Please provide primary endpoint data by country, region, and individual study site for Studies 32, 33, and 34.
3. In the subset of patients who had CR in the delayed phase, please provide the % of patients who also had CR in the acute phase for studies 32, 33, and 34.

We request you provide your response to the above by Friday January 23, 2015.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350
Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
01/21/2015

From:	Strongin, Brian K
To:	"GRossi@tesarobio.com"
Cc:	Strongin, Brian K; Chung, Mary
Subject:	NDA 206500 (rolapitant) Information Request
Date:	Tuesday, December 23, 2014 3:11:00 PM

Hi. I'm Mary Chung's supervisor and am sending this information request on her behalf since she is on vacation. Please submit a response by 1/9/15.

*Please provide a dataset with subject level CYP2D6 genotype data (e.g. *1/*10), CYP2D6 metabolizer status (e.g. EM, IM), and PK parameters for all subjects in Study PR-10-5001-C. Additionally, please provide your classification system for determining metabolizer status based on genotype.*

Please let me know if you have any questions.

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

/s/

BRIAN K STRONGIN
12/24/2014

From:	Chung, Mary
To:	GRossi@tesarobio.com
Cc:	Chung, Mary
Subject:	NDA 206500 rolapitant Biostatisics Information Request
Date:	Wednesday, December 03, 2014 12:42:19 PM

Dear Gabriela,
Reference is made to your New Drug Application (NDA) 206500 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant hydrochloride received on September 5, 2014.

We have the following request for additional information. Please provide the following information for the Phase 2 Study P04351:

1. As used in the analysis of the Phase 3 studies, please apply Cochran-Mantel-Haenszel test stratified by gender (SAS CMH test) to compare the treatment effects based upon the complete response rates for the delayed, acute, and overall phases. In addition, for each phase (delayed, acute or overall), please treat missing data as a non-responder (failure) in the efficacy comparison analysis. This means that if a subject had missing data for any phase of the complete response endpoint, he/she is treated as a non-responder (failure) in the corresponding efficacy analysis.

   Please submit the analysis results along with the SAS programs and the data set with needed variables used for the efficacy comparisons to the Agency for review. The SAS programs should be modified to input data from the dataset you provided.

   Please provide your dataset with variables in an electronic format consistent with the FDA Data Specifications document: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

   Please note that adherence to CDISC standards are recommended but not required.

2. In section 9.7.3, it is noted that an interim analysis was applied for the phase-2 trial. Please provide justification for your chosen alpha levels of 0.001 (b) (4) used for the interim and final analyses, including the reference publication.

3. It is noted that Sections 9.7.1.3 and 11.4.2.5 of the study report provide the multiplicity adjustment method used to strongly control overall two-sided Type I error rate of 5% for the efficacy comparisons, using complete response endpoint assessed in the overall, delayed, and acute phases. We could not find where you pre-specify this method in the original protocol. Please identify the document where the multiplicity adjustment method was pre-specified and the date it was pre-specified.

We request you provide your response to the above by COB Tuesday December 9, 2014.

Regards,
Mary

Mary Chung, PharmD.
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER/ FDA

10903 New Hampshire Avenue, Bldg. 22, Room 5350

Phone: 301-796-0260 /fax: 301-796-9904
mary.chung@fda.hhs.gov

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

/s/

MARY H CHUNG
12/03/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206500

PROPRIETARY NAME REQUEST
UNACCEPTABLE

Tesaro, Inc.
1000 Winter Street North
Suite 3300
Waltham, MA 02451

ATTENTION: Gabriela Rossi
Director, Regulatory Affairs

Dear Ms. Rossi:

Please refer to your New Drug Application (NDA) dated and received September 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rolapitant Hydrochloride Tablets, 100 mg.

We also refer to your correspondence, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name (b) (4) and the products share overlapping product characteristics that may increase the risk of wrong drug errors.

(b) (4)

(b) (4)

In addition to the orthographic similarity of these names, both products are solid oral dosage forms that share overlapping product characteristics, which include route of administration (oral), and dose (two tablets). Although the strengths (b) (4) do not overlap

(b) (4) we are concerned that the difference in strength will not adequately prevent confusion between the name pairs given the overwhelming similarity of the names. We have identified post-marketing reports of confusion between products marketed in different strengths when strong orthographic or phonetic similarity exists. As an example, a report from Institute for Safe Medication Practices describes confusion between Prenexa and Ranexa where a written prescription for Ranexa 500 mg was dispensed instead of Prenexa[1]. The patient took Ranexa for one year thinking that it was a prenatal vitamin. This error occurred despite the differences in products strengths (Ranexa is available in 500 mg and 1000 mg and Prenexa is a single strength prenatal multivitamin) and frequency of administration (Ranexa should be administered twice daily vs. Prenexa should be administered once daily). Another example includes confusion between Brintellix (vortioxetine) and Brilinta (ticagrelor)[2]. The fact that Brintellix is a 10 mg tablet (also available in 5, 15, and 20 mg tablets) and Brilinta is a 90 mg tablet did not prevent this selection error. Thus, the differences in strength and frequency of administration may not prevent a medication error arising from names that are very similar. As it relates to (b) (4)

Furthermore, since (b) (4) the familiarity with this name may cause confirmation bias (seeing that which is most familiar, while overlooking any disconfirming evidence). Confirmation bias has been identified as a major contributing factor to confusion between products that are orthographically similar, as exhibited by the products Reminyl (Galantamine hydrobromide) and Amaryl (Glimeperide)[3]. In this case, because prescriptions for Amaryl were more commonly written and dispensed and Reminyl was approved (6 years after Amaryl) in 2001, pharmacists and nurses mistakenly dispense or administer Amaryl instead of Reminyl. Thus, similar confirmation bias could occur with (b) (4) as well.

We recognize this conclusion differs from that of Drug Safety Institute (DSI) name study submitted in support of the proposed proprietary name. DSI identified and acknowledged that (b) (4) but they noted that the two products differ significantly with respect to dosage strength, frequency of administration, and usual dose. However, as described in detail above, the differences in strength and frequency of administration may not prevent a medication error arising from names that are very similar. Therefore, based on post-marketing experience, orthographic similarities, and overlapping product characteristics, the proposed product (b) (4) are vulnerable to medication errors due to name confusion.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,*

[1] Institute for Safe Medication Practices. Safety briefs: Ranexa and Prenexa too similar. ISMP Med Saf Alert Community/Ambulatory Care. 2012;11(3):1-4.
[2] https://www.ismp.org/newsletters/ambulatory/showarticle.aspx?id=7
[3] The Institute of Safe Medication Practices. Safety Alert. September 9, 2004. Volume 9 Issue 18. Accessed August 16, 2013

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you require additional information on developing proprietary names for drugs, we recommend that you review the draft Guidance for Industry, *Best Practices in Developing Proprietary Names for Drugs*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Chung Mary, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
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/

KELLIE A TAYLOR
11/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206500

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

TESARO, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Rossi:

Please refer to your New Drug Application (NDA) dated and received September 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for rolapitant hydrochloride.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm). Therefore, the user fee goal date is September 5, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 12, 2015. In addition, the planned date for our internal mid-cycle review meeting is February 3, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

CLINICAL

We will review the evidence you have submitted to support your proposed labeling claims for rolapitant's efficacy in combination with other antiemetic agents in adults for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including but not limited to, highly emetogenic chemotherapy. Based on our preliminary review of your phase 2 study (p04351) and phase 3 studies (p04832, p04833, p04834), substantial evidence of (b) (4)

PRODUCT QUALITY

1. (b) (4)

2. In addition to the above comment, please be aware that your product name and strength will need to conform to the USP naming policy and your labeling will need to be modified accordingly.

3. (b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

6. Provide comparative dissolution profile data using the proposed dissolution method to (b) (4)

CLINICAL PHARMACOLOGY

7. It appears that the significant inhibitory effect of rolapitant on CYP2D6 activity in CYP2D6 extensive metabolizers is observed 7 days after single dose administration of rolapitant. Provide any available information on how long the inhibitory effect is estimated to last.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also request that you submit the following information:

CLINICAL PHARMACOLOGY

1. Please provide hyperlinks to individual study reports which support the clinical pharmacology related labeling sections, i.e., Sections 7, 8, and 12 in the annotated labeling.
2. The location of study reports PR-10-5000-C and XBL11064-RPT02279 are switched in Section 5.3.1.2. Please correct the study report locations or correct the title of the folders containing the study reports.
3. Please provide the method by which the genotype for CYP2D6 was determined in Study PR-10-5001-C.
4. Submit all model codes or control streams for all major model building steps, e.g., base structural model (Model 006xl), covariates models, final model (Model 200o), and

validation model (posterior predictive check). These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

5. Conduct and submit a safety analysis for renal impairment in phase 2 and 3 trials.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

During our preliminary review of your submitted labeling, we have identified labeling issues. Our labeling comments or questions are provided as an enclosure.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by December 9, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

---

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

/s/

DONNA J GRIEBEL
11/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206500

REQUEST FOR METHODS VALIDATION MATERIALS

Tesaro, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street North
Suite 3300
Waltham, MA 02451
grossi@tesarobio.com

Dear Gabriela Rossi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (Rolapitant) tablet, 100 mg.

We will be performing methods validation studies on (b) (4) (Rolapitant) tablet, 100 mg, as described in NDA 206500.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Rolapitant hydrochloride monohydrate assay and related impurities HPLC method (b) (4)

Rolapitant tablets HPLC assay and impurity method (b) (4)

Samples and Reference Standards

500 mg Rolapitant hydrochloride monohydrate drug substance
2 x 500 mg Rolapitant hydrochloride monohydrate reference standard
50 (b) (4) (Rolapitant) tablets, 100 mg
(b) (4) mg (b) (4) impurity if available
(b) (4) mg (b) (4) impurity if available
(b) (4) mg (b) (4) impurity if available

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
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/

MICHAEL L TREHY
11/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206500

NDA ACKNOWLEDGMENT

TESARO, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Rossi:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: rolapitant hydrochloride

Date of Application: September 5, 2014

Date of Receipt: September 5, 2014

Our Reference Number: NDA 206500

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 4, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/

MARY H CHUNG
09/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072754

MEETING MINUTES

TESARO, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Rossi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rolapitant (SCH 619734).

We also refer to the meeting between representatives of your firm and the FDA on July 2, 2014. The purpose of the meeting was to discuss the overall format and content of the NDA planned for submission.

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

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, PharmD.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minute

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	July 2, 2014 10:00 AM- 11:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 072754
Product Name:	rolapitant (SCH 619734)
Indication:	Prevention of chemotherapy induced nausea and vomiting
Sponsor/Applicant Name:	TESARO, Inc.
Meeting Chair:	Ruyi He, M.D.
Meeting Recorder:	Mary Chung, PharmD.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Ruyi He, M.D.	Medical Team Lead
Nancy Snow, D.O.	Medical Reviewer
Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Tamal Chakraborti, Ph.D.	Pharmacology Reviewer
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff
Mary Chung, PharmD.	Regulatory Project Manager

Office of Clinical Pharmacology

Sue-Chih Lee, Ph.D.	Team Lead
Dilara Jappar, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics III

Freda Cooner, Ph.D.	Statistical Team Lead
Wen Jen Chen, Ph.D.	Statistical Reviewer

Office of Compliance/ Office of Scientific Investigations
Susan Leibenhaut, M.D. Scientific Investigator

CDER/Controlled Drug Substances Staff
Michael Klein, Ph.D. Director
Alicja Lerner, M.D., Ph.D. Reviewer
Sandra Saltz Team Lead

EASTERN RESEARCH GROUP ATTENDEES
So Hyun Kim Independent Assessor

SPONSOR ATTENDEES
Mary Lynne Hedley, Ph.D., President and Chief Scientific Officer
Robert Martell, M.D., Chief Medical Officer
Allen Poma, M.D., Senior Medical Director
Sujata Arora, MS, Biostatistics Consultant
(b) (4)
Vikram Kansra, Ph.D., Senior Director, Clinical Pharmacology
Zhi-Yi Zhang, Ph.D., Director, DMPK
John Zhang, M.D., Ph.D., DABT Director, Toxicology and Safety Pharmacology
Jennifer Christensen, MS, Director, Program Development
Lori Rudolph-Owen, Ph.D., Vice President, Portfolio Management, Research and Development
Gina McGinnis, MS, Director, Regulatory Operations
Sophia Prophete-Hyppolite, Senior Regulatory Affairs Associate
Tanya Lewis, Vice President, Regulatory Affairs
Gabriela Rossi, Director, Regulatory Affairs
Xiaodong Wang, Ph.D. Director, Clinical Pharmacology
(b) (4)

1.0 BACKGROUND

TESARO is developing rolapitant (also referred to as SCH 619734), a neurokinin-1 receptor antagonist, for the proposed indication of prevention of (b) (4)
(b) (4)

The rolapitant clinical development program for the indication of prevention of CINV includes three phase 3 studies in subjects receiving cisplatin-based, highly emetogenic chemotherapy (HEC; TS-P04832, TS-P04833) or moderately emetogenic chemotherapy (MEC; TSP04834), and one phase 2 dose range-finding study in subjects receiving HEC (P04351).

Studies TS-P04832, TS-P04833 and TS-P04834 are complete. All three studies enrolled greater than 20% subjects in the U.S., and the MEC study (TS-P04834) enrolled >50% subjects who received anthracycline-cyclophosphamide (AC) therapy.

The results from the phase 2 dose range-finding study demonstrated that the rolapitant 200 mg group achieved greater complete response rates in the overall phase compared to the placebo group. Complete response rates in the secondary endpoints of acute and delayed phase were also greater in the rolapitant 200 mg group compared to control (b) (4)

On April 5, 2010, an End of Phase 2 meeting was held to discuss the rolapitant phase 3 development program. A Type C meeting was held July 5, 2011 to clarify clinical pharmacology points discussed at the End of Phase 2 meeting, and to discuss the endpoint analysis for the phase 3 trials and the revised clinical development program for rolapitant. In addition, a separate CMC End-of-Phase 2 meeting was held on January 28, 2013.

On April 23, 2014, TESARO requested a meeting to discuss the overall format and content of the NDA planned for submission. This meeting was granted and scheduled for July 2, 2014. A separate pre-NDA CMC meeting has been requested to FDA to discuss CMC specific issues.

2. DISCUSSION

2.1 Nonclinical

Question 1:
Does FDA concur that the completed nonclinical program as outlined in the Appendix of the briefing document is adequate to support registration of rolapitant for the proposed indication?

FDA response to Question 1:
Yes. Your nonclinical program appears to be adequate to support the NDA for the proposed indication.

2.2 Clinical and Clinical Pharmacology

Question 2:
Does FDA agree that the completed clinical pharmacology and pK studies listed in the Appendix of the briefing document are adequate to support registration of rolapitant for the proposed indication?

FDA response to Question 2:
Regarding your proposed clinical pharmacology package to support the registration of rolapitant, we have the following comments.

Please clarify whether you have evaluated the following as previously requested by the Agency:

- **PK of rolapitant in CINV patient population; the PK of all major metabolites of rolapitant; the effects of the major metabolites on CYP enzymes and P-gp transporters in vitro; the potential drug-drug interactions between rolapitant and**

concomitant chemotherapeutic agents that are CYP2D6 or BCRP substrates; the effect of age, gender, BMI and other covariates on the PK of rolapitant (e.g, population PK analysis) and the exposure-response relationships for safety and efficacy.

- **We acknowledge that you have conducted food effect study with a tablet formulation. (b) (4) Please clarify if the food effect study was conducted with the to-be-marketed tablet formulation. Please also tabulate formulations used in each clinical study (all phase 1, 2 and 3 trials).**

- **As you have not conducted dedicated renal impairment study, please clarify if you have assessed the effect of kidney function on the PK of rolapitant and the active metabolite(s) using the data from phase 2 and/or phase 3 trials.**

- **In your hepatic impairment study, you have only evaluated the rolapitant PK in patients with mild and moderate hepatic impairment and not in patients with severe hepatic impairment. Please address your plan on providing dosing recommendation for patients with severe hepatic impairment in the label.**

- **You have stated that "Rolapitant is extensively metabolized (b) (4) primarily by CYP3A4 to SCH 720881 (active metabolite)." However, PK of rolapitant is unaffected by ketoconazole (CYP3A4 inhibitor), and hepatic impairment (mild and moderate) did not significantly alter the PK of rolapitant. Please clarify if there are other major metabolizing enzymes responsible for rolapitant metabolism. Also, please clarify what the major elimination pathways are.**

- **In DDI study CYP2D6 and BCRP substrates, rolapitant had increased the exposure of dextromethorphan and sulfasalazine by several folds as inhibitor of CYP2D6 and BCRP. Please clarify how long these inhibitory effects last.**

- **Rolapitant appears to induce of CYP1A2 based on in vitro study. Please address the in-vivo relevance of this interaction.**

- **Since rolapitant has a very long half-life (7-10 days), please indicate the most frequent dosing interval that was evaluated in the phase 3 studies and clarify if there was any difference in the safety profile based on the dosing frequency. See FDA response to question 3.**

Question 3:

Does FDA concur that the completed Ph2 and Ph3 clinical program is adequate to support registration approval of rolapitant for the proposed indication (b) (4) (b) (4)

FDA Response to Question 3:

The completed phase 2 and phase 3 clinical program seems adequate to support filing of rolapitant for CINV indication. The final indication is a review issue and will be based on your study population and results. We are moving away from the HEC and MEC designations, and embracing a broader CINV indication.

Additional Comments:
Your safety analysis should address potential neurotoxicity issues based on the long half-life of the product and its cumulative effects with over multiple chemotherapy cycles. Your analysis should address:

- **Clarification on the most frequent dosing regimen tested during the clinical development program**
- **How you intend to label your drug product with respect to dosing**
- **How you will address the possibility of more frequent dosing**
- **Clarification on whether you plan to label your product for administration** (b) (4)
- **The differential CNS toxicity over 3 weeks vs. 4 weeks**
- **Toxicities associated with ifosfamide exposure**

Question 4:
The total number of subjects that have been exposed to oral rolapitant was 2799, with 1567 of them being CINV patients, in agreement with FDA's recommendation to include slightly less than 1500 patients for short term exposure to rolapitant for safety review. The total number of patients in the Phase 3 HEC and MEC studies combined with the Phase 2 HEC study that have been exposed to rolapitant 200mg for one cycle is 1294. The total number of patients in the Phase3 HEC and MEC studies as well as in the Phase 2 HEC study that have been exposed to rolapitant 200mg for 6 cycles is estimated to be 319, which is consistent with guidelines that suggest 300-600 (ICH Guideline for Industry E1A) patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of adverse drug events (ADEs) over time. Does FDA agree that the safety database is sufficient to support the chronic administration of rolapitant in patients receiving HEC or MEC?

FDA Response to Question 4:
In light of the fact that rolapitant will be administered intermittently and treatment

would generally be completed in less than a year, the safety database seems acceptable.

Question 5:

TESARO plans to submit datasets in the NDA according to Table 1 below. Does FDA agree with the proposed plan?

FDA Response to Question 5:

Yes, we agree. Particularly, please provide the following for each adequate and well-controlled clinical study (per 21 CFR 314.126) that you plan to include in your eventual NDA submission:

1. **All clean/locked clinical data sets presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.**
2. **All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm). We recommend that the data definition file comply with the latest CDISC/Define.XML standard.**
3. **A Study Data Reviewer's Guide (SDRG) along with an Analysis Data Reviewer's Guide (ADRG).**
4. **A well commented and organized software program written for each analysis dataset and efficacy table created.**
5. **Please submit all the PK dataset for all phase 1, 2, 3 studies in SAS transport file (concentration time profile and PK parameters).**

Please also see Office of Scientific Investigations (OSI) comments under FDA Additional Comments.

Question 6:

Does FDA concur with the proposed pooling strategy and analysis plan for the ISE as outlined below?

For the ISE, integration (side by side presentation) is limited to the Phase 3 CINV studies, where all endpoint definitions, data collection, study and analysis methodology were consistent. Because of the difference in emetogenic potential of the chemotherapy used, data will not be pooled across the HEC and MEC studies; Table 2 shows how data will generally be presented.

Table 2: Proposed Data Presentation for ISE							
Ph 3 HEC (TS-P04832)		Ph 3 HEC (TS-P04833)		Ph 3 HECs Pooled		Ph 3 MEC (TS-P04834)	
200 mg	Control	200 mg	Control	200 mg	Control	200 mg	Control

Tables, Listings and Figures for the ISE will be included in Module 5, section 5.3.5.3 (Reports of Analyses of Data from More than One Study) while the narrative portion of the ISE will be included in Module 2, section 2.7.3, (b) (4).

In addition, data from each individual CINV study including the Phase 2 CINV study will be summarized and discussed in the (b) (4)

FDA Response to Question 6:
The results based on the pooled data set are exploratory (b) (4) **In addition to the proposed data presentation listed in the table 2, please pool all 3 trials together as an additional pooling analysis.**

Question 7:
Does FDA concur with the proposed pooling strategy and analysis plan for the ISS as outlined below?

The ISS will include two groups of subjects from the rolapitant development program: 1) the CINV target patients and 2) the healthy subjects receiving a single dose (SD) of rolapitant as monotherapy.

PoolingGroup1 (CINVPatientsPopulation)

Pooling Group 1 includes all subjects from the Phase 2 and 3 double-blind, randomized, parallel comparison studies in the CINV patient population. Subjects in this pooling group received HEC or MEC. The protocol-defined treatment regimens for study drug, dexamethasone, and 5-HT3 antagonist therapy were similar across all studies. The safety and efficacy assessments were carried out on a similar schedule.

This is the primary pooling group in the ISS that will be used to compare the safety profile of rolapitant to the control in the intended patient population.

For this pooling group, two levels of integrated summaries are planned.

- *For Level 1 integration, subject data from the rolapitant 200 mg treatment group in the HEC studies will be pooled as a single group. Subject data from the rolapitant 10, 25, and 100 mg treatment groups in the Phase 2 HEC study will be pooled as another single group. Data will be summarized by treatment group, defined as <200 mg and 200 mg rolapitant dose and control groups.*
- *For Level 2 integration, subject data from the rolapitant 200 mg treatment groups will be pooled from the HEC and MEC studies. Similarly, subject data from the control groups from these studies will be pooled. Additionally, subject data from the rolapitant 10, 25, 100 and 200 mg from the HEC and MEC studies will be pooled to form the "all rolapitant dose combined" group.*

Table 3 shows how data will generally be presented.

Table 3: Proposed ISS Data Presentation in CINV Population							
Level 1 Integration					**Level 2 Integration**		
HEC (TS-P04832, TS-P04833,			**MEC (TS-P04834)**		**Overall CINV**		
Control	<200 mg Rolapitant	200 mg Rolapitant	Control	200 mg Rolapitant	All Control Combined	200 mg Rolapitant	All Rolapitant Dose

PoolingGroup2
(Healthy Subjects Receiving SingleDose of Rolapitant Monotherapy)

Pooling Group 2 includes subjects from the Phase 1 studies. To avoid confounding effects by other medications or procedures, data from healthy subjects receiving single dose rolapitant as monotherapy are included in this group. Studies included in Pooling Group 2 are listed in Table 4.

Table 4: Studies to be Included in ISS Pooling Group 2			
Study	**Phase**	**Rolapitant Dose(s) to be Included in**	**Study Description**
P03670	1	5, 10, 25, 50*, 100, 200 mg at fasted state *(* Includes subjects who receive 50 mg rolapitant in the fasted and fed state)*	Rising single and multiple Dose, Food Effect, and DDI: Midazolam
P04328	1	200 mg	ADME
P04852	1	200, 400, 600, 800 mg	Thorough QT/QTc
P04854	1	(b) (4) mg	BE/FE: (b) (4) mg capsules vs (b) (4) mg tablet; DDI:
PR-10-5000-C	1	(b) (4) mg	equivalence (BE): 4x50mg capsules vs. (b) (4) mg
PR-10-5004-C	1	200 mg *(Include healthy subjects only)*	Hepatic Impairment Study
PR-10-5007-C	1	200 mg	Pilot bioavailability (BA): 4x50mg capsules vs. 2x100mg (b) (4) tablets and
PR-10-5013-C	1	200 mg	Pivotal BE: 4x50mg capsules vs. 2x100mg (b) (4) tablets; food effect (FE): 2x100mg
PR-10-5014-C	1	200 mg	Pivotal BE: 4x50mg capsules vs. 2x100mg (b) (4)

For this pooling group, subject data will be grouped into placebo, <200 mg, 200 mg, or >200 mg rolapitant dose groups. Additionally, subjects from these studies who received any rolapitant dose will be included into "all rolapitant doses combined" group. Table 5 shows how data will generally be presented.

Table 5: Proposed ISS Data Presentation: Healthy Subjects Receiving Single Dose Rolapitant

Placebo	<200 mg Rolapitant	200 mg Rolapitant	>200 mg Rolapitant	All Rolapitant Combined

Tables, Listings and Figures for the ISS will be included in Module 5, section 5.3.5.3 (Reports of Analyses of Data from More than One Study) while the narrative portion of the ISS will be included in Module 2, section 2.7.4, Summary of Clinical Safety.

In addition, data from each individual CINV study, (b) (4)

FDA Response to Question 7:
Yes, we agree.

2.3 Regulatory

Question 8:
Does FDA concur with the proposed table of contents for the rolapitant NDA as described and as provided in the Appendix of the briefing document?

FDA Response to Question 8:
Please ensure your table of contents of the eCTD NDA submission is consistent with guidance provided in the following guidances and specifications.

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

> **Specifically reference the associated specification, Comprehensive Table of Contents Headings and Hierarchy for the comprehensive listing of headings and hierarchy which is accessible at:**
> **http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf**

Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163187.pdf

2.4 Controlled Substance / Abuse-Potential

Question 9:
TESARO plans to submit the final Drug Abuse Liability Evaluation of rolapitant (8-factor draft report attached) as a stand-alone report in Module 1.11.4 of the NDA. Does the Agency agree with the proposed overall organization of the attached 8-factor draft report?

FDA Response to Question 9:

Yes. Recommendations for the organization of abuse potential related data are provided in the FDA draft *Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010*: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf (see Recommendations). You should provide active links for any cited or referenced material in the text studies or NDA section. You should include a tabular listing (with active links) to all pre-clinical and clinical abuse related studies.

Question 10:

The analysis of abuse-related adverse events (AEs) will be reported in the following categories:

a. *Healthy subjects from Phase 1 studies or subsets of Phase 1 studies in which single doses of rolapitant were administered as monotherapy*
b. *Patients from Phase 2 and Phase 3 chemotherapy-induced nausea and vomiting (CINV) studies*

(b) (4)

Does the Agency agree with the proposed presentation strategy (section 6.2 of attached 8-factor draft report)?

FDA Response to Question 10:

We agree with point "a" and "b," but do not agree with point "c."

For point "a": the healthy volunteers should be also divided by single dose and multiple dose regimens.

For point "c": the categories of patients should be separated by disorders. AEs for healthy subjects should be a part of Phase 1 evaluation in point "a." Again, there should be clear separation of single dose and multiple dose regimens. The data for patients and healthy volunteers should not be presented together.

You can additionally pool data for all healthy subjects and all patients, but this should be done in 2 separate tables.

Also, the tabulation of all subjects' AEs should be broken down by gender and age 0-18 yo (if you have such a population), 18-55 yo, and 55+ yo.

Discussion Summary:

Tesaro presented their proposal regarding the tabulation and presentation of the abuse related AEs for the NDA. Please refer to slide provided by sponsor. FDA concurred.

Question 11:
At the Type B (EOP2) meeting dated April 5, 2010, FDA provided OPKO Health, the previous sponsor, with a list of AEs related to abuse potential which the agency compiled based on experience to that date. The list included specific terms from the MedDRA 12.0 dictionary as well as frequently used verbatim terms, words or phrases. However, since then, CSS has presented a standardized list of preferred terms, based on a compilation and comprehensive review of available data sources. TESARO proposes the abuse-related AE search terms be based upon those presented by Love and colleagues (2013). Does the Agency agree with the list of AE search terms included in Appendix 13.1 of the draft 8-factor report?

FDA Response to Question 11:
No. We advise you to analyze the AE terms recommended in the Guidance (by subject/patient population, gender, age, dose, duration, level of severity, outcome, etc.). You may conduct additional analyses of AE terms with justification and reference.

Discussion Summary:
Tesaro clarified the abuse related search terms (which was provided in the preliminary comments provided) that will be used in the tabulated summaries. FDA concurred.

Question 12:
To facilitate review of the frequency and pattern of reported abuse-related AEs, a tabular format of AEs as presented in section 13 of the 8-factor draft report is proposed. Does the Agency agree with the proposed presentation?

FDA Response to Question 12:
Yes. In addition to demographic data on subjects and onset and duration and severity of the AE data, you should include the categories: abuse, misuse, overdose, dependence.

Question 13 a:
Does the Agency agree that (b) (4) *are required to evaluate the abuse potential of rolapitant, based on the following:*

a. *the evaluation of the chemical structure of rolapitant, which demonstrates that rolapitant is not structurally related to scheduled substances;*
b. *the nonclinical data,* (b) (4) *does not induce physical dependence following chronic dosing and is not self-administered at levels above saline or vehicle in monkeys previously trained to self-administer cocaine;*
c. *the available clinical PK/PD data for rolapitant showing that rolapitant has a PK profile inconsistent with abuse liability;*
d. *the summary of available post-market evidence for aprepitant, a structurally related NK-1 receptor antagonist, supporting lack of abuse of this pharmacological class;*
e. (b) (4)

FDA Response to Question 13 a:
No, we disagree.
(b) (4)

(b) (4)

B. Non-clinical studies show the following:

- **Receptor binding study for rolapitant shows >50% binding inhibition on a number of abuse related targets: 88% at dopamine transporter, 80% at Cl- channel GABA-gated, 73% norepinephrine transporter, 72% at sigma opioid receptor, 57% at cannabinoid CB1 receptor; and for the main metabolite SCH 720881: 56% at dopamine transporter, 70% at Cl- channel GABA-gated, 55% norepinephrine transporter.**
- **We concluded that the self-administration study in monkeys is uninterpretable for the following reasons:**

1. **The study design does not adequately address the relationship of the 21 hr half-life of rolapitant to collection of relevant PD data. There are two concerns regarding this pharmacokinetic parameter that may affect interpretation of the self-administration data:**

   a) **The long half-life means that drug accumulation may occur during the 5-day access period allowed for each dose of rolapitant, which may reduce self-administration over time if rolapitant has rewarding properties.**
   b) **The 2-day washout period between different (increasing) doses of rolapitant may be insufficient. If there is considerable drug accumulation from the lower dose of rolapitant still present when the higher dose is introduced, the amount of self-administration may be reduced if rolapitant has rewarding properties.**

2. **In the absence of a priori criteria for the elimination of an animal, it is not appropriate to remove the two animals (from total number of six) from the study data evaluation after the data have been collected.**

3. **It is unclear from the data whether there was a statistically significant difference between saline and cocaine during reinstatement testing. If not, then the study is not valid because there is no stability in responding between a rewarding and non-rewarding substance.**

4. **The cumulative amount of rolapitant that was self-administered should be calculated according to amount per plasma volume (ng/mL) to determine if animals were exposed to therapeutic or greater levels of rolapitant.**

5. **The drug histories of the monkeys were not provided, but can influence the likelihood that a monkey will self-administer a novel substance. The specific drug histories of the monkeys and the length of washout time between this study and the study that immediately preceded it should be provided.**

6. **Use of an FR30 schedule of reinforcement is too high of a behavioral requirement when testing an unknown substance that may have rewarding properties that are less than those of the training drug (cocaine). An FR10 schedule of reinforcement is preferable for novel CNS-active drugs.**

7. **The number of animals used in a study should be determined by an a priori power analysis.** (b) (4) **rats may be substituted.**

- **Dependence study in monkeys did not show signs of dependence.**

  The data from the physical dependence study do not show any withdrawal signs during the first 14 days after drug discontinuation. Pharmacokinetic data show that plasma levels of rolapitant are reduced to nearly zero within 3 days of drug discontinuation, so the behavioral observation timeframe is appropriate.

C. **PK data for humans and monkeys differed considerably and are difficult to assess. We recommend a human abuse potential study. If the drug has abuse potential, dependence in humans needs to be assessed. The adverse events after the drug discontinuation should be collected for 1 month only in healthy subject populations.**
D. **We are concerned about neurobehavioral activity of the drug that may relate to abuse potential of rolapitant and CNS adverse events observed in pharm-tox studies, such as:**
   - **in monkeys: hypoactivity, weakness, ataxia, prostration, convulsions, excessive vocalization in the male, hyperactivity in the female;**
   - **in rats: hypoactivity, ataxia, labored breathing, tremors, convulsions, prostration;**
   - **in mice: convulsions, tremor.**
E. **See response to Question 13b, below.**

Question 13 b: *Does the Agency agree that rolapitant is unlikely to be a scheduled drug under the Controlled Substances Act?*

FDA Response to Question 13b:
We cannot answer this question without reviewing the entire clinical and pre-clinical abuse related data until the NDA is submitted and filed.

Discussion Summary
Sponsor clarified that the effective T ½ of rolapitant was 4-6 hours rather than 21 hours, which obviates the concern about accumulation in monkeys. A priori elimination of animals was elaborated in the protocol and the two monkeys eliminated conformed to this criteria. The sponsor confirmed that the saline and cocaine access during each cycle was statistically significant from each other, and therefore validated the study. The sponsor provided information that the cumulative amount of rolapitant during self-administration was as high as 2-3 times the therapeutic maximum plasma levels in humans. Regarding the FR30 schedule of reinforcement, the sponsor explained that this was a commonly used schedule during self-administration. FDA indicated FR10 is preferable for NMEs and for drugs with unknown abuse potential (as explained in the draft Guidance). However, FDA recognizes that FR30 was approved in the protocol previously. The sponsor will provide information regarding the drug histories and wash out periods of monkeys before the initiation of the study.

FDA clarified that a human abuse potential study would be required before submission of this NDA. This NDA will be submitted under PDUFA V, and the NDA is expected to be complete upon submission. FDA clarified that if the sponsor does not agree with conducting a human abuse potential study, the sponsor should submit to FDA justification clarifying their reasons. FDA also indicated the sponsor should provide the PK data for the monkeys. These submissions will need to be reviewed by CSS and deemed acceptable prior to submitting the NDA.

General Recommendations

According to 21 CFR § 314.50 (5) (vii), the abuse potential section of an NDA includes a proposal for scheduling and all scientific data that form the basis of the proposal. The abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:

- **Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)**
- **Pharmacokinetics and pharmacodynamics (including all data on receptor binding of the drug and its active metabolites)**
- **Primary data from abuse potential studies in animals including:**
  - **discrimination study**
  - **self-administration**
  - **dependency study**
- **Primary data from abuse potential studies in humans including:**
  - **human abuse potential study**
  - **dependence in humans must be assessed**
- **Adverse events related to abuse potential from clinical studies**
- **Information and data related to abuse potential in integrated summaries of safety and efficacy (ISS and ISE)**
- **Information related to overdose**
- **Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies**
- **Epidemiological data related to abuse.**

In the NDA, the Sponsor should provide the following information and data related to abuse potential from all clinical studies, including raw data and adverse events coded with the most recent MedDRA terminology that includes:

- **Descriptions and details of all reports in all clinical studies, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for, and related to drug withdrawal and withdrawal symptoms, and any other indication of dependence.**
- **Adverse events data related to abuse should be broken down by gender, age (non-elderly, elderly) and by population healthy volunteers, patients with other disorders treated with rolapitant.**
- **Case narratives of patients in clinical trials who are discontinued from studies for lack of compliance to study medication or procedures, or who discontinue participation without returning the study medication.**

- **Tabulation of patients who were discontinued from the study, or dropped out for reasons related to potential abuse and diversion, including narratives describing reasons and follow-up information.**
- **All post-marketing safety reports of AEs related to potential abuse.**
- **The details of abuse potential evaluation are described in the FDA draft Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf**

CSS invites the Sponsor to submit protocols prior to conducting the studies which we will review and provide comments to the Sponsor.

Please see below Abuse-Related AE Terms for Use in Clinical Efficacy Studies

All clinical studies should be evaluated for indicators of abuse potential. The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA 12.0 dictionary as well as frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes are key observations that may influence the assessment of abuse potential and a recommendation for scheduling. However, all data submitted in an NDA are critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-related terms:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as “high blood pressure,” etc.)

Elevated mood: mood elevated, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laugher, inappropriate mood elevation.

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic terms:

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia.

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

FDA ADDITIONAL COMMENTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is

requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

    a. Site number

    b. Principal investigator

    c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

    d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

    a. Number of subjects screened at each site

    b. Number of subjects randomized at each site

    c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:

    a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

    b. Subject listing for treatment assignment (randomization)

    c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

f. By subject listing, of AEs, SAEs, deaths and dates

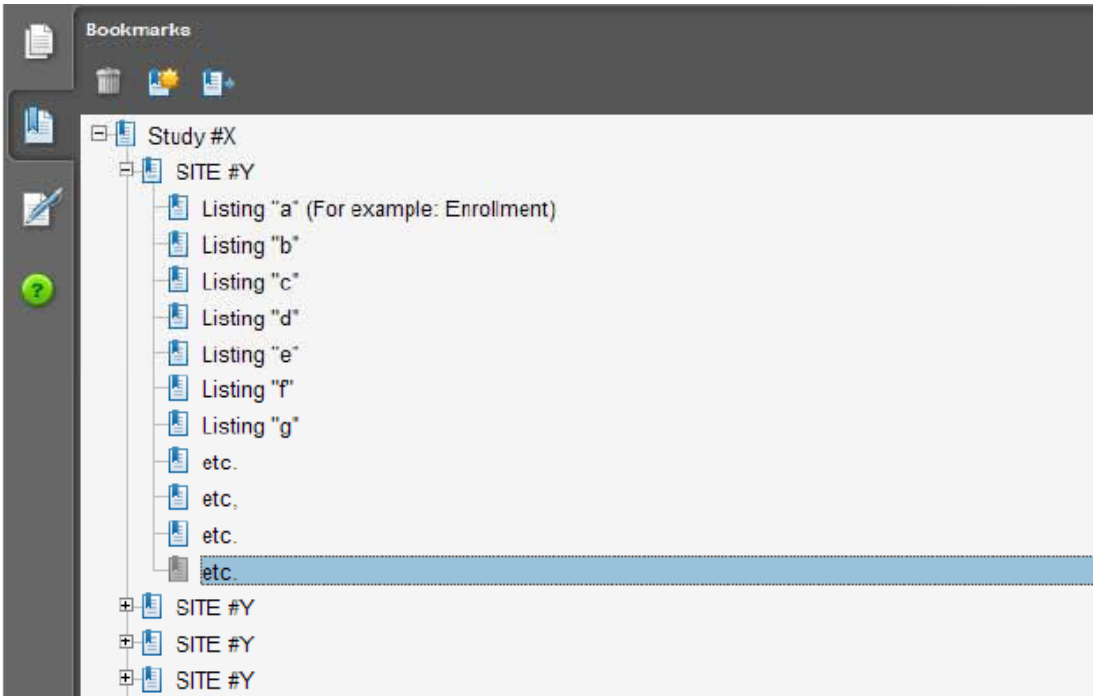
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

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

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

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

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

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

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

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

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

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- **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.**
- **We cannot comment on the need for a REMS for this application at this time.**
- **Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.**

4.0 ADDITIONAL COMMENTS

PREA REQUIREMENTS

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

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

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

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

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

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."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

5.0 ATTACHMENTS AND HANDOUTS

Below attached slides were presented by the sponsor during the July 2, 2014 face-to-face meeting.

Below attached sponsor's written response titled *"Written Responses to the Pre-NDA Preliminary Meeting Comments for rolapitant to FDA's Preliminary Comments"* were provided to FDA on July 2, 2014 prior to the meeting, but were not discussed during the meeting.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MARY H CHUNG
08/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72754

MEETING MINUTES

Tesaro, Inc.
Attention: Tanya Lewis
1000 Winter Street, Suite 3300
Ealtham, MA 02451

Dear Ms. Lewis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rolapitant (SCH 619734).

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2013. The purpose of the meeting was to discuss the chemistry, manufacturing and control strategy of the drug product.

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 me at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	Monday, January 28, 2013 at 1:00 PM- 2:00 PM
Meeting Location:	FDA, White Oak Building 22, Room 1421
Application Number:	IND 72754
Product Name:	Rolapitant (SCH 619734)
Indication:	Prevention of chemotherapy-induced nausea and vomiting
Sponsor Name:	Tesaro
Meeting Chair:	Marie Kowblansky, Ph.D.
Meeting Recorder:	Cathy Tran-Zwanetz

FDA ATTENDEES

Office of New Drug Quality Assessment
Marie Kowblansky, Ph.D., CMC Lead
Yichun Sun, Ph.D., ONDQA Reviewer
Cathy Tran-Zwanetz, Regulatory Health Project Manager

Office of Compliance
Vipul Dholakia, Ph.D., Interdisciplinary Scientist-Chemist

Office of Clinical Pharmacology
Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer

Office of New Drug, Division of Gastroenterology and Inborn Errors Products
Jagjit Grewal,M.P.H, Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Khawla Abu-Izza, Ph.D., Director, Drug Product Development
Mary Lynne Hedley, Ph.D., President and Chief Scientific Officer
Heidi Kempinski, Vice President, Research and Development Operations
Tanya Lewis, Vice President, Regulatory Affairs
George Wu, Ph.D., Senior Director, API Pharmaceutical Development
Gabriela Rossi, Director, Regulatory Affairs

1.0 BACKGROUND

The primary purpose of the meeting is to discuss the chemistry, manufacturing and control (CMC) strategy of Rolapitant. Topics for discussion include the determination of drug substance regulatory starting materials, drug product scale-up, plans to demonstrate bioequivalence of clinical trial and commercial formulations, as well as the planned drug substance and drug product registration data package, stability, shelf-life and process validation plans. Preliminary meeting comments were sent January 25, 2013.

2.0 DISCUSSION

Regulatory Starting Material

(b) (4)

FDA RESPONSE:
Based on the information that you have provided in your briefing package, we find your

(b) (4)

information will be further evaluated in the context of your full NDA submission.

DISCUSSION:
The sponsor accepted the responses, and no further discussion was needed.

(b) (4)

FDA RESPONSE:
It is the company's responsibility to conduct all studies necessary to assure that the commercial manufacturing process for drug substance is capable of consistently delivering quality product. The number of lots included in a process validation study is not a performance criteria. FDA does not approve process validation plan, protocols, or specific batches used in process validation studies. The actual protocols, acceptance criteria and study outcomes will be evaluated during an inspection.

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will

depend on multiple factors, some of which are specific to the complexity of the product and process. Process validation for drug substances is also enforceable under the FD&C Statute 501(a)(2)(b).

DISCUSSION:
The sponsor accepted the responses, and no further discussion was needed.

(b) (4)

FDA RESPONSE:
You will not be able to submit your proposed change as an amendment while the NDA is under review. (b) (4)

DISCUSSION:

(b) (4)

Post-Meeting comment
FDA would like to confirm that all the above information will be required at the time of NDA submission, as discussed at the meeting, and to clarify that comparitive dissolution profile data should be obtained by both the proposed "QC" and the "discriminating " methods which are described in the meeting package. We also request that you provide dissolution method reports with complete data, for both dissolution methods. Preferably, these should be submitted under the IND.

As an additional comment, based on the dissolution data that has been provided, the proposed dissolution of Q = (b) (4) To support the proposed acceptance

criterion, dissolution profile data for n=12 units (i.e., 15, 20, 30, 45, 60, etc.) for the pivotal PK & clinical batches and the registration batches should be provided in the NDA submission.

(b) (4)

FDA RESPONSE:

(b) (4)

supporting data that you have provided and you have not produced enough batches to conclude with certainty that such testing is not required. (b) (4)

DISCUSSION:

(b) (4)

(b) (4)

FDA RESPONSE:

The retest period needs to be based on stability data for drug substance prepared by the final commercial process and final testing procedures. Since you have not described the differences in the manufacturing process or test procedures for the registration batches and supporting batches, we cannot comment on the usefulness of the supporting data in establishing a retest period.

DISCUSSION:

The sponsor accepted the responses, and no further discussion was needed.

DRUG PRODUCT

Drug Product Formulation Development

6. TESARO plans to complete the pivotal program for rolapitant with 4 x 50 mg capsules and introduce a new formulation at launch if comparability is demonstrated in a separate bioequivalence (BE) study in healthy volunteers. Does the Agency agree with introducing the new formulation at launch based on the results from this BE study and supporting dissolution and stability data?

FDA RESPONSE:

The approach you propose above is acceptable as long as your to-be-marketed formulation is demonstrated to be bioequivalent to the phase 3 trial formulation (4 x 50 mg capsules). Please note that for an NME application under PDUFA V, all major components of the application are expected to be included in the original NDA and are not subject to agreement for late submission. As such, data supporting bioequivalence of the clinical vs. to-be-marketed formulations will need to be provided at the time of NDA submission.

Additional Clinical Pharmacology comments: You should also address the food-effect information for your new formulation in the NDA submission for labeling purposes. You may consider inclusion of a third crossover group (test drug administered with food) in your proposed BE trial.

DISCUSSION:

The sponsor proposed to conduct a single dose, randomized, parallel group study with 3 treatment arms (Test-fasted, Reference-fasted, and Test-fed) in order to evaluate the bioequivalence (vs. reference product) and food-effect of the new formulation. The parallel design is being proposed due to the long elimination half life of rolapitant (~ 170 h). FDA agreed and recommended that the Sponsor should consult the relevant guidances for industry (i.e. BA/BE and Food-Effect BA guidances) for the appropriate conduct of the proposed study.

(b) (4)

FDA RESPONSE:

In view of your proposed commercial batch size, (b) (4) batch will likely be acceptable as a registration batch for the drug product.

DISCUSSION:

The sponsor accepted the responses, and no further discussion was needed.

Drug Product Process Validation

8. TESARO plans to complete drug product process validation with 3 consecutive batches at the projected commercial scale. The resulting process performance qualification data will be available for PAI inspection. Does the Agency agree with our strategy?

FDA RESPONSE:

FDA does not specify or require completing three consecutive full-scale process validation batches before the approval of the application. However, full-scale process validation studies are required to be completed prior to distribution of the commercial product. Prior to marketed product distribution, it is necessary for firms to justify and confirm earlier process design and development work for their proposed scale up to commercial scale. Firms need to have justification for their process parameters, component characteristics, and how these relate to the final product attributes, demonstrated at commercial scale.

DISCUSSION:

The sponsor accepted the responses, and no further discussion was needed.

Drug Product Specifications

(b) (4)

(b) (4) Does the Agency agree with the general approach and proposed drug product specifications?

FDA RESPONSE:

Your proposed specification is reasonable, but will be further scrutinized when you submit your NDA and have provided copies of all testing procedures. Also, you will need to

(b) (4)

DISCUSSION:

Sponsor will be providing new dissolution data in a future IND submission.

Drug Product Stability

(b) (4)

FDA RESPONSE:

(b) (4)

(b) (4)

DISCUSSION:
The sponsor accepted the responses, and no further discussion was needed.

(b) (4)

FDA RESPONSE:
In establishing a shelf-life for your product, the trends exhibited in the stability data will need to be considered. Therefore, we cannot agree to your proposed shelf-life at the present time. In addition, you should be aware that we generally require the submission of

(b) (4)

DISCUSSION:
The sponsor accepted the responses, and no further discussion was needed.

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

/s/

CATHERINE A TRAN-ZWANETZ
02/08/2013

MARIE KOWBLANSKY
02/08/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206500

LATE-CYCLE MEETING MINUTES

TESARO, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Rossi:

Please refer to your New Drug Application (NDA) dated September 5, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for rolapitant hydrochloride.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 3, 2015.

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 Mary Chung, Regulatory Project Manager at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Division Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 3, 2015 3:00 to 4:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1417
Silver Spring, Maryland 20903

Application Number: NDA 206500
Product Name: rolapitant
Applicant Name: TESARO, Inc.

Meeting Chair: Donna Griebel, M.D.
Meeting Recorder: Mary Chung, PharmD.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D.	Director
Amy Egan, M.D.	Deputy Director
Maria Walsh, RN, B.S.	Associate Director for Regulatory Affairs
LCDR Richard Ishihara	Regulatory Scientist

Division of Gastroenterology and Inborn Errors Products

Donna Griebel, M.D.	Director
Joette Meyer, PharmD.	Associate Director of Labeling
Aisha Peterson Johnson, M.D.	Medical Reviewer
Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Tracy Behrsing, Ph.D.	Pharmacology Reviewer
Mary Chung, PharmD.	Regulatory Project Manager

Office of Clinical Pharmacology

Insook Kim, Ph.D.	Clinical Pharmacology Reviewer
Sarah Dorff, Ph.D.	Genomics Reviewer

Division of Biometrics III

Stephen Wilson, Ph.D.	Director
Mike Welch, Ph.D.	Deputy Director
Yeh-Fong Chen, Ph.D.	Statistical Team Lead
Wen-Jen Chen, Ph.D.	Statistical Reviewer

Office of Surveillance and Epidemiology

LCDR Sukhminder Sandhu	Team Lead, Division of Epidemiology
Kimberly Swank, PharmD.	Safety Evaluator, Division of Pharmacovigilance

Controlled Substances Staff
Alicja Lerner, M.D., Ph.D. Medical Reviewer

Office of Pharmaceutical Quality
Charles Jewell, Ph.D. CMC Reviewer

Office of Scientific Investigations/ Division of Clinical Compliance Evaluation
Susan Leibenhaut, M.D. Medical Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES
Mary Lynne Hedley, Ph.D., President and Chief Scientific Officer, Tesaro
Tanya Lewis, Regulatory Affairs Vice President, Tesaro
Gabriela Rossi, Regulatory Affairs Director, Tesaro
Thomas Perrone, Ph.D., Regulatory Affairs Director (CMC), Tesaro
Robert Martell, M.D., Ph.D., Chief Medical Officer, Tesaro
(b) (4)
(b) (4)
Vikram Kansra, Ph.D., Vice President, Clinical Pharmacology, Tesaro
Jennifer Christensen, Director, Program Development, Tesaro
Hajira Koeller, Ph.D., Associate Director Clinical Scientist, Tesaro
(b) (4)

1.0 BACKGROUND

NDA 206500 was submitted on September 5, 2014 for Varubi (rolapitant hydrochloride).

Proposed indication: Prevention of nausea and vomiting associated with cancer chemotherapy

PDUFA goal date: September 5, 2015

FDA issued a Background Package in preparation for this meeting on May 20, 2015.

2.0 DISCUSSION

1. Introductory Comments

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Biostatistics/ Clinical

Discussion Summary
Sponsor presented the reasons they believe that there is adequate evidence in (b) (4) ***Please see attached slides presented by sponsor.***

Sponsor will provide written comments regarding their position on the evidence (b) (4)

FDA and Sponsor will continue to work on labeling in parallel with ongoing discussions regarding (b) (4) .

3. Discussion of Minor Review Issues

Clinical

We look forward to discussing your plans for how you intend to assure that providers prescribe the correct dose of dexamethasone with rolapitant to assure overall antiemetic regimen efficacy, in light of the reduced doses of dexamethasone administered with other drugs in the class and the possibility that providers will not comprehensively read the label.

Discussion Summary
(b) (4)

Controlled Drug Substances Staff

(b) (4)

4. Information Requests

At the time of developing this agenda, we are waiting for your response to Clinical Information Request dated May 12, 2015 regarding safety analyses for chemotherapeutic agents that are substrates of BCRP or CYP2D6.

5. Postmarketing Requirements/ Postmarketing Commitments

a. PREA Post Marketing Requirement

Your proposed pediatric plan, which is based on the agreed iPSP established September 4, 2014, was presented to the Pediatric Review Committee (PeRC). PeRC and the Division agree with the timelines and proposed studies, and your request for a deferral of the below studies.

GLP toxicology study in juvenile animals
Protocol submission: May 2015
First Dose: Dec 2015
Final study report submission: Nov 2016

(b) (4) PK/PD and clinical effectiveness in pediatric patients
Protocol submission: Nov 2016
First Dose: Aug 2017
Final study report submission: Nov 2020

Confirmatory clinical effectiveness and safety study in pediatric patients
Protocol submission: Nov 2020
First Dose: Aug 2023
Final study report submission: Aug 2026

b. Clinical Pharmacology Post Marketing Commitment

We are considering a PMC for an in vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant.

Discussion Summary
Sponsor stated that they agreed, in principle, to the proposed PMC. Sponsor indicated they will provide information regarding an ongoing in vivo study for rolapitant (b) (4). for FDA review. FDA will review if the protocol design will adequately address this drug interaction issue for (b) (4) rolapitant.

We are considering a PMC for an in vitro study to evaluate an inhibitory potential of rolapitant on OATP1B1 and OATP1B3.

We are considering a PMC for in vitro studies to evaluate an inhibitory potential of rolapitant on renal transporters i.e., organic cation transporter 2 (OCT2), multidrug

and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3).

6. Review Plans

   PDUFA date: September 5, 2015

7. Wrap-up and Action Items

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

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

DONNA J GRIEBEL
07/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206500

LATE CYCLE MEETING
BACKGROUND PACKAGE

TESARO, Inc.
Attention: Gabriela Rossi
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Ms. Rossi:

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

We also refer to the Late-Cycle Meeting (LCM) scheduled for June 3, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time:	June 3, 2015 3:00 to 4:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	NDA 206500
Product Name:	rolapitant
Indication:	Prevention of nausea and vomiting associated with cancer chemotherapy
Sponsor/Applicant Name:	TESARO, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issue has been identified to date:

Clinical/ Biostatistics

The Division is concerned that the data submitted in the rolapitant NDA may not provide adequate evidence to support the efficacy of rolapitant for the prevention of chemotherapy induced nausea and vomiting (CINV) (b) (4)

(b) (4)

As previously indicated, an unblinded interim analysis of the phase 2 Study 51 was conducted by sponsor personnel for planning future studies. It is not clear that adequate procedures were in place to ensure that results of the analysis were not revealed to persons connected with the study. This is especially problematic since the study did not use an independent third party or an independent data monitoring committee (IDMC). 21 CFR 314.126(b)(5) states in part that sponsors of well-controlled studies should take adequate measures to minimize bias with respect to the analysis of the data. Since your study data may have been compromised through the unblinded interim analysis, we do not feel that the phase 2 Study 51 meets our usual requirements for being an adequate and well-controlled study.

We note that the phase 2 Study 51 was completed before the data analysis plan (DAP) was finalized. Your approach to dealing with missing data in the DAP is not consistent with what is stated in the clinical study report. Additionally, the primary analysis should be based on the intent to treat population. Accordingly, we would treat patients with missing data as treatment failures for the responder analysis. The results of the analysis of the delayed phase changed when a single patient with missing data was excluded from the analysis (b) (4)

(b) (4)

(b) (4)

To offset this result, we would need at least two positive adequate and well-controlled trials. We do not consider the phase 2 Study 51 to be a positive adequate and well-controlled trial.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

At this stage, we do not believe that a REMs is necessary to ensure benefits of this product outweigh the risks.

LCM AGENDA

1. Introductory Comments – 3 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes

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

   Biostatistics/ Clinical

3. Discussion of Minor Review Issues – 10 minutes

   Clinical

   We look forward to discussing your plans for how you intend to assure that providers prescribe the correct dose of dexamethasone with rolapitant to assure overall antiemetic regimen efficacy, in light of the reduced doses of dexamethasone administered with other drugs in the class and the possibility that providers will not comprehensively read the label.

   Controlled Drug Substances Staff

   (b) (4)

4. Information Requests – 5 minutes

   At the time of developing this agenda, we are waiting for your response to Clinical Information Request dated May 12, 2015 regarding safety analyses for chemotherapeutic agents that are substrates of BCRP or CYP2D6.

5. Postmarketing Requirements/ Postmarketing Commitments – 15 minutes

   a. PREA Post Marketing Requirement

      Your proposed pediatric plan, which is based on the agreed iPSP established September 4, 2014, was presented to the Pediatric Review Committee (PeRC). PeRC and the Division agree with the timelines and proposed studies, and your request for a deferral of the below studies.

GLP toxicology study in juvenile animals
Protocol submission: May 2015
First Dose: Dec 2015
Final study report submission: Nov 2016

(b) (4) PK/PD and clinical effectiveness in pediatric patients
Protocol submission: Nov 2016
First Dose: Aug 2017
Final study report submission: Nov 2020

Confirmatory clinical effectiveness and safety study in pediatric patients
Protocol submission: Nov 2020
First Dose: Aug 2023
Final study report submission: Aug 2026

b. Clinical Pharmacology Post Marketing Commitment

We are considering a PMC for an in vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant.

We are considering a PMC for an in vitro study to evaluate an inhibitory potential of rolapitant on OATP1B1 and OATP1B3.

We are considering a PMC for in vitro studies to evaluate an inhibitory potential of rolapitant on renal transporters i.e., organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3).

6. Review Plans

PDUFA date: September 5, 2015

7. Wrap-up and Action Items – 5 minutes

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

/s/

DONNA J GRIEBEL
05/14/2015