CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209299Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 209299 SUPPL # HFD # 161

Trade Name Tavalisse™

Generic Name fostamatinib

Applicant Name Rigel Pharmaceuticals, Inc.

Approval Date, If Known April 17, 2018

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)

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

YES ☒ NO ☐

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

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years of marketing exclusivity

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☐ NO ☒

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

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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

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"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:

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(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

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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:

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(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: Rachel McMullen, MPH, MHA
Title: Regulatory Project Manager
Date: 4/13/18

Name of Division Director signing form: Ann T. Farrell, MD
Title: Director Division of Hematology Products

Reference ID: 4249958

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

Reference ID: 4249958

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

/s/

RACHEL S MCMULLEN
04/17/2018

ANN T FARRELL
04/17/2018

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 209299	NDA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Tavalisse™ Established/Proper Name: fostamatinib disodium hexahydrate Dosage Form: tablets		Applicant: Rigel Pharmaceuticals Agent for Applicant (if applicable):
RPM: Rachel McMullen, MPH, MHA		Division: Division of Hematology 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 • User Fee Goal Date is April 17, 2018	☒ 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.

Reference ID: 4250973

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1- New Molecular Entity (NME)
(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

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

NDAs: Subpart H
☐ 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: Burst; Public outreach via social media
❖ 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
❖ 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)* (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval: April 17, 2018
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
• Original applicant-proposed labeling	☒ Included April 15, 2017
❖ 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
• Original applicant-proposed labeling	☒ Included April 15, 2017
❖ 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 April 10, 2018
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	• Conditionally acceptable letter: August 2, 2017 • DMEPA Review: August 1, 2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: June 29, 2017 DMEPA: February 22, 2018, January 12, 2018, October 20, 2017 DMPP/PLT (DRISK): November 8, 2017 OPDP: November 8 & 9, 2017 SEALD: ☐ None CSS: ☐ None Product Quality: January 26, 2018 Other: ☐ None
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	RPM Filing Review: June 29, 2017 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)

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

❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Drug Designation	
• 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 OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	• April 4, 2018 • April 3, 2018 • March 22, 2018 • March 5, 2018 • February 12, 2018 (2) • February 2, 2018 (2) • January 31, 2018 • January 23, 2018 • December 15, 2017 • December 4, 2017 (2) • November 29, 2017 • November 6, 2017 • October 26, 2017 • October 19, 2017 • September 27, 2017 • September 26, 2017 • September 16, 2017 • September 7, 2017 • July 17, 2017 • July 12, 2017 • July 3, 2017 • June 29, 2017 • June 21, 2017 • May 26, 2017 • May 25, 2017 • May 16, 2017 • May 11, 2017 • May 5, 2017

	• April 26, 2017
❖ 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)	Memo: Sponsor Statement re: application status & website error: April 12, 2018
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A
• Pre-NDA/BLA or BPD Type 4 meeting *(indicate date of mtg)*	Pre-NDA meeting: April 5, 2016 (IND 074939)
• EOP2 meeting *(indicate date of mtg)*	EOP2 meeting: October 8, 2013 (IND 074939)
• Mid-cycle Communication *(indicate date of mtg)*	Mid-Cycle Meeting: September 28, 2018
• Late-cycle Meeting *(indicate date of mtg)*	Late cycle Meeting: January 11, 2018
• Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ 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
Division Director Summary Review *(indicate date for each review)*	See DD Review in Section 17 Page 223 of Multidisciplinary Review DD Memo: April 16, 2018
Cross-Discipline Team Leader Review *(indicate date for each review)*	See Executive Review in Section 1 Page 15 of Multidisciplinary Review CDTL Memo: April 17, 2018
PMR/PMC Development Templates *(indicate total number)*	2 PMCs
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See Section 7 Page 83 of Multidisciplinary Review
• Clinical review(s) *(indicate date for each review)*	April 17, 2018 Multidisciplinary Review – See Section 7 Page 83 Clinical Memo: April 26, 2018
• 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 page 204 of Multidisciplinary Review

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ 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)*	DRISK REMS Review: December 14, 2017 ☐ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	Letter: December 4, 2017 (3) OSI Inspection Summary: September 14, 2017
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)*	See Section 7 Page 83 of Multidisciplinary Review
Statistical Review(s) *(indicate date for each review)*	See Section 7 Page 83 of Multidisciplinary Review Stats Memo: March 5, 2018
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)*	See Section 6 Page 64 of Multidisciplinary Review
Clinical Pharmacology review(s) *(indicate date for each review)*	See Section 6 Page 64 of Multidisciplinary Review Clin Pharm Memo: December 14, 2017 QT-IRT Review: November 29, 2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	OSIS Memo: October 24, 2017 OSIS Review: September 22, 2017 OSIS Memo: August 21, 2017

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

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	See Section 5 Page 28 of Multidisciplinary Review Nonclinical Supervisory Review: December 26, 2017
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	See Section 5 Page 28 of Multidisciplinary Review Nonclinical Reviews: December 26, 2017 & December 7, 2017
❖ 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)*	December 6, 2017
❖ ECAC/CAC report/memo of meeting	December 5, 2017 - ECAC Final Study minutes
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• 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)*	• Risk Assessment of Elemental Impurities: March 19, 2018
	• Compiled IQA Review with executive summary: January 29, 2018
	  ○ DS Review: December 11, 2017
	  ○ DP Review: December 20, 2017
	  ○ CMC Labeling Review: January 26, 2018
	  ○ Process Review: September 13, 2017
	  ○ Facilities Review: January 16, 2018
	  ○ Biopharm Review: November 21, 2017
	  ○ Attachment I Final Risk Assessments: January 29, 2018

❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None

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

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date) (all original applications and all efficacy supplements that could increase the patient population)*	See page 7 of Compiled IQA Review with Executive Summary
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ 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	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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

/s/

RACHEL S MCMULLEN
04/19/2018

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 12, 2018

Application Number: NDA 209299
Product Name: fostamatinib
Sponsor/Applicant Name: Rigel Pharmaceuticals

Subject: Rigel Statement Regarding Application Approval and Website Error

FDA Participants :

- Rachel McMullen, MPH, MHA ; Senior Regulatory Manager

Sponsor/Applicant Participants

- Dana Pizutti, MD, Senior VP, Regulatory Affairs and Clinical Compliance
- Yvonne Kim, Senior Director, Regulatory Affairs

1.0 BACKGROUND:

On April 17, 2017, Rigel pharmaceuticals submitted a new drug application (NDA 209299) for fostamatinib. This NME application is in the PDUFA V "Program" and is under a standard review timeline. The applicant has orphan drug designation for this indication.

The proposed indication for use for TAVALISSE is as "*a spleen tyrosine kinase (SYK) inhibitor indicated for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment*."

2.0 DISCUSSION:

On April 12, 2018, Rigel Pharmaceuticals contacted the Division of Hematology Products to provide notification of an error regarding the NASDAQ-hosted website for Rigel. The Sponsor reported that an error made by the external host of its investor relations website had resulted in inaccurate information being conveyed regarding the approval status of this application. Specifically, it was erroneously reported that NDA 209299 for fostamatinib was already approved.

The Sponsor also noted that this error had caused a brief fluctuation in the NASDAQ, but indicated that the company had taken pertinent steps to remedy the situation and that the website had been corrected.

The FDA is continuing its review of the NDA and the Prescription Drug User Fee Act (PDUFA) action date is April 17, 2018.

Reference ID: 4249349

3.0 ACTION ITEMS:

The Sponsor was asked to provide a written communication to the Agency in follow up to the phone notification. As a result, Rigel provided an electronic copy of the press release which they issued to address the issue.

A copy of this press release is also attached for reference.

Rigel Makes Statement Regarding Website Error

SOUTH SAN FRANCISCO, Calif., April 12, 2018 /PRNewswire/ -- Rigel Pharmaceuticals, Inc. (Nasdaq:RIGL), reported that due to an error by the external host of its investor relations website, inaccurate information was displayed regarding the U.S. Food and Drug Administration's (FDA) review of the New Drug Application (NDA) for fostamatinib for the treatment of adult patients with chronic immune thrombocytopenia (ITP). The website has been corrected. The FDA is continuing its review of the NDA and the Prescription Drug User Fee Act (PDUFA) action date is April 17, 2018.

About Rigel (www.rigel.com)

Rigel Pharmaceuticals, Inc., is a biotechnology company dedicated to discovering, developing and providing novel small molecule drugs that significantly improve the lives of patients with immune and hematologic disorders, cancer and rare diseases. Rigel's pioneering research focuses on signaling pathways that are critical to disease mechanisms. The company's current programs include clinical studies of fostamatinib, an oral spleen tyrosine kinase (SYK) inhibitor, in a number of indications. Rigel has an NDA under review with the FDA for fostamatinib in patients with chronic immune thrombocytopenia (ITP). In addition, Rigel has product candidates in development with partners BerGenBio AS, Daiichi Sankyo and Aclaris Therapeutics.

Forward Looking Statements

This release contains forward-looking statements relating to, among other things, the information displayed on its website and its current clinical trials and those programs which are partnered. Any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Words such as "planned," "will," "may," "should," "expect," and similar expressions are intended to identify these forward-looking statements. These forward-looking statements are based on Rigel's current expectations and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, the timing, completion and results of clinical trials; market competition; as well as other risks detailed from time to time in Rigel's reports filed with the Securities and Exchange Commission, including its Quarterly Report on Form 10-K for the period ended December 31, 2017. Rigel does not undertake any obligation to update forward-looking statements and expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein.

Contact: Raul Rodriguez
Phone: 650.624.1302
Email: ir@rigel.com

Media Contact: David Polk
Phone: 310.309.1029
Email: david.polk@syneoshealth.com

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/s/

RACHEL S MCMULLEN
04/16/2018

From:	McMullen, Rachel
To:	"Yvonne Kim"
Cc:	"Anne-Marie Duliege"; "Dana Pizzuti"; McMullen, Rachel
Subject:	NDA 209299/Tavalisse _ FDA Proposed Labeling _USPI (Response DUE: COB Thursday, April 5)
Date:	Wednesday, April 04, 2018 4:21:32 PM
Attachments:	image001.png NDA 209299_Tavalisse USPI_FDA Proposed Labeling (4-4-18).docx
Importance:	High

Good evening Yvonne,

With reference to **NDA 209299/Tavalisse**, FDA's current edits/comments on the USPI are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **COB (ET) on Thursday, April 5, 2018** followed by an official submission of the label to the NDA file. The clean version of the label which you submit officially to your NDA file will constitute the final agreed upon labeling.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
04/04/2018

From:	McMullen, Rachel
To:	"Yvonne Kim"
Cc:	"Anne-Marie Duliege"; "Dana Pizzuti"; McMullen, Rachel
Subject:	NDA 209299/Tavalisse _ FDA Proposed Labeling _PPI (Response DUE: COB Thursday, April 5)
Date:	Tuesday, April 03, 2018 4:23:26 PM
Attachments:	image001.png NDA 209299_ Tavalisse PPI_FDA Proposed Edits (4-3-18).docx

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Good evening Yvonne,

With reference to **NDA 209299/Tavalisse**, FDA's current edits/comments on the PPI are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

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Please update your labels and submit your revised labeling response to me via email by **COB (ET) on Thursday, April 5, 2018** followed by an official submission of the label to the NDA file. The clean version of the label which you submit officially to your NDA file will constitute the final agreed upon PPI.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
04/04/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	"Anne-Marie Duliege"; "Dana Pizzuti"; McMullen, Rachel
Subject:	NDA 209299/Tavalisse _ FDA Proposed Labeling _USPI (Response DUE: Noon Tuesday, March 27, 2018)
Date:	Thursday, March 22, 2018 4:36:02 PM
Attachments:	image001.png NDA 209299_Tavalisse USPI_FDA Proposed Labeling (3-22-18).docx
Importance:	High

Good evening Yvonne,

With reference to **NDA 209299/Tavalisse**, FDA's current edits/comments on the USPI are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

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Please update your labels and submit your revised labeling response to me via email by **noon (ET) on Tuesday, March 27, 2018** followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
03/23/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_FDA Proposed Labeling (Response DUE: COB, Thursday, March 8th)
Date:	Monday, March 05, 2018 3:46:06 PM
Attachments:	image001.png NDA 209299_Tavalisse USPI_FDA Proposed Labeling (3-5-18).docx
Importance:	High

Good afternoon Yvonne,

With reference to **NDA 209299/Fostamatinib**, FDA's current edits/comments on the USPI are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

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Please update your labels and submit your revised labeling response to me via email by **COB on Thursday, March 8, 2018** followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
03/05/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel (Rachel.Mcmullen@fda.hhs.gov)
Subject:	NDA 209299_ Information Request (Response DUE: noon ET, tomorrow, Feb 13th)
Date:	Monday, February 12, 2018 3:24:00 PM
Attachments:	image001.png
Importance:	High

Good afternoon Yvonne,

With reference to **NDA 209299/Fostamatinib**, please see the additional information request below.

Information Request:

Please provide the definition for the "duration of stable platelet response" used in the label for the extension study for the (b) (4) patients who maintained platelet response of (b) (4) 50 x 10^9/L for 12 or more months. Also, provide the subject IDs of the (b) (4) patients.

Please respond to me via email NLT noon (ET) tomorrow, Tuesday, February 13th, followed by a subsequent formal submission to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
02/12/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_ Information Request (Response DUE: COB today)
Date:	Monday, February 12, 2018 10:17:56 AM
Attachments:	image008.png
Importance:	High

Good morning Yvonne,

With reference to **NDA 209299/Fostamatinib**, the FDA review team is requesting a prompt response to the following:

Information Request:

In your February 8th response to FDA labeling comments/edits, you state that in the 049 trial, of the 44 subjects treated with placebo in the prior study and evaluated for stable response for TAVALISSE, ten subjects (including a single subject who was classified as a placebo responder in the prior study) met the criteria for stable response. The number of stable responders is not consistent with the 049 CSR, table 11-2, page 51 (second version of the primary endpoint). If you claim there were 10 responders, provide the subject IDs of these responders.

Please respond to me via email by COB today, followed by a subsequent formal submission to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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you.

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/s/

RACHEL S MCMULLEN
02/12/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	"Anne-Marie Duliege"; "Dana Pizzuti"; McMullen, Rachel
Subject:	RE: NDA 209299_FDA Proposed Labeling _ PPI (Response DUE: Noon Thursday, February 8, 2018)
Date:	Friday, February 02, 2018 4:32:43 PM
Attachments:	image001.png NDA 209299_ Tavalisse PPI_FDA PRoposed Edits (2-2-18).docx
Importance:	High

Good afternoon Yvonne,

With reference to **NDA 209299/Fostamatinib**, FDA's current edits/comments on the PPI are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **noon (ET) on Thursday, February 8, 2018** followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
02/02/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	"Anne-Marie Duliege"; "Dana Pizzuti"; McMullen, Rachel
Subject:	NDA 209299_FDA Proposed Labeling (Response DUE: Noon Thursday, February 8, 2018)
Date:	Friday, February 02, 2018 3:19:13 PM
Attachments:	image001.png NDA 209299_Tavalisse USPI_FDA Proposed Labeling (2-2-18).docx NDA 209299_Container Labeling Recommendations (2-2-18).pdf
Importance:	High

Good afternoon Yvonne,

With reference to **NDA 209299/Fostamatinib**, FDA's current edits/comments on the labeling (USPI and container labels) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **noon (ET) on Thursday, February 8, 2018** followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
02/02/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_ Clin Pharm Information Request (DUE: Feb 1, 2018)
Date:	Wednesday, January 31, 2018 1:15:00 PM
Attachments:	image001.png
Importance:	High

Good afternoon Yvonne,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

-

Clinical Pharmacology Information Request:

Reference is made to the response to FDA information request received on 1/29/2018 under NDA 209299. We acknowledged your alternative approach to provide the information of shift in blood pressure in Study D4300-033. Please provide the percentage of patients whose blood pressure reversed to baseline within 1 week following TAVALISSE discontinuation while they had blood pressure increased to = 140/90 mmHg in the fostamatinib arm during the treatment. Please respond by noon 2/1/2018.

Please submit a response via email to me by **2pm (ET) on February 1, 2018** and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/31/2018

From:	McMullen, Rachel
To:	Yvonne Kim
Cc:	Dana Pizzuti; McMullen, Rachel (Rachel.Mcmullen@fda.hhs.gov)
Subject:	NDA 209299_ Information Request (DUE: Jan 29, 2018)
Date:	Tuesday, January 23, 2018 12:51:00 PM
Attachments:	image001.png
Importance:	High

Good afternoon Yvonne,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Clinical Pharmacology Information Request:

Reference is made to Study D4300-033 under NDA 209299. Please calculate the median time (minimum, maximum) of blood pressure returning to the levels similar to baseline after discontinuation of fostamatinib. The data will be used to update the labeling language in section 12.2. Please respond by 1/29/2018.

Please submit a response via email to me by **noon on January 29, 2018** and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
01/23/2018

Executive CAC Final Study Minutes
Date of Meeting: December 5, 2017

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
John Leighton, PhD, DHOT, Alternate Member
Christopher Sheth, PhD, DHOT, Pharm Tox Supervisor
Brian Cholewa, PhD, DHOT, Presenting Reviewer

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

NDA# 209299
Drug Name: Tavalisse (fostamatinib)
Sponsor: Rigel Pharmaceuticals

Background: Fostamatinib (R935788) is a prodrug that rapidly metabolizes to the active compound R940406 [R406]). R406 is a small molecule spleen tyrosine kinase (SYK) inhibitor. SYK plays a role in the immune system by mediating signal transduction of Fc-activating receptors and is involved in B-cell maturation. NDA 209299 seeks approval of Tavalisse (fostamatinib) taken orally at a maximum dose of 300 mg/day in adult patients with persistent or chronic immune thrombocytopenia purpura (ITP) who have had an insufficient response to a previous treatment.

Mouse Carcinogenicity Study:

The study in Crl:CD1(ICR) mice evaluated fostamatinib at doses of 50, 150, 500/250, or 1200 mg/kg/day based on 4- and 13-week studies with ECAC concurrence. The MTD was not reached in previous studies, thus the high dose was selected to reach a saturated exposure and was expected to hit a target AUC of ~600,000 ng*h/mL. Water and a vehicle control of 0.1% carboxymethylcellulose sodium, 0.1% methylparaben sodium and 0.02% propylparaben sodium in purified water (w/w) were utilized in this study. The dose of 1200 mg/kg/day was not tolerated and males and females at this dose were terminated on day 14 and 44, respectively. The 500 mg/kg/day dose was reduced to 250 mg/kg/day on day 352. The males and females in the 500/250 mg/kg/day group were terminated on day 555 and day 494 of the study, respectively. The FDA survival analysis demonstrated a statistically significant dose response relationship in mortality across two controls and treated groups in both male and female mice ($p<0.001$). No tumor findings achieved statistical significance in male or female mice administered fostamatinib when compared to water or vehicle controls.

Rat Carcinogenicity Study:

The study in Crl:CD(SD) rats investigated fostamatinib administered at doses of 10, 25, 45, and 80 mg/kg/day in males and 5, 12, 24 and 40 mg/kg/day in females based on the results of a 26-week study with ECAC concurrence. The high dose was selected based on hematology parameters in males and reduced body weight gain in females. The dose spacing was based on AUC exposures not being dose proportional and the difference in dosing between sexes accounted for the increased exposure in females. Dose groups were compared to vehicle controls of 0.1% carboxymethylcellulose sodium, 0.1% methylparaben sodium and 0.02% propylparaben sodium in purified water (w/w). The dose of 80 mg/kg/day was not tolerated in males and this dose group was terminated on day 95. Because of decreased survival, dosing was stopped in females in the 40 mg/kg/day group on day 410, males in the 45 mg/kg/day group on day 612, and females in the 24 mg/kg/day group on day 619. The FDA survival analysis showed a statistically significant dose response relationship in mortality in males and females when compared to vehicle controls. No tumor findings achieved statistical significance in male or female rats administered fostamatinib when compared to vehicle controls.

Executive CAC Conclusions

Mouse

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 2-year mouse carcinogenicity study in either males or females.

Rat

- The Committee concurred that the study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 2-year rat carcinogenicity study in either males or females.

Karen Davis Bruno, Ph.D.
Chair, Executive CAC

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/s/

STEPHANIE J QUINN
12/08/2017

KAREN L DAVIS BRUNO
12/08/2017

From:	McMullen, Rachel
To:	"Kathy Dumas"
Cc:	"Anne-Marie Duliege"; "Dana Pizzuti"; McMullen, Rachel
Subject:	NDA 209299_Clin Pharm Information Request (Response DUE: December 13th)
Date:	Monday, December 04, 2017 3:38:34 PM
Attachments:	image001.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, please note the following information request from the team.

Clinical Pharmacology Information Request:

-

Please update the numbers in section 12.2 of our updated label as shown below based on the new blood pressure guidelines.

-

[redacted] (b) (4) **mean treatment-related increases of 2.93 and 3.53 mmHg over placebo** [redacted] (b) (4) **were observed following TAVALISSE doses of 100 mg twice daily.** [redacted] (b) (4) **blood pressure** [redacted] (b) (4) **within 1 week following TAVALISSE discontinuation.**

Please provide a response by COB on December 13, 2017, and also follow up with an official submission to your NDA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
12/04/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_FDA Proposed Labeling (Response DUE: COB, Wednesday, December 13, 2017)
Date:	Monday, December 04, 2017 3:30:25 PM
Attachments:	Tavalisse USPI_ FDA Proposed Edits #1.docx NDA 209299_Fostamatinib PPI_FDA Proposed Edits#1.docx NDA 209299_Container Labeling Recommendations.docx image001.png
Importance:	High

Good afternoon Kathy,

With reference to **NDA 209299/Fostamatinib**, FDA's current edits/comments on the labeling (USPI, PPI and container labels) are attached.

Please review and provide revisions/comments to the attached FDA proposed labeling. Using the same draft, please provide your comments in the following manner:

- Where you agree with the labeling revisions, "accept" the tracked changes.
- Where you disagree with the labeling revisions, provide your comments, edits and proposed language (in tracked changes). If necessary, edit but do not "reject" the FDA-proposed changes.

In addition to content, we often make significant revisions to the format in our review of patient labeling. Therefore, it is important that you use the version of the patient labeling that we have attached to this email as the base document for making subsequent changes. Please accept all formatting changes. Using our attached document will ensure specifically that the formatting changes are preserved. Attempting to copy and paste formatting revisions into another document often results in loss of valuable formatting changes (including the font, bulleting, indentation, and line spacing).

Please update your labels and submit your revised labeling response to me via email by **COB, Wednesday, December 13, 2017** followed by an official submission of the label to the NDA file. The resubmitted labeling will be used for further labeling discussions.

Please *confirm* receipt of this email.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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

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/s/

RACHEL S MCMULLEN
12/04/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_ Clinical Information Request (Response DUE: December 5th)
Date:	Wednesday, November 29, 2017 4:32:05 PM
Attachments:	image001.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, please note the following information request from the team.

Clinical Information Request:

Provide the numbers of patients who developed hypertension and had undergone fostamatinib dose modification, interruption, discontinuation or other invervention (addition or increase dose of anti-hypertensive medication) in the ITP studies, the rheumatoid arthritis studies (including the ambulatory blood pressure study) and the healthy volunteer studies and provide cases that did not resolve after these interventions.

Please provide a response by noon on December 5, 2017, and also follow up with an official submission to your NDA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
11/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

INFORMATION REQUEST

Rigel Pharmaceuticals, Inc..
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd.
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 15, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, **no later than November 20, 2017**, in order to continue our evaluation of your NDA.

Drug Substance:

1. In Section 3.2.S.2.3, you provided the specifications for 'all other materials' used in the drug substance synthesis. It was noted that [redacted] (b) (4) is accepted based on vendor certificate of analysis. [redacted] (b) (4), provide information regarding how the identity of each batch is established upon receipt (e.g., visual examination of the containers, labels, recording of batch numbers, etc.) before the material is used in the manufacturing process.

2. In Section 3.2.S.4.1, your proposed limits for specified impurities [redacted] (b) (4) [redacted] are not qualified and should be reduced to the ICH Q3A qualification threshold. Reduce the limit for each of these impurities to ≤ [redacted] (b) (4)% each. In addition, your total impurity limit of ≤ [redacted] (b) (4)% is not justified and should be reduced to ≤ [redacted] (b) (4)%. Revise the drug substance specification accordingly.

3. In Section 3.2.S.4.5, you indicate that a residual solvent test will not be included in the drug substance specification. [redacted] (b) (4)

(b) (4). However, the residual solvent test, method, and acceptance criteria should be included in the drug substance regulatory specification table (b) (4). Revise the drug substance specification accordingly.

4. In Section 3.2.S.4.5, you stated that a test for metal impurities is not necessary in the drug substance specification. However, per ICH Q3D, the following elemental impurities should be assessed for oral drug products: (b) (4)). If the elemental impurity levels can be shown to be less than 30% of their permitted daily exposure (PDE) limits in 3 representative production-scale lots or 6 representative pilot-scale lots, additional controls would not be required. Provide the data to show that routine monitoring of elemental impurities is not necessary or include a test, method, and acceptance criteria for elemental impurities in your drug substance specification.

5. In Section 3.2.S.6, you provided the specification for the primary packaging material, (b) (4) However, your specification does not include an identification test. Provide the test, method, and acceptance criteria for (b) (4) identification, which should be utilized upon receipt of all incoming batches.

6. In Section 3.2.S.7.2, you indicated that the first 3 drug substance batches manufactured post-approval and every 3rd lot thereafter would be placed on stability. Because you have already placed 3 commercial-scale drug substance validation batches into stability studies, you do not need to place 3 additional commercial-scale drug substance batches into stability studies post-approval. One batch placed into stability studies each year (instead of every 3rd batch) would be sufficient for your annual stability studies. Revise your post-approval stability commitment accordingly.

If you have any questions, please contact me, at (240) 402-6153.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S

Digitally signed by Rabiya Haider -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Haider -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2017.11.06 13:50:35 -05'00'

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_Clinical Information Request (Response Due: 10 am on Monday, Oct. 30th)
Date:	Thursday, October 26, 2017 1:02:06 PM
Attachments:	image001.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Clinical Information Request:

-
"Patient (b) (6) randomized to the placebo arm in the 048 trial was classified as a responder. Please provide what "rescue medication" this patient received."

Please respond to me via email by **10 am on Monday, Oct. 30th** and also follow up with a formal submission to your NDA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
10/26/2017

M E M O R A N D U M

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

DATE: 10/24/2017

TO: Division of Hematology Products
Office of Hermatology and Oncology Products

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

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

RE: NDA 209299

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

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

SHILA S NKAH
10/24/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	NDA 209299_Clinical Information Request (Response Due: noon on Tuesday, October 24)
Date:	Thursday, October 19, 2017 4:24:18 PM
Attachments:	image001.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Clinical Information Request:

1. For your [redacted] (b) (4) in the proposed package insert, for each row please provide the number and a listing of patients who had a dose modification, interruption or discontinuation or other intervention (e.g., addition or increase dose of antihypertensive, addition of antidiarrheal) due to the listed reaction.

2. You included the following statement in section 5.2 of the label, "Transaminases recovered to baseline levels within 2 to [redacted] (b) (4) weeks of dose modification."
   Please provide the time of transaminases recovery to baseline for the 16 patients in the 047, 048 and 049 trials that ALT and/or AST increase >3 x ULN following dose modification to support the statement.

Please respond to me via email by noon on Tuesday, October 24th and also follow up with a formal submission to your NDA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
10/19/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; Dana Pizzuti; McMullen, Rachel
Subject:	RE: NDA 209299_ Information Request (Response DUE: September 28, 2017) - Clarification
Date:	Wednesday, September 27, 2017 2:59:07 PM
Attachments:	image001.png image031.png
Importance:	High

Good afternoon Kathy,

With reference to your query below, please note the following clarification for Item #3 from the team:

(3) Please submit a XPT file of correction factors (beta) of QTCI for each subject
XPT – SAS transport file (*.xpt)
QTCI – Individually corrected QT interval

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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From: Kathy Dumas [mailto:kdumas@rigel.com]
Sent: Wednesday, September 27, 2017 11:22 AM
To: McMullen, Rachel
Cc: Anne-Marie Duliege; Dana Pizzuti
Subject: RE: NDA 209299_ Information Request (Response DUE: September 28, 2017) - clarification
Importance: High

Rachel –
The team has asked for clarification of #3. We are not familiar with the abbreviation, and would

appreciate if you would provide more information on what exactly you would like to receive.

Kind Regards,

Kathy

Kathleen Dumas
Regulatory Affairs Consultant
Rigel Pharmaceuticals, Inc.
email: kdumas@rigel.com

From: McMullen, Rachel [mailto:Rachel.Mcmullen@fda.hhs.gov]
Sent: Tuesday, September 26, 2017 11:45 AM
To: Kathy Dumas <kdumas@rigel.com>
Cc: McMullen, Rachel <Rachel.Mcmullen@fda.hhs.gov>
Subject: NDA 209299_ Information Request (Response DUE: September 28, 2017)
Importance: High

Good afternoon Kathy,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Information Request:

With regards to Study C-935788-013:

(1) Please Upload the digital ECG waveforms with annotations to the ECG warehouse (www.ecgwarehouse.com).
(2) For EG.XPT dataset, please include EGTPT, EGTPTNUM to identify nominal ECG time points.
(3) Please submit a XPT file of correction factors (beta) of QTCI for each subject

Please submit a response via email to me by **noon on September 28, 2017** and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
10/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

MID-CYCLE COMMUNICATION

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.

We also refer to the teleconference between representatives of your firm and the FDA on September 28, 2017. 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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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: September 28, 2017; 1:00– 2:00 PM (ET)

Application Number: NDA 209299
Product Name: TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.
Indication: Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Applicant Name: Rigel Pharmaceuticals, Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Hyon Zu Lee, PharmD, Medical Officer
Qin Ryan, MD, PhD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager
Diane Leaman, BS, Safety Project Manager

OHOP/Division of Hematology Oncology Toxicology
Chris Sheth, PhD, Pharmacology/Toxicology Team Leader
Brian Cholewa, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Qi Liu, PhD, Clinical Pharmacology Team Leader
Runyan Jin, PhD, Clinical Pharmacology Reviewer
Jee Eun Lee, PhD, Pharmacometrics Reviewer
Jiang Liu, PhD, Pharmacometrics Team Leader

Office of Product Quality
Sherita McLamore-Hines, PhD, Team Leader
William Adams, PhD, Product Quality Reviewer
Kaushal Dave, PhD, Biopharmaceutics Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Statistical Team Leader

Office of Surveillance and Epidemiology
Carolyn McCloskey, MD, MPH, Medical Officer Epidemiologist
Mei-Yean Chen, PhD, Safety Reviewer

APPLICANT ATTENDEES
Rigel Pharmaceuticals Inc.
Anne-Marie Duliege, MD, Executive VP and Chief Medical Officer
Sandra Tong, MD,VP, Clinical Sciences and Drug Safety
Scott Henley, VP, Clinical Operations
Dana Pizzuti, MD, Senior VP, Regulatory Affairs and Clinical Compliance
John Aitken, Executive Director, Regulatory Operations
Kathleen Dumas, Regulatory Affairs Consultant
(b) (4), Regulatory Affairs Consultant
Hany Zayed, PhD, Executive Director, Data Science
Dan Shui, Director, Statistical Programming
(b) (4), Acting VP, Technical Operations (Consultant)
Matt Duan, Senior Director, Pharmaceutics & Manufacturing
Michael Roth, Senior Director, Quality Assurance
Raul Rodriguez, President and Chief Executive Officer

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:

- We have some concerns regarding the lack of robustness of the efficacy analysis findings for the studies. See statistical comments listed below.

Statistics:

- Due to the high dropout rate due to lack of response in Study 047, we have concerns about the interpretability of the results from the primary efficacy analysis.
- We have concerns about the appropriateness of the multiple imputation technique used to handle missing platelet counts in Study 048.
- We have concerns about the confidence intervals for the difference in response based on Normal approximation for the primary efficacy analysis, which are reported in the CSR.

Reference ID: 4162747

The Normality assumption is invalid due to the low response and small sample size in the control arm in both studies.

Clinical Pharmacology:

- (b) (4)

3.0 INFORMATION REQUESTS

We have the following information requests:

Clinical:

Please provide the following:

1. Case report forms for all responders in Study 047 and Study 048.
2. A graph displaying platelet count at time of withdrawal versus time of withdrawal for patients who discontinued study due to lack of response for each treatment arm in Study 047 and Study 048.

Please provide a response by October 16, 2017.

Chemistry, Manufacturing and Controls (CMC):

A separate communication will be sent requesting a teleconference to discuss outstanding CMC deficiencies.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time and there is currently no need for a REMS.

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 Late-Cycle Meeting between you and the review team is currently scheduled for January 11, 2018. We intend to send the briefing package to you approximately 12 days in advance of the

Reference ID: 4162747

meeting. If these timelines change, we will communicate updates to you during the course of review.

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 requirement/commitment requests by November 15, 2017.

Reference ID: 4162747

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/s/

KATHY M ROBIE SUH
10/04/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	McMullen, Rachel
Subject:	NDA 209299_ Information Request (Response DUE: September 28, 2017)
Date:	Tuesday, September 26, 2017 2:45:22 PM
Attachments:	image001.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Information Request:

With regards to Study C-935788-013:

(1) Please Upload the digital ECG waveforms with annotations to the ECG warehouse (www.ecgwarehouse.com).
(2) For EG.XPT dataset, please include EGTPT, EGTPTNUM to identify nominal ECG time points.
(3) Please submit a XPT file of correction factors (beta) of QTCI for each subject

Please submit a response via email to me by **noon on September 28, 2017** and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
09/26/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Dana Pizzuti; Anne-Marie Duliege; McMullen, Rachel
Subject:	NDA 209299_ Response to Information Request (DUE: 9/26/17)
Date:	Saturday, September 16, 2017 4:08:32 PM
Attachments:	image002.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Clinical Information Request:

"Provide the rationale why the dose of fostamatimib was increased to 150 mg BID **starting at Week 4** versus at other time point during the studies (047, 048 and 049)."

Please submit a response via email to me by noon on Tuesday, September 26th and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
09/16/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

INFORMATION REQUEST

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd.
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 15, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, **no later than September 14, 2017**, in order to continue our evaluation of your NDA.

Biopharmaceutics:

1. Please provide individual vessel dissolution profile data (individual, mean, SD) for the pivotal clinical and exhibit batches. If you have already submitted these data, please provide information about the data file location within the CTD.

If you have any questions, please contact me, at (240) 402-6153.

Sincerely,

Rabiya Haider, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Haider -S

Digitally signed by Rabiya Haider -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Haider -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2017.09.07 10:28:41 -04'00'

M E M O R A N D U M

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

DATE: 8/16/2017

TO: Division of Hematology Products
Office of Hermatology and Oncology Products

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

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

RE: NDA 209299

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

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

ANGEL S JOHNSON
08/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Rigel Pharmaceuticals, Inc.
1180 Veterans Blvd
South San Francisco, CA 94080

ATTENTION: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Disodium Tablets, 100 mg and 150 mg.

We also refer to your correspondence, dated and received May 22, 2017, requesting review of your proposed proprietary name, Tavalisse.

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

If any of the proposed product characteristics as stated in your May 22, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Wana Manitpisitkul, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4156. For any other information regarding this application, contact Rachel McMullen, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

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

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
08/02/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	McMullen, Rachel
Subject:	NDA 209299_ Information Request (Response DUE: August 3, 2017)
Date:	Monday, July 17, 2017 3:56:24 PM
Attachments:	image001.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299, the FDA team is requesting a prompt response to the following:

Clinical Information Request:

Provide two figures of platelet count changes over time for all responders in the fostamatinib arm for the phase 3 trials (i.e., one figure for study 047 with plots of of platelet count changes on y axis and dates of platelet count on the x axis in different colors for the 9 responders; and another figure for study 048 with the same).

Please submit a response via email to me by **noon on August 3rd** and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
07/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

INFORMATION REQUEST

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd.
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 15, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, **no later than August 9, 2017**, in order to continue our evaluation of your NDA.

1. Regarding the proposed labels and labeling, neither the proposed stability protocols nor the submitted stability studies are adequate to support approval of this application with the proposed storage and handling statement, "[redacted] (b) (4)". We recommend that you revise this statement to use the USP definition for controlled room temperature and provide additional stability data to support the temperature range in this statement.

2. Regarding the information in module 3.2.P.2:
   a) Provide data to establish [redacted] (b) (4) in the proposed tablets. The product development studies indicate [redacted] (b) (4) (b) (4)
   b) Provide the forced degradation study referenced in module 3.2.S.3.2 and 3.2.P.2.2, and update the method descriptions or validation studies to incorporate this information.

3. Please specify whether [redacted] (b) (4) will be held for up to [redacted] (b) (4) months [redacted] (b) (4) [redacted] (b) (4) packaging system described in the application before primary packaging.

If yes, this would mean that the manufacturing process [redacted] (b) (4) which necessitates that the following revisions be made to the NDA:

a) Establish a control strategy which addresses the maximum hold time, storage conditions, packaging system and the specifications for the acceptance and release [redacted] (b) (4)
b) Specify whether batches may be combined for primary packaging and how this is addressed in the batch numbering system.
c) Revise the stability protocol to define time zero for the finished product shelf life as [redacted] (b) (4) and revise the post approval stability protocol to address the hold time for [redacted] (b) (4)

4. Regarding the excipient information in module 3.2.P.4:
   a) Provide a copy of the supplier certificate of analysis (CoA) for each lot of each excipient used in the NDA exhibit batches of tablets. Each CoA should indicate the trade name and material grade.
   b) Provide acceptance specifications for each excipient [redacted] (b) (4). The excipient specifications should include identity, key physicochemical, residual moisture and residual solvents.
   c) Identify the tests performed on each lot of each excipient by Patheon for acceptance, and specify which test values are accepted from the supplier CoA.

5. Regarding the specifications in module 3.2.P.5.1:
   a) For the specification for [redacted] (b) (4):
      i. Revise the specification to include a test, method and criterion for [redacted] (b) (4) This parameter has been shown to correlate to product stability.
      ii. Revise the limits for degradation products to correlate to product quality based on test results observed in the submitted stability studies. The proposed limits are based [redacted] (b) (4) and would allow for the acceptance of batches that have failed on stability.
      iii. Describe the sampling scheme for the test for unit dose uniformity.
   b) For the specification for packaged tablets:
      i. Revise the appearance test to include any printing on the desiccant canister.
      ii. Establish a release specification for the proposed 30-count and 60-count physician sample products.

6. Regarding the information in module 3.2.P.5.2:
   a. For method CTMLP-3536.01 ([redacted] (b) (4) by HPLC):
      i. For the proposed alternate [redacted] (b) (4), specify when it will be used and how this will be indicated on the release CoA; and provide system suitability criteria for the use of this [redacted] (b) (4)
      ii. Revise the [redacted] (b) (4) test sample to obtain the same drug substance concentration as in the reference standard.

iii. Revise the method to report mean and range.
iv. Provide an example chromatogram for placebo and the 150 mg test sample.

b. For method CTMLP-3584.01 (dissolution [redacted] (b) (4)):
   i. Provide example [redacted] (b) (4) placebo, and 150 mg test sample.
   ii. Revise the method to report the profile of results for stability samples.

c. For method: CTMLP-3585.02 (identification, assay and degradation products by HPLC):
   i. For the proposed [redacted] (b) (4), specify when it will be used and how this will be indicated on the CoA; and provide system suitability criteria for the use of this [redacted] (b) (4)
   ii. For the proposed system suitability criteria, justify the need for the proposed wide ranges for drug substance retention time ([redacted] (b) (4) [redacted] (b) (4) and tailing factor ([redacted] (b) (4)); and establish an acceptable range for theoretical places.
   iii. Add a system suitability criterion for target relative retention time of specified impurities [redacted] (b) (4) The values vary significantly in the example HPLCs.
   iv. For the calculations, either delete the statement "may be calculated" regarding assay and degradation products or provide a detailed description of the alternate calculation; and provide the calculation for Total Degradation Products.
   v. Provide an example chromatogram for placebo.
   vi. Specify whether the example HPLCs in figures 14 and 20 were obtained using the same test samples solution.
   vii. Provide the system suitability test results for the resolution solution chromatogram and explain how the peak at [redacted] (b) (4) minutes meets the criteria.

7. Regarding the studies in module 3.2.P.5.3:
   a) Provide the batch analysis test results for OFC-I tablet batches 3096, 91307J11, 20217J12 and 10220E12.
   b) Identify the tablet batch used in report RITA.00-458-791.2.0.
   c) Provide the results of an acceptable validation study for ruggedness in method CTMLP-3585.02. Report RITA.000-461.588.2.0 addresses a different analytical method and does not use tablets. Reports RIG-AR-141-0815-R0 and RITA.000-4113.324.5.0 do not include validation for method ruggedness.

8. Regarding the bulk and primary packaging information in module 3.2.P.7:
   a) For each component, provide the acceptance specification used by Patheon, and a copy of a CoA from the proposed component supplier.
   b) For each lot of each component, specify which test values will be taken from the supplier CoA for acceptance.
   c) Specify the minimum wall thickness for the [redacted] (b) (4) and provide information establishing its [redacted] (b) (4) capability.

d) Provide an engineering drawing for the proposed [redacted] (b) (4). This should include the [redacted] (b) (4)
e) For the proposed desiccant canister, provide the following:
   1. a copy an engineering drawing with dimensions and indicating any printing on the canister;
   2. the composition of the desiccant and the amount per canister; and
   3. describe the rate of moisture absorption and the maximum amount of moisture that each canister will absorb.
f) For the bulk tablet packaging system, provide the following:
   i. [redacted] (b) (4)
   ii.
   iii.

9. Regarding the stability information in module 3.2.P.8.1:
   a) Provide long term stability data for tablets stored in bottles at temperature [redacted] (b) (4) [redacted] (b) (4)°C. Indicate the conditions of storage (temperature and humidity) in those studies.
   b) Provide test data that establishes that the levels of [redacted] (b) (4) [redacted] content do not change over time and the range of the label storage conditions for tablets stored in the [redacted] (b) (4) primary packaging systems.

10. Regarding the post approval protocols in module 3.2.P.8.2:
   a) Revise the protocol to include physician samples in the 45cc HDPE bottle, and the contiguous storage of tablets in the [redacted] (b) (4) primary container closure systems.
   b) Revise the proposed storage conditions to include the ICH long term (25°C, 65%RH) conditions.
   c) Revise the specification to include testing for [redacted] (b) (4). Both of these parameters are measures of product stability.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 7/12/2017 01:20:13PM
GUID: 508da7230002a24fd4abdd8018af2a08

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

INFORMATION REQUEST

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd.
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 15, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response, **no later than August 3, 2017**, in order to continue our evaluation of your NDA.

1. We have noted several discrepancies between the process parameters and controls described in the drug product manufacturing flow diagram (3.2.P.3.3), the defined control strategies (3.2.P.2), and the representative master batch record (3.2.R.1.P). Update 3.2.P.3.4 with the intended parameters and controls to be used at commercial scale and provide supporting justification. For example:

   A.

   B.

   C.

(b) (4)

D. (b) (4)

2. (b) (4)

3.

4.

5.

If you have any questions, please contact me, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Teshara G. Bouie, MSA, RAC, OTR/L
CDR, USPHS, Quality Assessment Lead (Acting)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Teshara Bouie

Digitally signed by Teshara Bouie
Date: 7/03/2017 01:25:24PM
GUID: 508da7230002a24fd4abdd8018af2a08

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 17, 2017 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.

We also refer to your amendment(s) dated May 22 and 24, 2017.

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**. Therefore, the user fee goal date is April 17, 2018. 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.

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 requirement/commitment requests by November 15, 2017. In addition, the planned date for our internal mid-cycle review meeting is September 15, 2017. 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:

1. It appears that the result of one of the registrational trials was not statistically significant. This will be a review issue.

2. The safety database of fostamatinib in ITP is a total of 164 patients. The adequacy of the safety database will be a review issue in the proposed indication.

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.

Information Requests:

We request that you submit the following information by July 15, 2017:

1. Update datasets in EX and PC domains for all studies including c406-001, c788-001, c788-003, c788-004, c788-014, c788-018, d4300-007, d4300-009, d4300-010, c4300-011, c4300-012, c4300-013, c4300-014, c4300-015, c4300-026, d4300-032, c4300-039 with following required, expected and permissible variables based on CDISC recommendations:
    - PC domain: PCDTC, VISITNUM, PCTPTNUM, PCSPEC, PCLLOQ, PCSTRESN,
    - EX domain: EXSTDTC, EXENDTC, EXTPTNUM, EXDOSE, EXDOSU, EXROUTE

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of

important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. The length of Highlights (HL) must be one-half page or less. Currently, the length of HL exceeds one-half page. Update the HL or submit a waiver request.
2. There should be ½ inch margins on all sides and between columns.
3. Date and page numbers are provided in the footer section on each page. Remove the date included in the footer section.
4. Remove space between the HL heading and the HL limitation statement.
5. Remove space between product title and initial U.S. Approval.
6. The numerical identifiers in parenthesis should not be bolded.
7. With reference to the Patient Counseling information statement at the end of HL: the words "PATIENT COUNSELING INFORMATION" must be in upper case letters.
8. Update the heading at the beginning of the TOC to read: "FULL PRESCRIBING INFORMATION: CONTENTS*."

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 19, 2017. 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. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

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 only to the above requests for information by July 15, 2017. 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 Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, 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.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
06/29/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	McMullen, Rachel
Subject:	NDA 209299_ Information Request (Response DUE: June 30, 2017)
Date:	Wednesday, June 21, 2017 10:22:20 AM
Attachments:	image013.png
Importance:	High

Good morning Kathy,

With reference to NDA 209299, please note the following information request from the FDA team:

Clinical Information Request:

1. Provide the number of investigators in the ITP trials (C788-047, C788-048, C788-049 and D4300C00022) who are sponsor employees (including both full-time and part-time employees).

2. Provide the reasons/patient narratives for TPO receptor agonist discontinuation for patients that had previously received a TPO receptor agonist medication and achieved a stable platelet response in the fostamatinib arm in both phase 3 trials (C788-047: 4 patients, C788-048: 3 patients).

3. Provide the patient profiles (plots of platelet count on y axis and dates of platelet count on the x axis) for all responding patients in both phase 3 trials.

4. The eligibility criteria of C788-047 and C788-048 trials required an average platelet count < 30,000/µL (and none > 35,000 unless as a result of rescue therapy) from at least 3 qualifying counts within the preceding 3 months (with at least 2 of the qualifying counts taken during the screening period). However, the first qualifying platelet counts (other than the ones taken on Screening A and B visits) were not included in the datasets. Provide the datasets that include all 3 qualifying counts within the preceding 3 months for all patients enrolled in both trials.

Please submit a response via email to me by **COB on Friday, June 30th** and following that also submit the response officially to your NDA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
06/21/2017

From:	McMullen, Rachel
To:	Anne-Marie Duliege; "Kathy Dumas"
Cc:	McMullen, Rachel
Subject:	NDA 209299_ Clin Pharm INFORMATION REQUEST (Response DUE: Monday, May 30th)
Date:	Friday, May 26, 2017 11:20:34 AM
Attachments:	image001.png
Importance:	High

Good morning Anne Marie and Kathy,
With reference to NDA 209299 for fostamatinib, the team is requesting a prompt response to the following information request.

Clinical Pharmacology Information Request

Due Date: May 30, 2017

Reference is made to your response to FDA information request in NDA 209299 submitted on May 24, 2017 with regard to the quality control of bioanalytical data and corresponding PK data and CSRs. We acknowledged the errors you identified and summarized in the report. However, our analyses cannot reproduce the same PK parameters as yours in 4 subjects as shown in the table below. Please verify PK parameters for these 4 subjects. In addition, please specify what algorithm method you used in the calculation of AUCs. Please provide your response by COB May 30, 2017.

Study	Subject ID
C406-001	(b) (6)
C788-008	
C788-013	
C788-016	

Please submit a response to me promptly via email by **COB on Monday, May 30, 2017** and also follow up with an official submission to the BLA file within 1 week.
Please confirm receipt.
Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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/s/

RACHEL S MCMULLEN
05/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

PROPRIETARY NAME ACKNOWLEDGEMENT

Rigel Pharmaceuticals, Inc.
1180 Veterans Blvd
South San Francisco, CA 94080

ATTENTION: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Disodium Tablets, 100 mg and 150 mg.

We acknowledge receipt of your correspondence, dated and received May 22, 2017, requesting a review of your proposed proprietary name, Tavalisse.

If the application is filed, the user fee goal date to review your proprietary name request will be August 20, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (240) 402-4156. For any other information regarding this application, contact Rachel Mcmullen, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Wana Manitpisitkul, PharmD, BCPS
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

WANA MANITPISITKUL
05/25/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; McMullen, Rachel
Subject:	NDA 209299 _ Information Request (DUE: Friday, May 19, 2017)
Date:	Tuesday, May 16, 2017 7:33:54 PM
Attachments:	image001.png
Importance:	High

Good evening Kathy,

With reference to NDA 209299 for fostamatinib, please note the following information request from the FDA review team:

Information Request:

1. ***Submit the following study subject data listing information grouped as pdf files, for James Bussel, M.D. (Site 063 NYC under Study Protocol C788-047):***
   - ***a) Subject discontinuations (If applicable, per treatment group: site, subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).***
   - ***b) Subject assignment per treatment arm (if applicable).***
   - ***c) Primary and other relevant study efficacy endpoint (if applicable, e.g., platelet counts per visit, palpable liver or spleen lesions, bone marrow biopsy results, cytogenetics, date of entry, date of death, prior treatment dates, survival calendar time points).***
   - ***d) Concomitant medication list (non-study medications).***
   - ***e) All adverse events (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no]).***
   - ***f) Laboratory relevant assessments to support the efficacy endpoint responses, other the items specified in item c) above.***
   - ***g) Any protocol deviations or violations.***

2. ***Submit the above requested information for Jiri Mayer, M.D. (Site 428: Brno, Czech, also under Study Protocol C788-048). The grouped pdf files for Dr. Mayer should be separate from the pdf file for Dr. Bussel.***

3. ***Confirm that your clinical trial data files are located at your headquarters in Rigel Pharmaceuticals, Inc., South San Francisco, CA 94080, should the Agency determine the necessity of a sponsor site audit. If not, provide a contact address and number where the CRO is located.***

Please respond to me via email by COB on Friday, May 19, 2017, and also follow up with an official submission of the response to your NDA file.

Please *confirm* receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

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RACHEL S MCMULLEN
05/23/2017

From:	McMullen, Rachel
To:	Kathy Dumas
Cc:	Anne-Marie Duliege; McMullen, Rachel
Subject:	NDA 209299_ Clin Pharm INFORMATION REQUEST (Due: May 23, 2017)
Date:	Thursday, May 11, 2017 1:16:44 PM
Attachments:	image002.png
Importance:	High

Good afternoon Kathy,

With reference to NDA 209299 for fostamatinib, please note the following information request from the team.

Clinical Pharmacology Information Request
Due Date: May 23, 2017

We have identified inconsistency between the concentration data reported in the bioanalytical reports and the corresponding PK concentration datasets as well as errors in the calculated PK parameters in multiple studies. You need to conduct a quality control check for the concentration data reported in the bioanalytical reports and the corresponding PK concentration datasets (pc.xpt) and the subsequently calculated PK parameter datasets (pp.xpt) , as well as the corresponding CSRs for all your biopharmaceutical and clinical pharmacology studies. Please submit all the new datasets in STDM and CSRs by May 23, 2017. In addition, please provide a listing of the corrected data, by study, and the reason for the inconsistency.

Please submit a response to me promptly via email by **4pm ET on May 23, 2017** and also follow up with an official submission to the BLA file.

Please confirm receipt.

Kind regards,

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Avenue |Silver Spring, MD 20993

Rachel.McMullen@fda.hhs.gov | 240-402-4574

U.S. FOOD & DRUG ADMINISTRATION

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RACHEL S MCMULLEN
05/11/2017

From: Manitpisitkul, Wana
To: "kdumas@rigel.com"
Cc: Kang_Sue
Subject: Submission of a Proposed Proprietary Name Request - NDA 209299/Fostamatinib Disodium
Date: Friday, May 05, 2017 3:02:00 PM

Dear Ms. Dumas,

Please refer to your New Drug Application (NDA) dated April 15, 2017, received April 17, 2017, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fostamatinib Disodium Tablets, 100 mg and 150 mg.

We understand the proposed proprietary name "Tavalisse" was found conditionally acceptable under IND 74939, however, the Guidance for the Contents of a Complete Submission for the Evaluation of Proprietary Names (link below) states that a complete name request must be submitted for review when the NDA/BLA is filed.

Please submit your proposed proprietary name request to the application following the procedure below to ensure that the document room codes for "Proprietary Name/Request for Review" accurately and opens an OSE PDUFA clock for the name review.

When submitting a proprietary name request for review to the Agency, it is crucial to:

- Check "Other" in Box 21 of the 356h form and write in "Proprietary Name/Request for Review"

- Additionally, include the statement **"REQUEST FOR PROPRIETARY NAME REVIEW"** in bold capital letters, at the **top** of your cover letter **and** on the **top** of the first page of the main submission document (refer to the complete submission guidance link below).

- Please clearly state in the cover letter and supporting documentation the exact name(s) you are requesting 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

Wana Manitpisitkul
Safety Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration
Tel: (240) 402-4156
Wana.Manitpisitkul@fda.hhs.gov

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/s/

WANA MANITPISITKUL
05/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

NDA ACKNOWLEDGMENT

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd
South San Francisco, CA 94080

Dear Dr. Duliege:

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: TAVALISSE™ (fostamatinib); tablet; 100 mg, 150 mg

Date of Application: April 15, 2017

Date of Receipt: April 17, 2017

Our Reference Number: NDA 209299

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 June 16, 2017, 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 Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, call me at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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RACHEL S MCMULLEN
04/26/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074939

MEETING MINUTES

Rigel Pharmaceuticals, Inc.
Attention: Kathleen Dumas
Acting Head of Regulatory Affairs
1180 Veterans Blvd.
South San Francisco, CA 94080

Dear Ms. Dumas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for R935788 (fostamatinib disodium).

We also refer to the meeting between representatives of your firm and the FDA on April 5, 2016. The purpose of the meeting was to discuss the content and format of the planned NDA for fostamatinib.

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 Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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: Pre-NDA

Meeting Date and Time: April 5, 2016; 2:00PM-3:00PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 074939
Product Name: R935788 (fostamatinib disodium)
Indication: Treatment of adult chronic/persistent immune thrombocytopenia
Sponsor/Applicant Name: Rigel Pharmaceuticals, Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD; Clinical Team Leader
Meeting Recorder: Rachel McMullen, MPH, MHA; Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Edvardas Kaminskas, MD, Deputy Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Andrew Dmytrijuk, MD, Medical Officer
Lori Ehrlich, MD, Medical Officer
Rachel McMullen, MPH, MHA, Regulatory Project Manager

Office of Hematology and Oncology Products (OHOP)
Tamy Kim, PharmD, Associate Director of Regulatory Affairs

Division of Hematology Oncology Toxicology Staff
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Natalie Simpson, PhD, Pharmacologist/Toxicologist

Office of Clinical Pharmacology
Gene Williams, PhD, Clinical Pharmacology Team Leader
Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacologist

Office of Biostatistics
Yuan Li Shen, PhD, Lead Statistician
Che Smith, PhD, Statistical Reviewer

SPONSOR ATTENDEES
Rigel Pharmaceuticals, Inc.
Elliott Grossbard, MD, Executive Vice President, Development and Chief Medical Officer
Anne-Marie Duliege, MD, Chief Medical Officer Designate
David Lau, PhD, Vice President, Drug Metabolism and Pharmacokinetics
Kathleen Dumas, Acting Head of Regulatory Affairs (Consultant)
Jonathan Gaynor, Senior Manager, Regulatory Operations
(b) (4) PhD, Statistical Consultant
(b) (4) MPH, Statistical Consultant

1.0 BACKGROUND

Fostamatinib is an orally administered spleen tyrosine kinase (SYK) inhibitor, that functions as a pro-drug, which produces systemic exposure to the active drug R940406 (R406). Under this IND fostamatinib is being developed for the treatment of thrombocytopenia in adult patients (18 years and older) with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. The product was granted orphan-drug designation on August 25, 2015.

Rigel conducted Phase 2a/2b clinical studies in patients with rheumatoid arthritis (RA), in parallel with exploratory Phase 2a studies in patients with B-cell and T-cell lymphomas and with ITP. Following a global license agreement in February 2010 with Rigel to develop and commercialize Fostamatinib, AstraZeneca conducted a comprehensive program for the treatment of RA (through Phase 3). Since fostamatinib did not affect bone erosion and joint destruction in 2 of the studies, AstraZeneca returned development rights to Rigel, despite significant consistent favorable effect with regard to RA signs, symptoms, and functional improvement (primary endpoint in all three Phase 3 studies). Thereafter, Rigel initiated Phase 3 studies in ITP, as well as Phase 2 studies in immunoglobulin A nephropathy (IgAN) and autoimmune hemolytic anemia (AIHA) populations.

ITP Development To Date
Whereas the mechanism of action for the two commercially approved products (eltrombopag and romiplostim) is to increase platelet production through binding and activation of the TPO receptor, fostamatinib appears to ameliorate platelet destruction by interrupting Fc receptor signaling via Syk inhibition. The sponsor states fostamatinib is a potent and selective inhibitor of Syk kinase. In a murine model of ITP, fostamatinib showed a significant effect on mitigation of antibody-induced thrombocytopenia that was dose-and schedule-dependent.

The sponsor reports a Phase 2 study in adults with refractory ITP (defined as platelet count < 30,000/mL for≥ 3 months), initiated under this ITP IND and now ongoing as an investigator sponsored study, has 2 patients remaining on study. All patients had failed at least 2 standard therapeutic regimens. Patients were treated with escalating doses of fostamatinib in cohorts of 3. After a cohort completed 4 weeks, a subsequent cohort could be initiated. Patients were required to complete 2 weeks at a given dose before the dose could be increased (by 25 mg twice daily). Dosing was initiated at 75 mg *bid* to 150 mg *bid*. Certain patients, who responded and then had their platelet counts decline, could have their dose further increased to a maximum of 175 mg bid. Eighteen patients entered the study. A patient was considered to have had a response if the

baseline platelet count increased by at least 20,000/µL to a total count of 30,000/µL or more while being treated with fostamatinib, and the patient had not received a dose of IVIg, or other concomitant therapy known to increase platelet counts, within 2 weeks of the increase in platelet count. The responder rate for the primary analysis was greater than 40% at all but 7 of the 35 time points evaluated, however this response rate was based on the number of patients in the study at that time.

At the end-of-Phase 2 meeting on 8 October 2013, the sponsor indicated that the majority of the safety data will be provided from clinical studies conducted for an earlier indication (over4000 patients with rheumatoid arthritis), for which an NDA has not been submitted. Efficacy and safety in ITP will be from one Phase 2 study and three ongoing Phase 3 international studies (two identical double-blind studies and one open-label extension study) in a total of 150 patients with ITP (with more than 100 patients exposed to fostamatinib). The Phase 3 protocol designs are based on the studies conducted for eltrombopag and romiplostim.

Additionally, in follow-up to the EOP2 meeting, Rigel submitted the Phase 3 protocols for review and comment. FDA provided comments/advice on the Statistics and the Clinical Pharmacology. Rigel did not submit the full Phase 3 double-blind protocol for Special Protocol Assessment.

2. DISCUSSION

FDA Preamble:

Based on the Background Package you have submitted for this meeting, we are concerned that your drug development program for fostamatinib in ITP is not sufficiently advanced to support consideration of an NDA submission at this time. To date it appears that for ITP you have completed only your Phase 2 study D4300-022 in which 18 adult patients with refractory ITP were enrolled. Your supportive information for the proposed indication comes primarily from drug development in disease settings other than ITP, i.e., in chemotherapy induced thrombocytopenia and rheumatoid arthritis. This data package is not sufficient to support filing of an NDA for the ITP indication. We urge you to complete your phase 3 studies(C-935788-047 and C-935788-048) in order to enhance the fostamatinib safety and efficacy database for the proposed indication. The results of these controlled, randomized trials may qualify fostamatinib for a regular approval.

DISCUSSION:

The Sponsor clarified that the NDA will contain the two Phase 3 trials. The enrollment is complete for those trials with the last patient visit scheduled for near the end of summer 2016. FDA acknowledges the clarification.

SPONSOR QUESTIONS AND FDA RESPONSES:

CLINICAL PHARMACOLOGY QUESTION

Question 1:
In follow-up to the Agency's Clinical Pharmacology comments/recommendations, does the Agency agree that the planned population PK/PD/Safety analyses will be sufficient to support the use of these doses in the target population?

Agency Response:
Your plan appears acceptable. However, you stated that you have two previously described population PK (PPK) models. One PPK model using data from Studies C-935788-006, C-935788-010, C-935788-011 and C-935788-013 sand the other PPK model using data from Studies D4300C00007, D4300C00012, D4300C00018, D4300C00033, D4300C00001, D4300C00002, and D4300C00003. It is not clear which PPK model you intend to use to describe the data from the ITP population and the rationale for our choice. You should also provide a rationale for not combining the data used in the two models.

Please refer to the following guidelines regarding general expectations of submitting pharmacometric data and models:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

DISCUSSION: The Agency clarified that the expectation is for all data to be included in the population PK analysis. The Sponsor will need to adequately justify the exclusion of any datasets.

CLINICAL/STATISTICAL QUESTIONS

Question 2:
The proposed NDA safety database will include data from all ITP studies, as well as all completed studies for other indications. Does the Agency have any comments?

Agency Response:

The proposed safety database appears to be acceptable in terms of numbers of patients exposed. However, there is little information for the ITP population. Note particularly that you have not yet completed studies to demonstrate efficacy of fostamatinib in ITP.

DISCUSSION: See discussion under Preamble.

Question 3:
Since the majority of the safety data will be from RA patients, Rigel proposes to include a separate Integrated Summary of Safety (ISS) for data from RA patients, in addition to an ISS for data from ITP patients (to be provided in NDA Module 5). Safety data from completed studies of other indications will not be included in an ISS but will be summarized within the CTD Summary of Clinical Safety in NDA Module 2, and included in the overall assessment of the safety of fostamatinib. Does the Agency agree with this approach?

Agency Response:

No. The ISS should contain an integrated summary of all safety data pertaining to fostamatinib.

DISCUSSION: The Sponsor described their proposed presentation of the safety database (see Table and Figure D in attached Sponsor response document). FDA stated that the proposal appears reasonable. FDA emphasized that the safety database will need to adequately reflect the population to be labeled including dose information and duration of exposure.

Question 4:
Rigel (or AZ) has completed 44 clinical studies using fostamatinib or R406, to date, with more than half from Phase 1 studies. Rigel is proposing that not all studies need to have datasets provided. Does the Agency agree with this proposed plan?

Agency Response:

No. You should submit the data from all the Phase 1 clinical studies.

DISCUSSION: **There was no discussion.**

Question 5:
Many of the clinical studies are older, and conducted by various sponsors/CROs; as a result, dataset consistency is not possible. For instance, among the 13 RA studies that will be included in the ISS-RA, only 4 studies have both SDTM and ADAM datasets, while the others only have SDTM and analysis datasets in legacy format available. Does the Agency agree it is acceptable to submit the datasets in its legacy format?

Agency Response:

Legacy data is acceptable. However, in order to keep traceability, the legacy CRF data, aCRF and define.pdf need to be submitted too if analysis datasets were derived from legacy data. Therefore, both SDTM folder and legacy folder should be included.

The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the submission.

Please submit all programs involving data analysis and the creation of derived datasets.

Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will appear in the label.

DISCUSSION: The Agency clarified that the program involving data analysis and the creation of derived datasets is only for the Phase 3 ITP studies.

Question 6:
Given the timing of when studies were conducted, different coding dictionaries were used to date for the various clinical studies. Rigel plans to up-version the codes for all adverse events (AEs)

and serious adverse events (SAEs) to the current MedDRA version 18.1. Does the Agency agree with proposed versioning strategy for the safety data to be included in the ISSs?

Agency Response:
We recommend that ISS MedDRA be same as the pivotal studies.

DISCUSSION: There was no discussion.

Question 7:
As part of reviewing the reports/supportive information for studies conducted by AstraZeneca (and provided to Rigel upon return of the program), Rigel has noted potential issues or inconsistencies within reports/data that will be included in the NDA (eg, unsigned nonclinical reports, or inconsistency between body of report and listings/data). Does the Agency agree with Rigel's proposed plan for dealing with these items?

Agency Response:

Your proposal is reasonable; however the acceptability of data will be a review issue. In cases where there are inconsistencies in any given report or in the clinical or nonclinical databases, describe the issue and its potential impact on study integrity or interpretability.

DISCUSSION: There was no discussion.

SAFETY QUESTION

Question 8:
Does the Agency agree with the proposed format for presenting the adverse event data in the package insert (eg, data from ITP studies versus data from the other indications)?

Agency Response:

You should consider the Guidance for Industry: Adverse Reactions Section of Labeling of Human Prescription Drug and Biological Products – Content and Format document. See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf.

Please also see the preamble. The data and wording to be included in the product label will be a review issue.

DISCUSSION: The Agency cannot say more at this time because this is a review issue.

REGULATORY/PROCESS QUESTIONS

Question 9:
Although the Phase 2 and 3 RA studies conducted by AstraZeneca would typically meet the definition of a covered study for purposes of financial disclosure, since the information from these studies was collected in regards to AstraZeneca as sponsor, these studies will not be considered as part of the certification/disclosure statements provided in the NDA by Rigel. Rigel

will only address studies in which they were they sponsor of the study. Does the Agency agree with this approach?

Agency Response:

No. Under 21 CFR part 54, you are required to submit financial information for covered studies upon marketing application submission. If AstraZeneca was the sponsor for the Phase 2 and 3 RA studies, you should contact AstraZeneca to obtain the financial disclosure information for submission with your marketing application. If you are unable to obtain financial disclosure information from AstraZeneca for the covered studies, then you should make reasonable efforts to contact the clinical investigators to obtain this information. Ultimately, if you are unable to obtain financial disclosure information for covered studies, you will need to certify that you acted with due diligence to try to obtain this information. Refer to the *Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators document* for additional information:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

DISCUSSION: **The Agency clarified that studies which may have been terminated early, would still be considered covered studies, and, as such, financial disclosure information would be required. The Agency recommended the sponsor to provide as complete information as possible. The Sponsor asked who should sign the certification and the Agency clarified that the Applicant is responsible for signing the financial disclosure certification.**

Question 10:
Does the Agency have any additional advice or guidance with regard to this planned NDA?

Agency Response:

Please see Preamble.

DISCUSSION: The sponsor sought clarification of some of the information conveyed in Section 3.0 of the Preliminary Meeting Comments. The Agency clarified as follows:

- **The Agency clarified that pivotal studies for the NDA are the ITP studies.**
- **The Agency indicated that the Sponsor is not required to submit a REMS with the initial NDA. The need for risk management activities will be a subject of discussion with the Sponsor as the review of the application proceeds.**

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor clarified that the NDA will contain the two Phase 3 trials. The enrollment is complete for those trials with the last patient visit scheduled for near the end of summer 2016.
- The Agency clarified that pivotal studies are the ITP studies.
- The Agency recommended the sponsor to provide topline results for their NDA.
- The Agency clarified that the expectation is for all data to be included in the population PK analysis. The Sponsor will need to adequately justify the exclusion of any datasets.
- The Sponsor described their proposed presentation of the safety database (see Table and Figure D in attached Sponsor response document). FDA stated that the proposal appears reasonable. FDA emphasized that the safety database will need to adequately reflect the population to be labeled including dose information and duration of exposure.
- The Agency clarified that the program involving data analysis and the creation of derived datasets is only for the Phase 3 ITP studies.
- The Agency clarified that studies which may have been terminated early, would still be considered covered studies, and as such financial disclosure information would be required. The Agency recommended the sponsor to provide as complete financial disclosure information as possible. The Sponsor asked who should sign the certification and the Agency clarified that the Applicant is responsible for signing the financial disclosure certification.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that the Sponsor is not required to submit a REMS at the time of the application submission. The need for risk management activities will be a subject of discussion with the Sponsor as the review of the application proceeds.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. The Sponsor stated it intends to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND**

submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

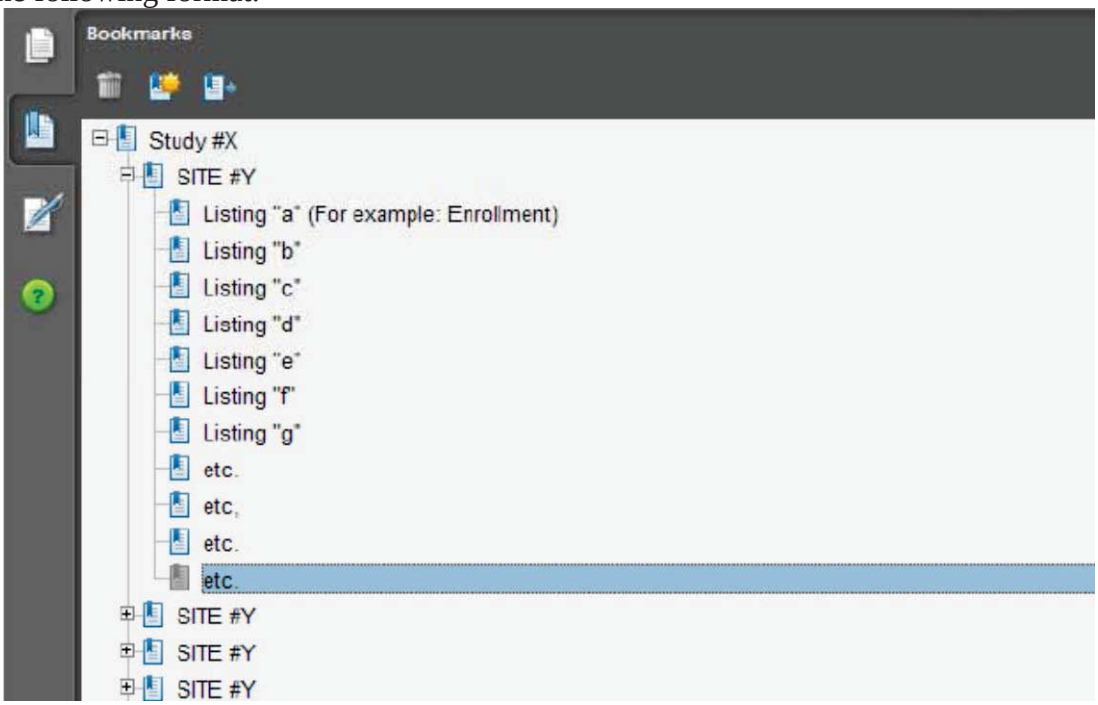
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

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

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed

and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

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.

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS:

A copy of the sponsor's response document is attached.

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

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

/s/

KATHY M ROBIE SUH
04/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074939

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Brian M. Abbott
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Abbott:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for R935788 (fostamatinib disodium) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 8, 2013. The purpose of the meeting was to discuss Rigel's approach for proceeding with Phase 3 studies.

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 Mara Miller, Regulatory Project Manager at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, M.D., Ph.D.
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
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: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: October 8, 2013 10:00 – 11:00 AM Eastern
Meeting Location: White Oak, Building #22

Application Number: IND 074939
Product Name: R935788 (fostamatinib disodium) Tablets
Indication: ITP
Sponsor/Applicant Name: Rigel

Meeting Chair: Kathy Robie Suh, M.D., Ph.D.
Meeting Recorder: Mara Miller, M.A.

FDA ATTENDEES

Office of Hematology and Oncology Products
Anthony Murgo, M.D., Associate Director

Division of Hematology Products
Edvardas Kaminskas, M.D., DHP Deputy Division Director
Kathy Robie Suh, M.D., Ph.D., Clinical Team Lead
Andrew Dmytrijuk, M.D., Clinical Reviewer
Mara Miller, M.A., Regulatory Project Manager

Office of Biostatistics
Lei Nie, Ph.D., Statistical Team Lead
Qing Xu, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology
Julie Bullock, Pharm.D., Clinical Pharmacology Team Lead

Office of Surveillance and Epidemiology
Yelana Maslov, Pharm.D., Team Lead, DMEPA
Tingting Gao, Pharm.D., Reviewer, DMEPA
Millie Brahmbhatt, Pharm.D., Fellow, DMEPA
Cynthia LaCivita, Pharm.D., Team Lead, DRISK
Anne Tobenkin, Pharm.D., Safety Evaluator, DPV

SPONSOR ATTENDEES

Elliott Grossbard, M.D., Executive Vice President, Development and CMO
Thomas Tarlow, M.S., Vice President, Regulatory Affairs
Bethany Goodrich, Sr. Regulatory Affairs Associate
(b) (4) Ph.D., Statistical Consultant
(b) (4) M.D., Medical Consultant (New York Presbyterian Hospital/ Weill Medical College of Cornell University)
(b) (4), M.D., Medical Consultant (New York Presbyterian Hospital/ Weill Medical College of Cornell University)

Reference ID: 3392854

1.0 BACKGROUND

In February, 2010, AstraZeneca signed a global license agreement with Rigel Pharmaceuticals Inc. to develop and commercialize fostamatinib disodium (fostamatinib). Prior to this agreement Rigel conducted Phase 2a/2b clinical studies in patients with rheumatoid arthritis (RA), in parallel with exploratory Phase 2a studies in patients with B-cell and T-cell lymphomas and with Immune Thrombocytopenic Purpura (ITP). AstraZeneca decided to initially focus only on RA. Although fostamatinib showed a significant consistent favorable effect with regard to RA signs, symptoms, and functional improvement (primary endpoint in all three Phase 3 studies), fostamatinib did not affect bone erosion and joint destruction in 2 of the studies, which led AstraZeneca to decide to return the development rights to Rigel.

Fostamatinib has been studied in multiple patient populations and notwithstanding the different underlying clinical situations, the safety profile has been consistent across the groups. The doses of fostamatinib across the studies ranged from 100 – 400 mg/day, with the majority of patients administered 150 – 200 mg/day. The reported adverse effects were in general reversible and manageable with appropriate therapy or dose reduction/discontinuation. In Phase 2 RA studies, there were approximately 1790 patient-years of exposure to fostamatinib (as of 6th December 2012 DSUR). The recently completed Phase 3 studies enrolled ~2120 patients total (patient exposure in the double-blind portion of Phase 3 exceeded 550 patient-years).

The toxicology studies have been completed including reproductive toxicology and carcinogenicity studies.

ITP Development
Rigel is planning to continue the development of fostamatinib for the treatment of ITP.

Fostamitinib is a potent and selective inhibitor of Syk kinase. In a murine model of ITP, fostamatinib showed a significant effect on mitigation of antibody-induced thrombocytopenia that was dose- and schedule-dependent.

A Phase 2 study in adults with refractory ITP (defined as platelet count < 30,000/mL for ≥ 3 months), initiated under this ITP IND and now ongoing as an investigator sponsored study, has 2 patients remaining on study (Bussel et al 2009). All patients had failed at least 2 standard therapeutic regimens. Patients were treated with escalating doses of fostamatinib in cohorts of 3. After a cohort completed 4 weeks, a subsequent cohort could be initiated. Patients were required to complete 2 weeks at a given dose before the dose could be increased (by 25 mg twice daily). Dosing was initiated at 75 mg *bid* to 150 mg *bid*. Certain patients, who responded and then had their platelet counts decline, could have their dose further increased to a maximum of 175 mg *bid*. Eighteen patients entered the study.

Rigel is planning to begin Phase 3 clinical studies next year and would like to have an "End-of-Phase 2" Clinical meeting with the Agency and gain concurrence on the approach for proceeding with the Phase 3 studies.

Reference ID: 3392854

2. DISCUSSION

QUESTION 1

In Phase 3, Rigel is proposing to investigate a narrow dose range of 100 to 150 mg bid fostamatinib, with adjustments made in the first weeks according to platelet response and tolerability. Does the Agency agree with this approach?

FDA Response:

No. It is not clear that an appropriate starting dose and subsequent dose escalation have been chosen for the indicated population. Dosing information on only 18 patients with ITP was provided in the background package.

Discussion

The Sponsor explained that based on human biomarker data that they have, a dose of 50 mg daily has minimal activity and the 100 mg bid dose was chosen because it had a demonstrated activity. The Sponsor proposed to conduct two studies with one study having a lower starting dose. The FDA commented that for interpretation it would be preferable to have the same starting dose and escalation in both studies. FDA agreed that for the Phase 3 study it does not seem scientifically reasonable to start at a dose likely to be ineffective. The Sponsor should submit the information related to the biomarkers and activity seen in the RA study in support of the proposed starting dose.

QUESTION 2

The proposed Phase 3 double-blind Study C788-047 has the primary efficacy endpoint as a stable platelet response by Week 12 (defined as a total count of ≥ 50,000/µL (as determined by the local clinical laboratory) on at least 4 of 6 specified visits between (b) (4) *Secondary efficacy endpoints will include additional assessments of platelet counts and the frequency and severity of bleeding over the 12-week period. Does the Agency agree with the study design and the proposed primary and secondary efficacy endpoints?*

FDA Response:

No. The primary endpoint chosen may not adequately reflect a durability of response because patients will only be treated for (b) (4) **You should consider a primary endpoint such as achieving a platelet count ≥ 50,000/µL for any 6 out of the last 8 weeks of a 24 week treatment period. Also, FDA has concerns regarding the clinical meaningfulness of the WHO Bleeding scale due to its subjective nature and the unclear clinical meaning of small incremental changes between bleeding levels.**

Reference ID: 3392854

Discussion

The Sponsor commented that requiring patients to be seen weekly for the full 6 months of the trial makes it difficult to enroll patients. Therefore, the Sponsor proposed that the durability of response will be assessed through a primary endpoint such as achieving a platelet count ≥ 50,000/µL for any 4 out of the last 6 visits of a 24 week treatment period. The FDA stated that this appears reasonable but will need to review the full protocol. The Sponsor commented that dose may need to be adjusted during the assessment period. FDA commented that dose adjustment would be acceptable but the criteria need to be specified in the protocol sufficiently to be clearly expressed in labeling. Sponsor asked about the possibility of allowing IVIG use early in the treatment course as it would not be expected to have an impact on results at 6 months. FDA commented that this should be proposed in the protocol with supporting information and justification.

QUESTION 3

Rigel proposes to have safety endpoints focus on blood pressure effects (especially as the dose is increased beyond 100 mg bid), liver function tests, gastrointestinal (GI) tolerability, infectious complications, neutrophil counts and adverse events (AEs). Does the Agency agree with this plan?

FDA Response:

Yes.

Discussion

No discussion occurred.

QUESTION 4

Assuming a single definitive Phase 3 study, and given uncertainty in the expected response rates for treatment and control, Rigel has determined the sample size for the double-blind Study C788-047 to be approximately 150 patients (100:50 [active:placebo] with an alpha level of 0.0025). Does the Agency agree with this proposed sample size?

FDA Response:

Sample size calculation should consider dropout rate. Please provide justification of placebo event rate of 0.05 in the sample size calculation.

We recommend establishing performance standards for having minimal missing data and monitoring the sites during the study on meeting the performance standards. Too much missing data undermine the reliability and confidence of the results.

Reference ID: 3392854

Discussion

The Sponsor understands the risk of under estimating the event rate for the sample size calculation for the placebo group. The Sponsor also understands the issue of missing data and will provide sensitivity analyses.

QUESTION 5

Rigel is proposing that the double-blind study be followed by a Phase 3 open-label extension trial (Study (b) (4)) to gain additional efficacy information from placebo patients who crossover to active drug and to evaluate the long-term efficacy and safety of fostamatinib. Does the Agency agree with the study design and the endpoints?

FDA Response:

FDA agrees that an extension study is an important component for the development of this drug. You should provide a clear definition of the primary endpoint for this study. See FDA response to Question 2 regarding concerns about the WHO bleeding scale.

Discussion

The Sponsor proposed a primary endpoint for the extension study of patients having platelet counts above 50,000 greater than 50% of the time. The Sponsor also said they would provide additional bleeding scale data. The FDA reiterated these bleeding scales have not been validated.

QUESTION 6

Although data to date in ITP patients are limited, there is a large safety data base in RA patients at similar doses of fostamatinib. If the results of the single Phase 3 double-blind study C788-047 show a highly statistically significant result (note alpha level in Question #4) of the primary endpoint, Rigel would plan to submit an NDA on the basis of this one Phase 3 study, together with the safety data from all earlier studies. Does the Agency agree with this plan?

FDA Response:

For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.

Approval for marketing based on a single study will require highly compelling results in both efficacy and safety. Safety information from the non-ITP studies for this drug could be considered supportive.

Reference ID: 3392854

Discussion
The Sponsor has accepted FDA's recommendation to conduct two efficacy studies.

QUESTION 7
Does the Agency have any other comments about the proposed Phase 3 studies?

FDA Response:

You should clarify stratification criteria in study C788-047.

Discussion

The Sponsor proposed to stratify on splenectomy/no splenectomy and platelet count above and below 15,000. The Sponsor will do a secondary analysis of the frequency of response in patients with a platelet count below 15,000 with regard to achieving a count greater than 30,000 and increased at least 20,000 from baseline as a secondary endpoint. The FDA stated that utility of the analysis would be a review issue.

QUESTION 8
Does the Agency agree that the completed and planned clinical studies will provide a complete package for NDA review?

FDA Response:

This question is premature at this time. See responses to Questions 1-7 above.

Discussion
No discussion occurred.

FDA Comment Regarding Questions 10 and 11
Because the following questions were not part of the original meeting request for a clinical meeting, we could not accommodate your request for additional response.
For Product Quality questions, you can request a Product Quality only meeting.

QUESTION 9
Does the Agency agree that the results of the bioequivalence study (Study D4300-020) conducted by AstraZeneca comparing the orange tablets and blue tablets are sufficient to support the use of the orange tablets in the Phase 3 double-blind study?

FDA Response:

Yes.

Reference ID: 3392854

Discussion
No discussion occurred.

QUESTION 10
Rigel plans to make the following changes with regard to the orange tablets prior to submission of the NDA. In each case, Rigel is planning to demonstrate the bioequivalence of the tablets through dissolution testing (using Q = (b) (4)% at 30 minutes as the criterion). Does the Agency agree that dissolution testing is acceptable for each change?

a. *Change in drug product manufacturing site*
b. *Change in appearance - add debossing*
c. (b) (4)

FDA Response:

See FDA Comment above.

Discussion
No discussion occurred.

QUESTION 11
Placebo tablets contain (b) (4) *. Does the agency agree it is acceptable to use these placebo tablets in the Phase 3 ITP study?*

FDA Response:

See FDA Comment above.

Discussion
No discussion occurred.

QUESTION 12
If Rigel uses existing orange tablets made by AstraZeneca in the double-blind Phase 3 study, would the FDA Inspectors include the AstraZeneca site as part of a pre-approval inspection or would the pre-approval inspection occur at the new manufacturer, which will provide the commercial product as well as the Phase 3 extension study supplies?

FDA Response:

Because this question was not part of the original meeting request, we could not accommodate your request for additional response.

Reference ID: 3392854

Discussion
No discussion occurred.

QUESTION 13
Since a substantial amount of the clinical safety data is coming from studies conducted under the RA (b) (4) *would the Division like to have copies of the RA clinical studies submitted to this IND?*

FDA Response:

This question is premature at this time.

Discussion
No discussion occurred.

QUESTION 14
Rigel would plan to submit an Integrated Summary of Safety from all fostamatinib studies, but not an Integrated Summary of Efficacy from RA studies. Is that acceptable to the Agency?

FDA Response:

This question is premature at this time.

Discussion
No discussion occurred.

QUESTION 15
Since the original IND was submitted in hard copy using the traditional IND organizational structure, would the Division like to see Module 2 summaries provided in support of the IND amendment for the Phase 3 protocols?

FDA Response:

This question is premature at this time.

Discussion

No discussion occurred.

QUESTION 16
Does the Agency have any other comments on any other aspect of the development plan or studies conducted to date?

Reference ID: 3392854

FDA Response:

The following are additional comments to consider during development of your Phase 3 Study:

Statistics:

- **Your proposed Holm's stepdown procedures adjusting multiplicity for the secondary efficacy endpoints are acceptable. However, because bleeding is a recurrent event, the Anderson-Gill model with a robust variance estimator is more appropriate for the secondary efficacy bleeding endpoint than your proposed Wilcoxon method.**
- **In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analyses of the primary endpoint cannot result in (either singly or in combination) an efficacy claim.**
- **Sensitivity analyses, including an appropriate method of imputation under the null, should be performed to account for the limitation of the data and to examine the potential impact of any missing data.**
- **Please include details in the randomization method, such as whether Permuted Block Randomization is used, information on who will prepare the randomization code, and who will implement the randomization and how in the protocol.**
- **Please submit the full protocol for review.**
- **Please submit a statistical analysis plan before the start of the trial. Subgroup analyses by such as age, gender, region and other important baseline characteristics should be also included in the protocol or the statistical analysis plan.**

Clinical:

- **You will need to address a pediatric development plan.**

Division of Medication Error Prevention and Analysis:

- **Provided that your proposed doses are 100 mg and 150 mg,** (b) (4)

Discussion

No discussion occurred.

Reference ID: 3392854

3.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. 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.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

5.0 ISSUES REQUIRING FURTHER DISCUSSION

That there were no issues requiring further discussion.

Reference ID: 3392854

6.0 ACTION ITEMS

There were no identified action items.

7.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Reference ID: 3392854

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

/s/

KATHY M ROBIE SUH
10/18/2013

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

LATE-CYCLE MEETING MINUTES

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) dated April 15, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 11, 2018.

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 Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	January 11, 2018; 2:00-3:00PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 209299
Product Name:	TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.
Indication:	Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
Applicant Name:	Rigel Pharmaceuticals, Inc.
Meeting Chair:	Kathy Robie Suh, MD, PhD, Clinical Team Leader
Meeting Recorder:	Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Angelo de Claro, MD, Clinical Team Leader
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Brenda Gehrke, PhD, Pharmacology/Toxicology Reviewer
Brian Cholewa, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Qi Liu, PhD, Clinical Pharmacology Team Leader
Runyan Jin, PhD, Pharmacology Reviewer

Office of Product Quality
Sherita McLamore Hines, PhD, Product Quality Team Leader
Monica Cooper, PhD, Product Quality Reviewer

Office of Biostatistics/Division of Biometrics V
Thomas Gwise, PhD, Deputy Division Director
Stella Karuri, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology
Leeza Rahimi, Pharm D, Reviewer
Mei-Yean Chen, Pharm D, Risk Management Analyst
Allison Lardieri, PharmD, BCPPS, Safety Evaluator
Jenny Kim, PharmD ,Safety Evaluator

APPLICANT ATTENDEES
Rigel Pharmaceuticals Inc.
Anne-Marie Duliege, MD, Executive VP and Chief Medical Officer
Sandra Tong, MD,VP, Clinical Sciences and Drug Safety
Dana Pizzuti, MD, Senior VP, Regulatory Affairs and Clinical Compliance
Yvonne Kim, Senior Director, Regulatory Affairs
(b) (4), Regulatory Affairs Consultant
Hany Zayed, PhD, Executive Director, Data Science

1.0 BACKGROUND

NDA 209299 was submitted on April 15, 2017 for TAVALISSE™ (fostamatinib); tablet; 100 mg, 150 mg

Proposed indication(s): Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

PDUFA goal date: April 17, 2018

FDA issued a Background Package in preparation for this meeting on December 15, 2017.

2.0 DISCUSSION

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 20 minutes

   Biostatistics:

   i. Due to the small sample size and high rates of attrition in Study 047 and 048, the statistical interpretation of the primary efficacy results was heavily dependent on the number of responders in the placebo arm in each study.
   ii. The LOCF imputation may not reflect the true platelet value. Furthermore due to the high discontinuation in both arms and in both studies, imputations are likely to have considerable weight on the efficacy results.
   iii. Study 049 was a non-randomized trial, and was not sized to detect a particular magnitude of an effect. No multiplicity adjustments were pre-specified and none of

Reference ID: 4206771

the two versions of the primary endpoint was pre-defined for formal statistical testing. Consequently, these analyses are considered exploratory.

Discussion: ***The agency's sensitivity analysis without LOCF imputation were consistent with the applicant's results. The agency has several concerns with regards to the applicants sensitivity analysis using MI in Study 048:***

1) ***Due to the high rate attrition prior to Week 14, the dataset used was small and consisted of 24 fostamatanib patients.***
2) ***Platelet counts were positively skewed, this violated the assumption of Normality***
3) ***The assumption of monotonicity was violated (patient (b) (6))***

3. Information Requests – 10 minutes

Clinical:

Provide the numbers of patients who developed hypertension and had undergone fostamatinib dose modification, interruption, discontinuation or other intervention (addition or increase dose of anti-hypertensive medication) in the ITP studies, the rheumatoid arthritis studies (including the ambulatory blood pressure study) and the healthy volunteer studies and provide cases that did not resolve after these interventions.

Discussion: ***The team has received the sponsor's response and is currently reviewing it.***

4. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

Chemistry, Manufacturing and Controls:

PMC-1: Test (b) (4) for elemental impurities and submit the data to FDA. (b) (4) (b) (4)

PMC Schedule Milestones: Study Completion: June 30, 2018

PMC-2: Develop a test method for (b) (4) and hardness for the drug product and submit the validation data to the FDA. Include tests for (b) (4) and hardness for drug product release and stability specifications with adequate justification.

PMC Schedule Milestones: Study Completion: June 30, 2018

Discussion: ***The Applicant indicated that they are in agreement with the Agency's post marketing requirements.***

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5. Major labeling issues – 5 minutes

   Refer to the prescribing information sent to you on December 4, 2017 for labeling recommendations. The Agency expects to receive back the labeling from you on or before December 20, 2017. Prior to the late cycle meeting, please inform the Agency of labeling-related issues that you wish to discuss at the late cycle meeting.

Discussion: ***The sponsor suggested including FIT-2 results and subset analyses in the label. The Agency commented on the limitations of the available data and the small study sizes. The Agency acknowledges the Applicant's position and this is still under Agency review and discussion.***

6. Review Plans – 10 minutes

   The Agency anticipates meeting the PDUFA timelines for the application review. During the remaining review time, the Agency will work with the Applicant to reach labeling agreement.

Discussion: ***There was no discussion.***

7. Wrap-up and Action Items – 5 minutes

Discussion*: The Applicant will provide additional information on fostamatinib patients who did not roll over into FIT3.*

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.

A copy of the sponsor's slide presentation is attached for reference.

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

Reference ID: 4206771

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

/s/

KATHY M ROBIE SUH
01/12/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209299

LATE CYCLE MEETING
BACKGROUND PACKAGE

Rigel Pharmaceuticals, Inc.
Attention: Anne-Marie Duliege, MD
Executive Vice President and Chief Medical Officer
1180 Veterans Blvd
South San Francisco, CA 94080

Dear Dr. Duliege:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 11, 2018. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at rachel.mcmullen@fda.hhs.gov, at least one week prior to the meeting.

For each foreign visitor, complete and email the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Late-Cycle Meeting Background Package
FDA Foreign Visitor Data Request Form

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: January 11, 2018; 2:00-3:00PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: NDA 209299
Product Name: TAVALISSE™ (fostamatinib) tablet; 100 mg, 150 mg.
Indication: Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
Applicant Name: Rigel Pharmaceuticals, Inc.

FDA ATTENDEES (tentative)

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Hyon Zu Lee, Pharm D, Clinical Reviewer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Chris Sheth, PhD, Pharmacology/Toxicology Team Leader
Brian Cholewa, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Qi Liu, PhD, Clinical Pharmacology Team Leader
Runyan Jin, PhD, Pharmacology Reviewer

Office of Product Quality
Sherita McLamore Hines, PhD, Product Quality Team Leader
Mike Adams, PhD, Product Quality Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Statistical Team Leader
Stella Karuri, PhD, Statistical Reviewer

Office of Surveillance and Epidemiology
Leeza Rahimi, Pharm D, Reviewer
Hina Mehta, Pharm D, Team Leader
Mei-Yean Chen, Pharm D, Risk Management Analyst
Wana Manitpisitkul, Project Manager

Reference ID: 4196224

APPLICANT ATTENDEES

Rigel Pharmaceuticals Inc.

Anne-Marie Duliege, MD, Executive VP and Chief Medical Officer
Sandra Tong, MD,VP, Clinical Sciences and Drug Safety
Scott Henley, VP, Clinical Operations
Dana Pizzuti, MD, Senior VP, Regulatory Affairs and Clinical Compliance
John Aitken, Executive Director, Regulatory Operations
Yvonne Kim, Senior Director, Regulatory Affairs
(b) (4), Regulatory Affairs Consultant
Hany Zayed, PhD, Executive Director, Data Science
(b) (4) Acting VP, Technical Operations (Consultant)

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

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued to date.

SUBSTANTIVE REVIEW ISSUES

There are no substantive review issues at this time which would affect approvability.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

Reference ID: 4196224

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 20 minutes

   Biostatistics:

   i. Due to the small sample size and high rates of attrition in Study 047 and 048, the statistical interpretation of the primary efficacy results was heavily dependent on the number of responders in the placebo arm in each study.
   ii. The LOCF imputation may not reflect the true platelet value. Furthermore due to the high discontinuation in both arms and in both studies, imputations are likely to have considerable weight on the efficacy results.
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   (b) (4)

Reference ID: 4196224

PMC Schedule Milestones: Study Completion: June 30, 2018

PMC-2: Develop a test method for (b) (4) and hardness for the drug product and submit the validation data to the FDA. Include tests for (b) (4) and hardness for drug product release and stability specifications with adequate justification.

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   Refer to the prescribing information sent to you on December 4, 2017 for labeling recommendations. The Agency expects to receive back the labeling from you on or before December 20, 2017. Prior to the late cycle meeting, please inform the Agency of labeling-related issues that you wish to discuss at the late cycle meeting.

6. Review Plans – 10 minutes

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7. Wrap-up and Action Items – 5 minutes

Reference ID: 4196224

OSO | Office of Security Operations
FOREIGN VISITORS DATA REQUEST FORM

VISITOR'S FULL NAME	**First**	**Middle**	**Last**
GENDER		DATE OF BIRTH (MM/DD/YYYY)	
COUNTRY OF ORIGIN / CITIZENSHIP			
PLACE OF BIRTH (CITY AND COUNTRY)			
PASSPORT NUMBER			
ISSUING COUNTRY			
ISSUANCE DATE			
EXPIRATION DATE (MM/DD/YYYY)			
VISITOR'S ORGANIZATION/EMPLOYER	Rigel Pharmaceuticals, Inc.		
MEETING START (DATE/TIME)	January 11, 2018; 2:00PM (ET)		
MEETING ENDING (DATE/TIME)	January 11, 2018; 3:00PM (ET)		
PURPOSE OF MEETING	Industry		
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building 22, Conference Room: 1419		
BUILDING ENTRANCE	White Oak Building 22		
FDA LABORATORIES TO BE VISITED	None		
HOSTING FDA CENTER	CDER		
HOSTING OFFICIAL	Name: Rachel McMullen		
	Title: Senior Regulatory Project Manager		
	Office/Bldg.: Building 22; Room 3224		
	Email: rachel.mcmullen@fda.hhs.gov	Phone: 240-402-4574	
ESCORT INFORMATION (If different from Hosting Official)	Name: Suria Yesmin		
	Title: Regulatory Project Manager		
	Office/Bldg.: Building 22; Room 3224		
	Email: suria.yesmin@fda.hhs.gov	Phone:301-348-1725	

Important: Forms must be typed. Handwritten forms will be returned.

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

/s/

ANN T FARRELL
12/15/2017