

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209299Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 209299
Product Name: Tavalisse™ (fostamatinib) Tablets, 100 and 150 mg

PMC #1 Description: 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. Submit a CBE-30 supplement to update the drug product specification.

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>06/30/2018</u>
Final Report Submission:	<u>08/15/2018</u>
Other:	<u>MM/DD/YYYY</u>

PMC #2 Description: Conduct and submit a risk assessment for the presence of elemental impurities as described in the ICH guidance *Q3D Elemental Impurities* (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf>). Your risk assessment should identify known and potential sources of elemental impurities that may be present in the drug product, and evaluate the presence of each particular elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the permitted daily exposure (PDE) established in ICH Q3D. If the risk assessment or testing results fail to show that an elemental impurity level is consistently less than the control threshold (defined as being 30 percent of the established PDE in the drug product), you should propose additional controls (e.g., component, in-process, or drug product controls) to ensure that the elemental impurity level does not exceed the PDE in the drug product. For additional information, also see: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm590075.htm> Submit a CBE-30 supplement with the data and/or update the drug product specification.

PMC Schedule Milestones:

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>06/30/2018</u>
Final Report Submission:	<u>08/15/2018</u>
Other:	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**

• **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

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

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

2. Describe the particular review issue and the goal of the study.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues

Other

Describe the agreed-upon study:

The applicant will develop a test method for (b) (4) and hardness for the drug product and submit the validation data to the FDA. Based on the data the applicant will either update the drug product release and stability specifications to include the tests or provide justification for the exclusion of these test.

(b) (4)

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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/s/

RABIYA HAIDER
04/04/2018

THOMAS F OLIVER
04/06/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: February 21, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 209299
Product Name and Strength: Tavalisse (fostamatinib) tablet
100 mg, 150 mg
Applicant/Sponsor Name: Rigel Pharmaceuticals
Submission Date: February 02, 2018
OSE RCM #: 2017-757-2
DMEPA Safety Evaluator: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Hina Mehta, Pharm.D.

1 PURPOSE OF MEMO

Division of Hematology Products (DHP) requested that we review the revised container labels and professional sample labels for Tavalisse (fostamatinib) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and professional sample labels are acceptable from medication error perspective. We have no further recommendations at this time.

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

^a Rahimi, L. Label and Labeling Review for Tavalisse (fostamatinib) (NDA 209299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 11. RCM No.: 2017-757-1.

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/s/

LEEZA RAHIMI
02/21/2018

HINA S MEHTA
02/22/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: January 11, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 209299
Product Name and Strength: Tavalisse (fostamatinib) tablet
100 mg, 150 mg
Applicant/Sponsor Name: Rigel Pharmaceuticals
Submission Date: December 21, 2017
OSE RCM #: 2017-757-1
DMEPA Safety Evaluator: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Hina Mehta, Pharm.D.

1 PURPOSE OF MEMO

Division of Hematology Products (DHP) requested that we review the revised container labels for Tavalisse (fostamatinib) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We identified areas of improvement in the container labels and have provided our recommendations for the Applicant in section 3 of our review.

3 RECOMMENDATIONS FOR RIGEL PHARMACEUTICALS

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

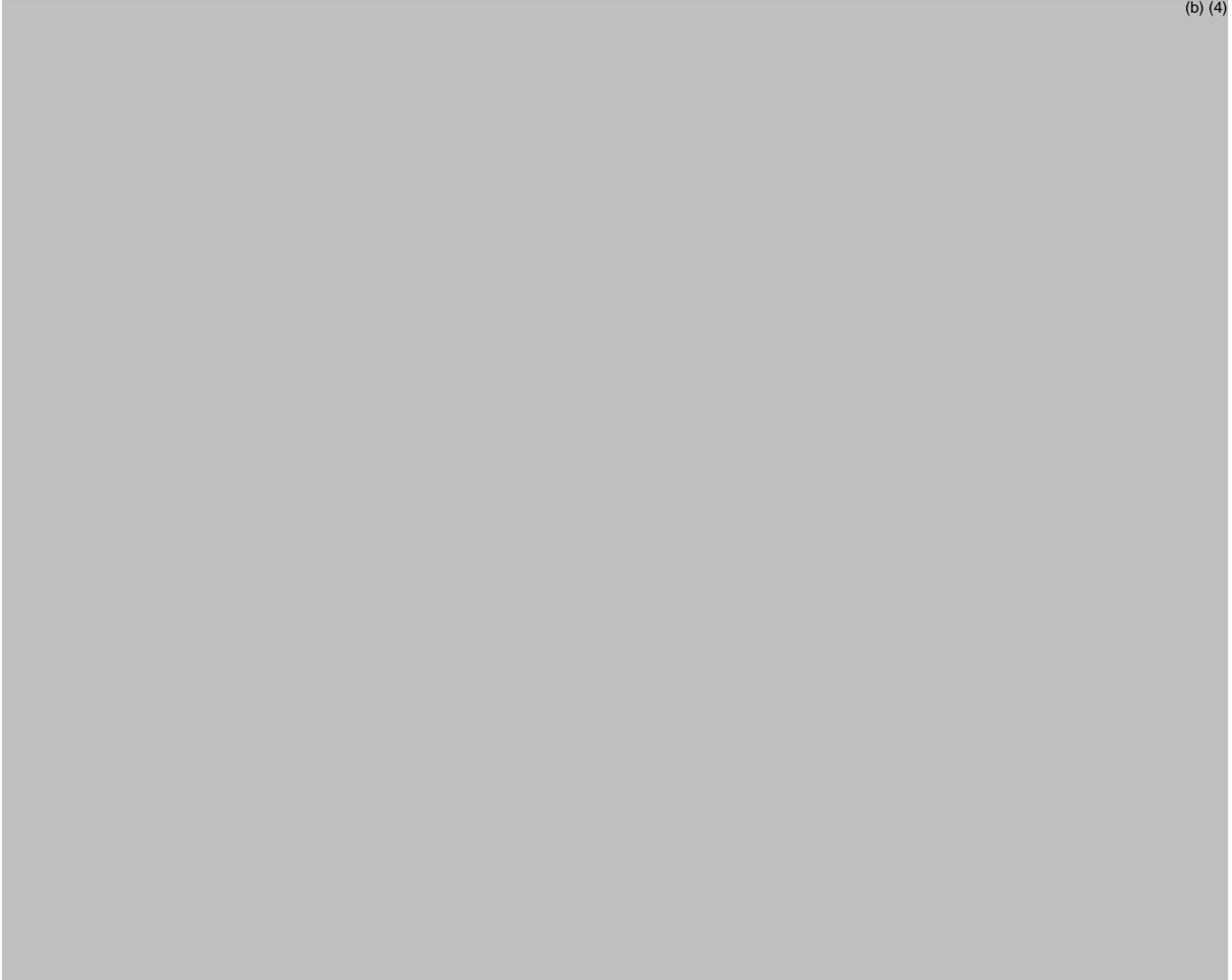
^a Rahimi, L. Label and Labeling Review for Tavalisse (fostamatinib) (NDA 209299). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 19. RCM No.: 2017-757.

Container Labels:

- A. We note that the revised container labels lack the intended location for the lot number and expiration. Please ensure that the lot and expiration numbers appear on all the container labels in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17. Please specify location of lot number and expiration.
- B. Please revise the storage information to be consistent with the updated Prescribing Information. Revise the information to read: “Store at room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].”
- C. Please submit the revised container labels for the 30 count bottles as well as the revised sample labels for both strengths of 100 mg and 150 mg.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 19, 2017

Container labels



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/s/

LEEZA RAHIMI
01/11/2018

HINA S MEHTA
01/12/2018

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

NDA	209299
Brand Name	Tavalisse®
Generic Name	Fostamatinib (R935788/R788; Prodrug)
Sponsor	Rigel Pharmaceuticals Inc.
Indication	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
Dosage Form	Film-coated Tablet (100 and 150 mg)
Drug Class	SYK inhibitor / Immunomodulatory agent
Therapeutic Dosing Regimen	Proposed regimen is to initiate treatment with 100 mg twice daily and increase dose to 150 mg twice daily after a month, if platelet count has not increased to $\geq 50 \times 10^9/L$
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	250 mg twice daily of R788 (C-935788-003), and 300 mg twice daily of R406 (C-940406-001)
Submission Number and Date	SDN 001; 15 Apr 2017
Review Division	DHP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of R935788 (R788) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between R788 (100 mg BID and 300 mg BID) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcF$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 1, indicating that assay sensitivity was established.

In this randomized, blinded, four-arm parallel study, 208 healthy subjects were randomized to receive R788 100 mg BID, R788 300 mg BID, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for R788 (100 mg BID and 300 mg BID) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Day	Treatment	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
4	R788 100 mg	8	0.5	(-3.4, 4.4)
4	R788 300 mg	23.5	5.2	(1.3, 9.2)
4	Moxifloxacin 400 mg*	3	13.9	(8.6, 19.2)

* Multiple endpoint adjustment of 4 time points was applied.

The suprathreshold dose (300 mg) resulted in mean C_{max} values of 3.9-fold higher than the mean C_{max} for the therapeutic dose (100 mg). Considering the established dose linearity, the anticipated exposures (C_{max}) for the maximum therapeutic dose of 150 mg is expected to offer ~2-fold margin. These concentrations are above those for the predicted worst case scenario (drug interaction with ketoconazole) and show that at these concentrations there are no detectable prolongations of the QT-interval.

R406 exposure was not higher in subjects with mild, moderate, or severe hepatic impairment when compared to subjects with normal hepatic function. Similarly, R406 exposure was not higher in end-stage renal disease or moderately renal impaired subjects when compared to subjects with normal renal function. Moreover, the exposure of R406 is not significantly influenced by age, gender, and race. Overall exposure of R406 is similar in patients and healthy subjects. However, there is a relationship between body weight and exposure, with lower body weight subjects having higher exposure to R406. Drug interaction study (#C788-001) confirmed that concomitant administration of fostamatinib with ketoconazole increases R406 exposures considerably (C_{max} and AUC_{inf} increased by 37% and 102%, respectively). The suprathreshold dose therefore provided sufficient margin over the therapeutic dose.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

Question: Do the data in the QT study support the labeling language?

Response: Yes. The data provided in the QT study are adequate to support the proposed labeling language.

2 PROPOSED LABEL

3 BACKGROUND

The sponsor included the following language in the proposed label:

Cardiac Electrophysiology:

At 2 times the maximum recommended dose, TAVALISSE did not prolong the QT interval to a clinically relevant extent.

The proposed labeling language appears acceptable to QT-IRT. However, we defer final labeling decisions to the Division.

3.1 PRODUCT INFORMATION

Fostamatinib (R935788 or R788), a prodrug of R940406 (R406) disodium, is an oral spleen tyrosine kinase (SYK) inhibitor. Fostamatinib appears to prevent platelet destruction by interrupting Fc receptor-mediated platelet engulfment on macrophages through inhibition of SYK signaling. Rigel Pharmaceuticals, Inc conducted initial nonclinical and clinical studies with (b) (4) R406. Since the prodrug of R406 had desirable pharmaceutical properties, the applicant selected fostamatinib over R406 for subsequent development activities. Following oral administration, Fostamatinib is rapidly converted to R406. The applicant has been developing fostamatinib for the treatment of multiple autoimmune diseases and fostamatinib tablets have been used in Phase 1, 2 and 3 clinical studies in various patient populations. Most the safety data are derived from other indications such as rheumatoid arthritis studies (including international Phase 3 studies), Phase 2 oncology studies, and Phase 1 studies in healthy subjects. In February 2010, AstraZeneca signed a global license agreement with Rigel Pharmaceuticals, Inc to develop and commercialize fostamatinib.

3.2 MARKET APPROVAL STATUS

Fostamatinib disodium is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Safety pharmacology studies were performed in telemetered Cynomolgus monkeys (cardiovascular), rats (CNS and pulmonary), and in vitro in the HERG channel assay. A slight reduction in heart rate and increase in RR interval was noted at 50 mg/kg in the cardiovascular study and a slight effect on a few behavioral parameters was also noted at 50 mg/kg in the CNS study; otherwise the safety pharmacology studies determined that R406 was well tolerated.

Study No./ Study Type	Species	No/Group (Total n)	Doses	Results
N-940406-0003 Non-GLP HERG Screen	Transfected HEK293 Cells	4	2 µM R406	No inhibition of HERG tail current
G-940406-0001 GLP Cardiovascular Safety Pharmacology	Telemeterized Cynomolgus Monkeys	4 M (Latin Square Design)	0, 5, 15 & 50 mg/kg R406	Well tolerated; slight reduction in heart rate at 50 mg/kg (max decrease of -30 bpm at 180 min post-dose) NOEL = 15 mg/kg

(Source: IB Ed.7, 15 Jun 2010)

3.4 CLINICAL EXPERIENCE

The Cardiovascular SMQ analysis identified a small number of RA patients overall with cardiovascular events in the Placebo-Controlled Studies: 1.8% vs 0.9% for fostamatinib vs placebo. Patient incidences for the following SMQ narrow preferred term searches (and their most frequent preferred terms) were as follows for fostamatinib vs placebo:

- Cardiac Arrhythmias, 1.2% vs 0.6%, respectively (electrocardiogram QT prolonged, 0.2% vs 0%; sinus bradycardia, 0.2% vs 0.3%, ventricular extrasystoles, 0.2% vs 0.2%)
- Cardiac Failure, 0.2% vs 0.1%, respectively (congestive cardiac failure, 0.2% vs 0%)
- Ischemic Heart Disease, 0.5% vs 0.3%, respectively (angina pectoris, 0.1% vs 0.2%)
- Myocardial infarction, 0.2% vs 0.2%, respectively (unstable angina, 0.1% vs 0.1%)
- Torsade De Pointes / QT Prolongation, 0.2% vs 0%, respectively (electrocardiogram QT prolonged, 0.2% vs 0%)
- The Cardiovascular SMQ search identified 4.5% of RA patients with a cardiovascular event during the blinded and open-label extension studies. The cardiovascular event SMQ search results and the most frequent events under each SMQ were as follows:
 - Cardiac Arrhythmias, 3.2% (sinus bradycardia, 0.7%, atrial fibrillation, 0.6%, ventricular extrasystoles 0.5%, electrocardiogram QT prolonged, 0.3%)
 - Cardiac Failure, 0.6% (congestive cardiac failure, 0.3)
 - Ischemic Heart Disease, 1.0% (angina pectoris, 0.3%)
 - Myocardial infarction, 0.4% (myocardial infarction, 0.2; unstable angina, 0.1%)
 - Torsade De Pointes / QT Prolongation, 0.3% (electrocardiogram QT prolonged, 0.3%)

There was no dose relationship in this class of AEs. [...] The incidence of adjudicated cardiovascular events reported in fostamatinib treated patients was comparable to the incidence rates of cardiovascular events in the control group as well as in RA patients not treated with fostamatinib from the registry cohorts.

(Source: Summary of Clinical Safety 2.7.4, 09 Apr 2017)

Reviewer's Comment: There was no dose relationship for incidences of cardiovascular AEs. The incidence of cardiovascular events observed in patients exposed to fostamatinib appeared comparable to that of similar patient populations not exposed to fostamatinib.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Fostamatinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study (b) (4)
 (b) (4) The sponsor submitted the study report C-935788-013 (b) (4)
 R08-0210) for R935788 (fostamatinib disodium), including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Double-Dummy, Randomized, Positive and Placebo Controlled, Parallel-Study of the Effects of Oral R935788, at the Proposed Therapeutic and at a Supra-Therapeutic Dose, on the QT/QTc Intervals in Healthy Subjects

4.2.2 Protocol Number

C-935788-013 ((b) (4) R08-0210)

4.2.3 Study Dates

05 Sep 2008 – 25 Nov 2008

4.2.4 Objectives

The primary objectives of this study were:

- To evaluate the effect of R788 on ventricular repolarization in healthy subjects compared to placebo after the proposed therapeutic dose of 100 mg bid.
- To evaluate the effect of R788 on ventricular repolarization in healthy subjects compared to placebo after a supra-therapeutic dose that was defined as 300 mg bid.

The secondary objectives of this study were:

- To determine if there was a pharmacodynamic relationship between the duration of the QT/QTc intervals and the plasma concentration of R406.
- To obtain additional pharmacokinetic information for oral R788 at the proposed therapeutic and supra-therapeutic dose.
- To generate additional safety information.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4-arm, parallel design with four dosing occasions.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were over-encapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 4 treatment arms:

- Group 1: daily therapeutic dose of R788 100 mg BID (QD on Day 4) and oral moxifloxacin placebo
- Group 2: daily suprathereapeutic dose of R788 300 mg BID (QD on Day 4) and oral moxifloxacin placebo
- Group 3: daily R788 placebo and moxifloxacin placebo
- Group 4: R788 placebo plus oral moxifloxacin placebo on Day 1, 2, and 3; R788 placebo plus moxifloxacin 400 mg QD on Day 4

4.2.6.2 Sponsor's Justification for Doses

In this thorough QT/QTc study, the sponsor proposed to use the 100 mg bid dose of R788 as the therapeutic dose. This was based on the recently completed Phase II clinical study (Study C-935788-006) of oral R788 for the treatment of RA.

The 300 mg bid dose was considered the supra-therapeutic dose. This dose level was based on the ongoing studies of patients with refractory ITP (Study C-935788-007) and B-Cell Lymphoma (Study C-935788-009), where a 200 mg bid dose has been proven to be tolerable. The 300 mg bid dose was expected to provide plasma concentrations that are greater than those obtained after any therapeutic usage. The 300 mg bid dose was expected to be tolerated by the subjects as it was only to be administered for 4 days.

It has been estimated that 3 to 4 days of dosing is needed to achieve steady state plasma levels of R406. The plan in this study was to dose subjects for 4 days prior to the evaluation of any possible effect of R788 on each subject's QT/QTc intervals.

It was anticipated that by decreasing the duration of dosing to 4 days; the supra-therapeutic dose level (300 mg bid, qd only on Day 4) chosen for this study will be adequately tolerated.

Reviewer's Comment: Previously, the protocol was reviewed [REDACTED] (b) (4) and the proposed suprathereapeutic dose with 3-fold greater exposure than the planned therapeutic dose was found to be acceptable. The sponsor proposed 300 mg bid as suprathereapeutic dose with the expectation that it would achieve a mean C_{max} of 2300 ng/ml on Day 4, which is 3-fold greater than the 100 mg bid dose. The observed C_{max} on Day 4 with 300 mg bid dose is approximately 4-fold greater (3020 ± 1180 ng/mL) than that observed for 100 mg bid dose (783 ± 224 ng/mL). Similar increase in AUC_{0-24h} and AUC_{ss} was also observed with 300 mg bid dose. Considering the established dose linearity, the anticipated exposures (C_{max}) for the maximum therapeutic dose of 150 mg is expected to offer ~2-fold margin. This exposure will cover the increase due to co-administration of a potent CYP3A4 inhibitor (increased C_{max} by ~37%). No metabolites were characterized in the present study, and per the summary of clinical pharmacology there are no major metabolites of R406.

4.2.6.3 Instructions with Regard to Meals

Subjects were to be in the fasted state for dosing. During the intense hours of ECG collection the subjects were to be kept fasting. A light meal was to be given between the 4th and 6th hours post-dose. The meal was to be concluded within 30 minutes allowing for 1.5 hours before the next ECG acquisition at 6.0 hours post-dose. The evening meal was to be scheduled between the 8th and 12th hour post-dose. Meals was to be consumed and doses taken at the same time on each occasion.

Reviewer's Comment: This was found to be acceptable during protocol (b) (4) (b) (4) review, as concomitant administration with a high-fat meal was associated with increased T_{max} and lowered the C_{max} .

4.2.6.4 ECG and PK Assessments

ECG Assessments: 12-lead ECGs extracted from Holter monitors were to be obtained 0.5 hours before dosing; Post-Dosing: 0.5, 1.0, 2.0, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, 16.0, 23.5 hours on Days -1 (baseline) and Day 4.

PK Assessments: Blood sample collection was to be obtained on Day 4 at 0.25 hours before dosing and following the 10 minute window of ECG extraction post-dosing at 45 minutes post-dose, 1 hr and 15 min, 2 hr and 15 min, 3 hr and 15 min, 3 hr and 45 min, 4 hr and 15 min, 6 hr and 15 min, 8 hr and 15 min, 12 hr and 15 min, 16 hr and 15 min, and 23 hr and 45 min to determined the R406 pharmacokinetics.

The plasma samples obtained at 0.25 hours pre-dose, and 1.0 hr and 15 min, 2.0 hr and 15 min, 4.0 hr and 15 min, 6.0 hr and 15 min, and 12.0 hr and 15 min were to also be assayed for moxifloxacin concentrations.

Reviewer's Comment: This was found to be acceptable during protocol (b) (4) (b) (4) review. The timing of ECG/PK sampling was acceptable as the steady-state T_{max} (1 to 2 hours for R406 in healthy subjects) were covered.

4.2.6.5 Baseline

Time-matched QT/QTc values on Day -1 were used as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 208 healthy adult subjects (114 males and 94 females) were randomized to the study. Of all randomized subjects, 205 completed the study as planned and 203 subjects had evaluable Day 4 holter data. Plasma concentrations from 205 completed subjects were used in PK analysis.

The average age of the 208 subjects was 27.5 years, ranging from 18 to 54 years. The majority of the subjects were White (170/208, 81.7%). Seventeen subjects (17/208, 8.2%)

were Black or African American. Nine subjects (9/208, 4.3%) were American Indian or Alaskan Native. Six subjects (6/208, 2.9%) were Asian.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The means and confidence intervals for the primary analysis were generated using a repeated measures mixed effects linear model that included the effects of subject, study drug, ECG time point, and study drug-by-ECG time point interactions.

The response of QTcF at the two doses was nearly identical. Late in the observation period the 300 mg group had slightly higher mean values. For all observations, for both doses, the upper bounds of the 95% one-sided confidence intervals were below 10 msec.

The largest observed difference from placebo was 5.83 msec and the largest upper confidence bound was 8.72 msec, both in the 300 mg group at 23.5 hours post dose, hence, the primary hypothesis was rejected and it was concluded that the largest time-matched difference from placebo was < 10 msec.

The sponsor’s results of primary analysis are displayed in the following Table 2.

Table 2: Difference from Placebo in Changes in QTcF (msec) for Each R788 Dose and Upper Bound of the 95% One-Sided Confidence Intervals (Sponsor’s Results)

Hours Post-Dose	R788 100 mg bid - Placebo		R 788 300 mg bid - Placebo	
	Mean	95% CI	Mean	95% CI
0.5	-0.23	2.62	-2.60	0.24
1.0	0.48	3.33	-2.25	0.59
2.0	1.58	4.44	-0.10	2.74
3.0	0.40	3.25	1.09	3.93
3.5	0.75	3.60	-0.24	2.59
4.0	1.93	4.79	0.63	3.46
6.0	-0.77	2.09	-1.36	1.48
8.0	1.36	4.22	0.04	2.88
12.0	1.12	3.97	1.12	3.96
16.0	0.40	3.26	2.41	5.24
23.5	2.62	5.52	5.83	8.72

Consistently, moxifloxacin treatment is associated with marked increases in QTcF. Assay sensitivity is assessed in Table 3 which shows the one-sided lower 95% confidence bounds for the difference between moxifloxacin and placebo in changes from baseline in QTcF. The lower confidence bounds were all > 5 msec, hence, the study showed assay sensitivity.

Table 3: Difference from Placebo in Change in QTcF (msec) for Moxifloxacin and Lower Bound of the 95% One-Sided Confidence Intervals (Sponsor’s Results)

Hours Post- dose	Moxifloxacin - Placebo	95%CI
2	10.34	7.41
3	12.87	9.95
3.5	11.57	8.65
4	11.92	8.99

(Source: the sponsor's clinical study report, Table 12.5.1.13-1, page 67)

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

From the sponsor's report for categorical analysis, only one subject (Subject (b) (6), R788 300 mg bid group) had at least one QTcF >450 ms. This subject also had multiple QTcF results >450 ms on Day -1 prior to treatment. No subjects had QTcF >480 ms at any time.

No subjects experienced change from baseline in QTcF (Δ QTcF) >30 ms in the study.

4.2.8.2.4 Additional Analyses

The sponsor displayed mean change from baseline in QTcF (Δ QTcF) by gender and analyzed gender-by-treatment interaction, which assessed whether the mean differences between males and females were equal among the three treatment groups.

The p-values for this interaction were <0.05 at only one time point (6 hours post dose), and close to 0.05 at two time points (8 and 12 hours post dose). Table 4 shows the placebo-subtracted differences for each gender at these three time points. Although females had greater differences from placebo than did males, the largest difference was only 5.1 msec. This suggests that R788 does not have a clinically meaningful effect on QTcF among females.

Table 4: Mean Placebo-Subtracted Differences in QTcF (msec) by Gender (for Time Points with or Nearing Statistical Significance (Sponsor's Results))

Hours Post Dose	R788 100 mg bid		R788 300 mg bid		Gender-by-Treatment Group p value
	Males	Females	Males	Females	
6.0	-2.02	0.87	-5.54	3.65	0.007
8.0	-1.21	4.53	-3.24	4.00	0.06
12.0	-0.34	2.78	-2.20	5.08	0.07

(Source: the sponsor's clinical study report, Table 12.5.1.8-1, page 65)

4.2.8.3 Safety Analysis

No death, other serious adverse events (AEs) or other significant AEs occurred during the study.

Two subjects were discontinued due to AEs. Subject (b) (6) (Dose Group 1) withdrew consent prior to Day 4 study hour -0.667 activities due to headache, nervousness, nausea, and pain. Subject (b) (6) (Dose Group 4) was dropped by the investigator prior to Day 3 study hour 12 activities due to pharyngitis streptococcal.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 5 (R406) and Table 6 (Moxifloxacin). C_{max} and AUC values in the thorough QT study were approximately 4-fold higher following administration of 300 mg bid dose compared with 100 mg bid dose of Fostamatinib, the intended clinical dose. The observed mean C_{max} of 3020 ng/mL was approximately 4-fold

higher than mean C_{max} of 783 ng/mL after therapeutic dose. Considering the established dose linearity, the anticipated exposures (C_{max}) for the maximum therapeutic dose of 150 mg is expected to offer ~2-fold margin. No R406 levels were detected in the plasma samples from Group 3 (placebo) and Group 4 (moxifloxacin) subjects.

Table 5: Mean (\pm SD) Pharmacokinetic Parameters of R406 on Day 4 Following Oral Administration of 300 mg bid dose or 100 mg bid dose of Fostamatinib (Sponsor's Results)

Group	R788 100 mg bid (n=50)	R788 300 mg bid (n=52)
t_{max} (h)	2.24 \pm 1.27	2.91 \pm 1.51
C_{max} (ng/mL)	783 \pm 224	3020 \pm 1180
$t_{1/2}$ (h)	19.1 \pm 10.1	20.5 \pm 12.5
AUC ₀₋₂₄ (ng*h/mL)	8800 \pm 2720	36300 \pm 14800
AUC _{ss} (ng*h/mL)	11600 \pm 3140	46600 \pm 18000

Table 6: Mean (\pm SD) Pharmacokinetic Parameters Following Single Oral Administration of 400 mg Moxifloxacin Tablets on Day 4 (Sponsor's Results)

Parameters	Mean \pm SD
t_{max} (h)	2.73 \pm 1.24
C_{max} (ng/mL)	1850 \pm 384
AUC ₀₋₂₄ (ng*h/mL)	15300 \pm 3060
$t_{1/2}$ (h)	8.49 \pm 1.91

No moxifloxacin levels were observed in Groups 1-3 (therapeutic, suprathreshold, and placebo), except for one sample (Subject ^{(b) (6)} at the 4.25 h timepoint).

Source: Applicant's Clinical Study C788-013, Appendix: 16.1.9 Documentation of Statistical Methods, Tables 6, 8, and 9.

4.2.8.4.2 Exposure-Response Analysis

Linear mixed-effects model with a random effect on the intercept and slope was used to explore the relationship between baseline-adjusted placebo- corrected QTc interval ($\Delta\Delta$ QTcF) and plasma concentrations of R406. The results of these analyses indicate a very weak association between the plasma concentrations of R406 concentrations and $\Delta\Delta$ QTcF interval that is not considered to be clinically significant.

The 300 mg group had slightly higher mean values at 23.5 h. It is less likely that the metabolites with long half-life are slowly appearing and only affecting 23.5 h data without influencing other observations taken on Day 4. The applicant indicated that the 23.5 h data, after placebo-subtraction, had slightly higher value compared to those earlier in the observation period.

Reviewer's Analysis: A plot of $\Delta\Delta$ QTc vs. drug concentrations is presented in Figure 4.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, i.e. mean changes ≤ 10 bpm (section 5.2.2). Therefore, no assessment of the QT/RR correction methodology is necessary, QTcF should be the correction method.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for R935788 (R788)

The statistical reviewer used mixed model with repeated measurements to analyze the Δ QTcF and $\Delta\Delta$ QTcF effect. The model includes treatment, time point, gender, treatment by time point, and gender by time point as fixed effects. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 7: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF on Day 4 for Treatment Group = 1: R788 100 mg BID

	Δ QTcF (ms) R788 100 mg (N=51)	Δ QTcF (ms) Placebo (N=52)	$\Delta\Delta$ QTcF (ms) R788 100 mg	
Time (hour)	LSmean	LSmean	LSmean	CI
-0.5	-1.4	-0.4	-1.0	(-4.9, 3.0)
0.5	-5.2	-3.9	-1.3	(-5.2, 2.6)
1	-3.4	-2.5	-0.9	(-4.9, 3.0)
2	-2.5	-2.2	-0.3	(-4.2, 3.6)
3	-4.4	-3.2	-1.1	(-5.1, 2.8)
3.5	-2.3	-1.4	-0.9	(-4.9, 3.0)
4	-2.8	-2.7	-0.1	(-4.0, 3.8)
6	-6.5	-6.4	-0.1	(-4.0, 3.9)
8	-6.6	-7.1	0.5	(-3.4, 4.4)
12	-6.6	-6.8	0.2	(-3.7, 4.1)
16	-4.4	-4.3	-0.1	(-4.0, 3.8)
23.5	-3.3	-3.5	0.2	(-3.8, 4.1)

Table 8: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF on Day 4 for Treatment Group = 2: R788 300 mg BID

	Δ QTcF (ms) R788 300 mg (N=52)	Δ QTcF (ms) Placebo (N=52)	$\Delta\Delta$ QTcF (ms) R788 300 mg	
Time (hour)	LSmean	LSmean	LSmean	CI
-0.5	-0.8	-0.4	-0.4	(-4.3, 3.5)
0.5	-4.8	-3.9	-0.9	(-4.8, 3.0)
1	-3.5	-2.5	-1.0	(-4.9, 2.9)
2	-2.0	-2.2	0.3	(-3.7, 4.2)
3	-1.8	-3.2	1.4	(-2.5, 5.3)
3.5	-0.1	-1.4	1.2	(-2.7, 5.1)
4	-1.8	-2.7	0.9	(-3.0, 4.8)
6	-6.5	-6.4	-0.1	(-4.0, 3.8)
8	-6.2	-7.1	0.9	(-3.0, 4.8)
12	-4.4	-6.8	2.4	(-1.5, 6.3)
16	-0.9	-4.3	3.4	(-0.5, 7.3)
23.5	1.8	-3.5	5.2	(1.3, 9.2)

The largest upper bounds of the 2-sided 90% CI for the mean differences between R788 100 mg BID and placebo, and between R788 300 mg BID and placebo were 4.4 ms and 9.2 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 10.0 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 8.6 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin

Time (hour)	Δ QTcF (ms) Moxifloxacin 400 mg (N=53)	Δ QTcF (ms) Placebo (N=52)	$\Delta\Delta$ QTcF (ms) Moxifloxacin 400 mg		
	LSmean	LSmean	LSmean	CI	Adjust 90% CI*
0.5	2.8	-3.9	6.7	(2.8, 10.6)	(1.4, 12.0)
1	8.3	-2.5	10.8	(6.9, 14.6)	(5.5, 16.1)
2	9.5	-2.2	11.7	(7.8, 15.6)	(6.4, 17.0)
3	10.7	-3.2	13.9	(10.0, 17.8)	(8.6, 19.2)
3.5	11.4	-1.4	12.8	(8.9, 16.6)	(7.5, 18.1)
4	9.9	-2.7	12.5	(8.6, 16.4)	(7.2, 17.8)
6	2.4	-6.4	8.8	(5.0, 12.7)	(3.5, 14.1)
8	2.6	-7.1	9.7	(5.9, 13.6)	(4.4, 15.1)
12	2.0	-6.8	8.8	(4.9, 12.7)	(3.5, 14.1)
16	3.0	-4.3	7.4	(3.5, 11.2)	(2.1, 12.7)
23.5	3.2	-3.5	6.7	(2.8, 10.6)	(1.4, 12.0)

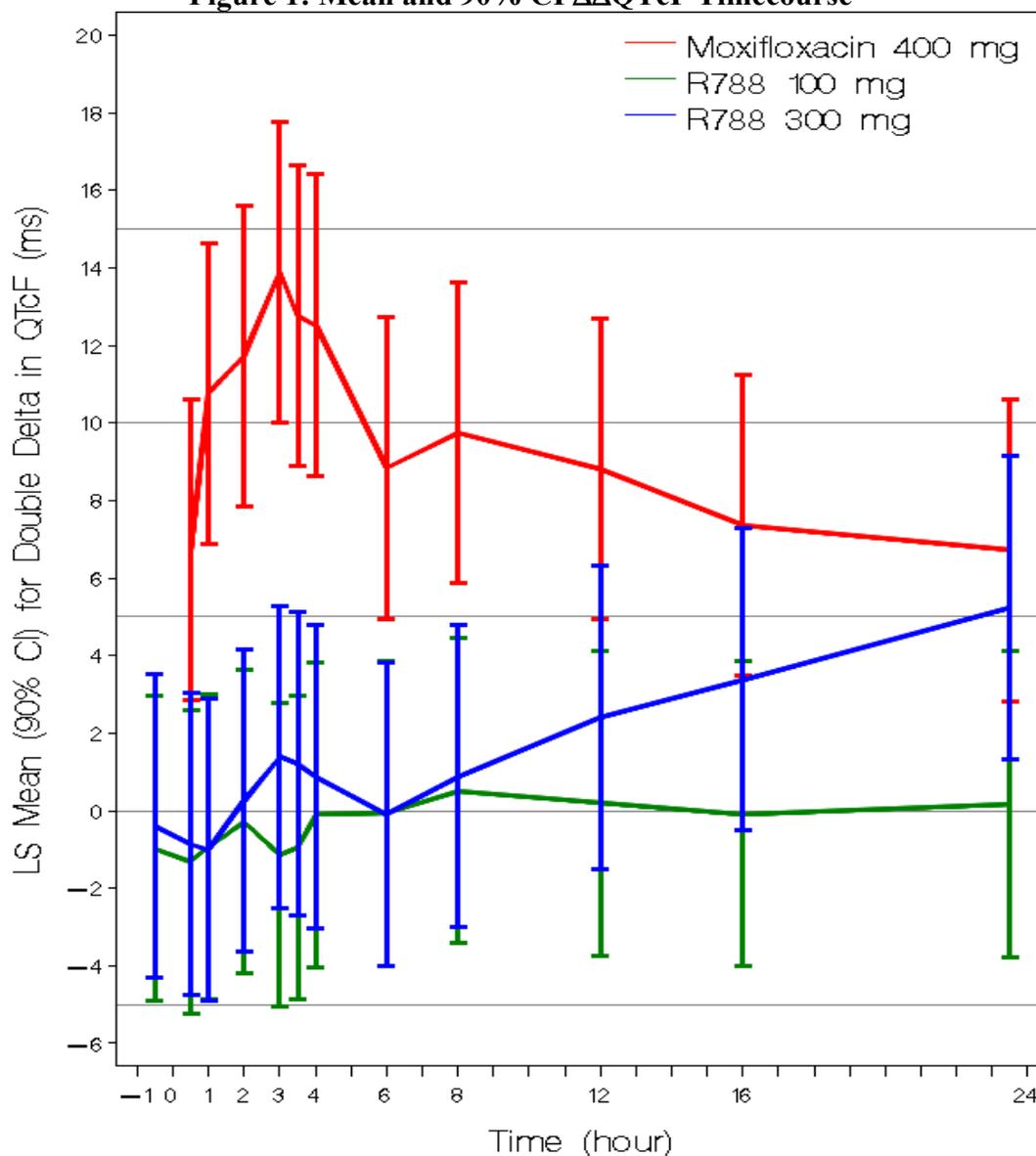
* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 4 time points around moxifloxacin C_{max} .

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

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

(Note: CIs are all unadjusted including moxifloxacin)

Figure 1: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

Treatment Group	Total N		QTcF ≤ 450 ms		450 $<$ QTcF ≤ 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	206	2512	203 (98.5%)	2503 (99.6%)	3 (1.5%)	9 (0.4%)

Treatment Group	Total N		QTcF≤450 ms		450<QTcF≤480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	51	612	51 (100%)	612 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	52	570	50 (96.2%)	563 (98.8%)	2 (3.8%)	7 (1.2%)
R788 100 mg	50	596	50 (100%)	596 (100%)	0 (0.0%)	0 (0.0%)
R788 300 mg	52	621	51 (98.1%)	617 (99.4%)	1 (1.9%)	4 (0.6%)

Table 11 lists the categorical analysis results for Δ QTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 11: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Δ QTcF≤30 ms		30< Δ QTcF≤60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	50	596	50 (100%)	596 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	52	569	50 (96.2%)	567 (99.6%)	2 (3.8%)	2 (0.4%)
R788 100 mg	50	594	50 (100%)	594 (100%)	0 (0.0%)	0 (0.0%)
R788 300 mg	51	605	51 (100%)	605 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

Similar statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest placebo-corrected mean changes from baseline in HR ($\Delta\Delta$ HR) were -3.2 bpm with a 90% CI of -5.8 bpm to -0.7 bpm for R788 100 mg BID and -7.7 bpm with a 90% CI of -10.6 bpm to -4.8 bpm for R788 300 mg BID. An HR lowering effect was observed for both doses.

The outlier analysis results for HR are presented in Table 13.

Table 12: Analysis Results of Δ HR and $\Delta\Delta$ HR on Day 4

	R788 100 mg (N=51)			R788 300 mg (N=52)		
	Δ HR (bpm)		$\Delta\Delta$ HR (bpm)	Δ HR (bpm)		$\Delta\Delta$ HR (bpm)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
-0.5	-4.2	-2.9	-1.3 (-3.7, 1.0)	-9.1	-2.9	-6.2 (-8.5, -3.8)
0.5	-5.3	-3.2	-2.1 (-4.6, 0.4)	-8.9	-3.2	-5.7 (-8.2, -3.3)
1	-3.7	-1.9	-1.8 (-4.3, 0.7)	-9.0	-1.9	-7.0 (-9.6, -4.5)
2	-3.8	-2.5	-1.2 (-3.6, 1.1)	-8.5	-2.5	-6.0 (-8.3, -3.6)
3	-3.2	-1.9	-1.3 (-3.8, 1.3)	-7.8	-1.9	-5.9 (-8.4, -3.3)
3.5	-3.5	-0.4	-3.0 (-5.5, -0.5)	-7.3	-0.4	-6.8 (-9.3, -4.4)
4	-2.9	0.3	-3.2 (-5.8, -0.7)	-7.0	0.3	-7.3 (-9.8, -4.7)
6	3.3	6.2	-2.9 (-5.9, -0.0)	-1.5	6.2	-7.7 (-10.6, -4.8)
8	0.8	2.0	-1.3 (-4.0, 1.5)	-4.6	2.0	-6.6 (-9.3, -3.9)
12	6.0	7.7	-1.7 (-4.6, 1.2)	2.4	7.7	-5.3 (-8.2, -2.4)
16	2.1	3.4	-1.3 (-4.2, 1.6)	-3.5	3.4	-6.9 (-9.7, -4.1)
23.5	2.2	2.7	-0.5 (-3.4, 2.4)	-2.7	2.7	-5.4 (-8.3, -2.6)

Table 13: Categorical Analysis for HR

	Total N	HR \leq 100 bpm	HR $>$ 100 bpm	HR $>$ 45 bpm	HR \leq 45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline/Predose	206	203 (98.5%)	3 (1.5%)	192 (93.2%)	14 (6.8%)
Placebo	51	51 (100%)	0 (0.0%)	47 (92.2%)	4 (7.8%)
Moxifloxacin 400 mg	52	50 (96.2%)	2 (3.8%)	52 (100%)	0 (0.0%)
R788 100 mg	50	50 (100%)	0 (0.0%)	43 (86.0%)	7 (14.0%)
R788 300 mg	52	52 (100%)	0 (0.0%)	40 (76.9%)	12 (23.1%)

5.2.3 PR Analysis

Similar statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest placebo-corrected mean changes from baseline in PR ($\Delta\Delta\text{PR}$) were 8.1 ms with a 90% CI of 3.5 ms to 12.7 ms for R788 100 mg BID and 11.0 ms with a 90% CI of 6.4 ms to 15.6 ms for R788 300 mg BID.

The outlier analysis results for PR are presented in Table 15.

Table 14: Analysis Results of ΔPR and $\Delta\Delta\text{PR}$ on Day 4

Time (hour)	R788 100 mg (N=51)			R788 300 mg (N=52)		
	ΔPR (ms)		$\Delta\Delta\text{PR}$ (ms)	ΔPR (ms)		$\Delta\Delta\text{PR}$ (ms)
	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
-0.5	7.0	1.0	6.0 (1.3, 10.8)	7.1	1.0	6.1 (1.4, 10.8)
0.5	6.5	0.9	5.6 (1.0, 10.3)	7.5	0.9	6.6 (2.0, 11.2)
1	6.0	0.1	5.9 (0.8, 11.0)	7.6	0.1	7.5 (2.4, 12.6)
2	6.9	-1.1	8.0 (3.0, 13.0)	8.4	-1.1	9.5 (4.5, 14.5)
3	6.3	-1.8	8.1 (3.5, 12.7)	9.2	-1.8	11.0 (6.4, 15.6)
3.5	5.2	-1.6	6.8 (2.0, 11.7)	7.8	-1.6	9.4 (4.5, 14.2)
4	4.3	-1.5	5.7 (1.1, 10.4)	7.5	-1.5	9.0 (4.3, 13.6)
6	1.2	-3.6	4.8 (0.4, 9.2)	3.8	-3.6	7.3 (3.0, 11.7)
8	1.4	-2.2	3.6 (-0.8, 8.0)	3.5	-2.2	5.7 (1.3, 10.1)
12	0.7	-2.2	2.9 (-1.5, 7.3)	4.0	-2.2	6.3 (1.9, 10.7)
16	4.7	-1.0	5.6 (1.1, 10.2)	5.8	-1.0	6.8 (2.3, 11.3)
23.5	2.1	-2.6	4.7 (0.0, 9.4)	5.6	-2.6	8.2 (3.5, 12.8)

Table 15: Categorical Analysis for PR

Treatment Group	Total N		PR \leq 200 ms		200<PR \leq 220 ms		PR>220 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	206	2512	199 (96.6%)	2483 (98.8%)	6 (2.9%)	21 (0.8%)	1 (0.5%)	8 (0.3%)
Placebo	51	612	51 (100%)	612 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Treatment Group	Total N		PR≤200 ms		200<PR≤220 ms		PR>220 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Moxifloxacin 400 mg	52	570	51 (98.1%)	560 (98.2%)	1 (1.9%)	10 (1.8%)	0 (0.0%)	0 (0.0%)
R788 100 mg	50	596	48 (96.0%)	584 (98.0%)	2 (4.0%)	12 (2.0%)	0 (0.0%)	0 (0.0%)
R788 300 mg	52	621	50 (96.2%)	617 (99.4%)	2 (3.8%)	4 (0.6%)	0 (0.0%)	0 (0.0%)

5.2.4 QRS Analysis

Similar statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The effect of R788 on QRS was clinically small and statistically insignificant at almost all time points.

The outlier analysis results for QRS are presented in Table 17.

Table 16: Analysis Results of Δ QRS and $\Delta\Delta$ QRS on Day 4

Time (hour)	R788 100 mg (N=51)			R788 300 mg (N=52)		
	Δ QRS (ms)		$\Delta\Delta$ QRS (ms)	Δ QRS (ms)		$\Delta\Delta$ QRS (ms)
	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
-0.5	-0.7	-1.6	0.9 (-1.3, 3.1)	-0.1	-1.6	1.5 (-0.7, 3.7)
0.5	-0.2	-1.0	0.8 (-1.3, 2.9)	0.4	-1.0	1.4 (-0.7, 3.6)
1	-0.6	-1.1	0.6 (-1.5, 2.7)	0.1	-1.1	1.2 (-0.9, 3.3)
2	-0.5	-1.6	1.1 (-1.1, 3.3)	0.1	-1.6	1.7 (-0.5, 3.9)
3	-1.0	-1.6	0.6 (-1.6, 2.8)	-0.1	-1.6	1.6 (-0.6, 3.7)
3.5	-0.9	-1.5	0.5 (-1.7, 2.8)	-0.1	-1.5	1.4 (-0.9, 3.6)
4	-1.1	-1.8	0.7 (-1.5, 2.8)	-0.5	-1.8	1.2 (-0.9, 3.4)
6	-1.0	-1.6	0.6 (-1.5, 2.8)	-0.2	-1.6	1.4 (-0.7, 3.6)
8	-1.4	-2.2	0.7 (-1.4, 2.9)	-0.3	-2.2	1.8 (-0.3, 4.0)
12	-0.8	-1.9	1.0 (-1.2, 3.3)	0.1	-1.9	2.0 (-0.2, 4.2)
16	-0.8	-2.1	1.2 (-1.0, 3.5)	0.5	-2.1	2.5 (0.3, 4.8)
23.5	-0.2	-1.1	0.9 (-1.4, 3.1)	0.4	-1.1	1.5 (-0.7, 3.8)

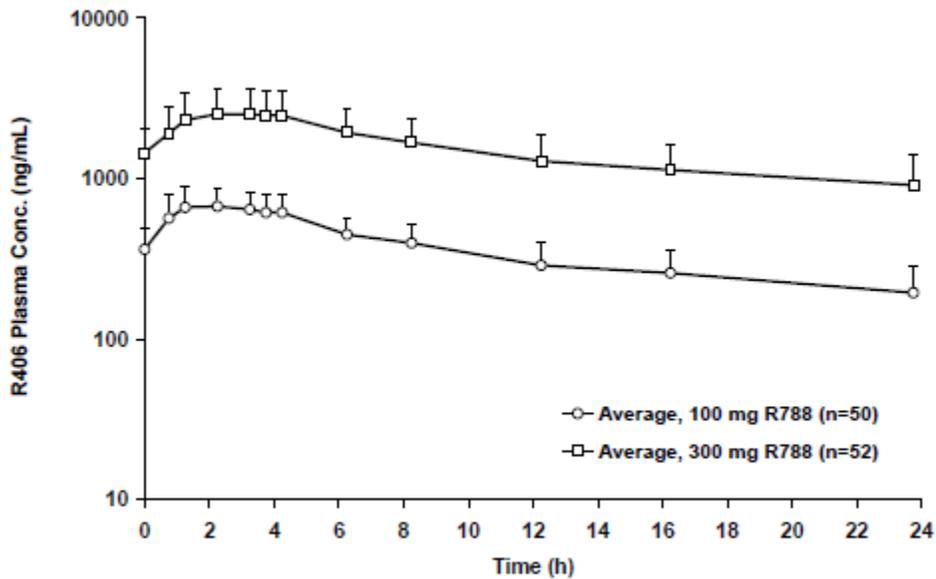
Table 17: Categorical Analysis for QRS

Treatment Group	Total N		QRS≤110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline/Predose	206	2512	198 (96.1%)	2443 (97.3%)	8 (3.9%)	69 (2.7%)
Placebo	51	612	49 (96.1%)	591 (96.6%)	2 (3.9%)	21 (3.4%)
Moxifloxacin 400 mg	52	570	51 (98.1%)	559 (98.1%)	1 (1.9%)	11 (1.9%)
R788 100 mg	50	596	49 (98.0%)	591 (99.2%)	1 (2.0%)	5 (0.8%)
R788 300 mg	52	621	49 (94.2%)	596 (96.0%)	3 (5.8%)	25 (4.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

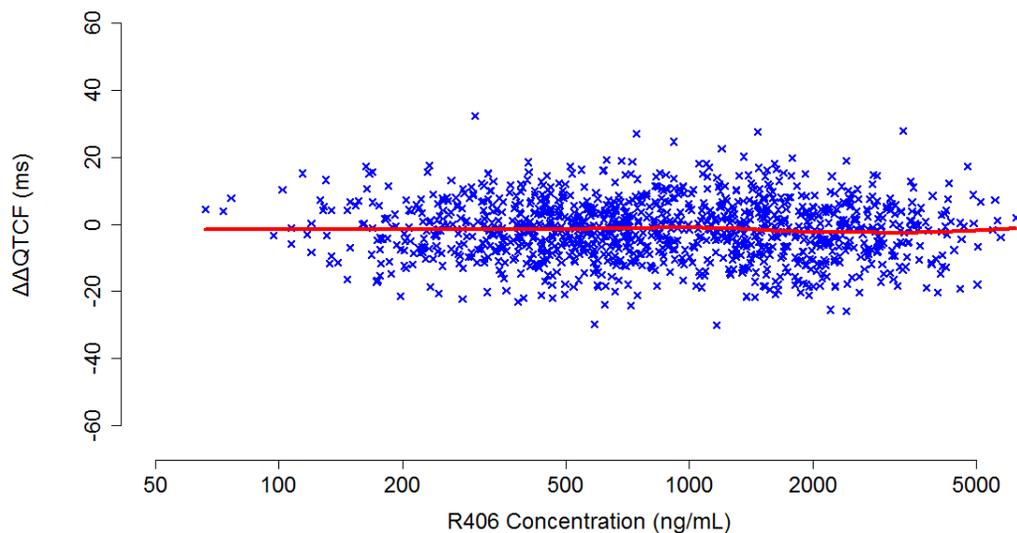
The mean (±SD) plasma R406 concentration-time profile is illustrated in Figure 2.

Figure 2: Mean (±SD) plasma R406 concentration-time profiles on Day 4 following twice daily administration of 100 mg (open circles) and 300 mg (open squares) of Fostamatinib in healthy volunteers



The relationship between $\Delta\Delta\text{QTcF}$ and plasma R406 concentrations is visualized in Figure 3 with no evident exposure-response relationship.

Figure 3: $\Delta\Delta\text{QTcF}$ vs. Plasma R406 concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

Two subjects (1 in each in the placebo and 300 mg dose arms) experienced syncope of moderate severity. Both AEs resolved without treatment discontinuation.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No changes in the QRS interval were observed and a mild dose-dependent increase in PR was observed (section 5.2.3), however, there no subjects had PR >220 ms in either treatment arm (Table 14).

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

This version of highlights of clinical pharmacology was submitted during protocol review

	(b) (4)
Therapeutic dose	100 mg BID of R788 for the RA (rheumatoid arthritis) study and 150-200 mg BID for the ITP (immune thrombocytopenic purpura) and lymphoma study.
Maximum tolerated dose	250 mg BID of R788 (C-935788-003), and 300 mg BID of R406 (C-940406-001)
Principal adverse events	Dose related neutropenia, diarrhea, elevations in blood pressure, mild elevations of liver transaminase
Maximum dose tested	Single Dose R406: 600 mg R406 in (b) (4) solution R788: 400 mg R788 (b) (4) suspension (C-935788-001) R788: 300 mg R788 Sodium tablet (C-935788-008)

	Multiple Dose	R406: 300 mg BID dose of R406 in (b) (4) solution (C-940406-001) R788: 250 mg BID dose of R788 (b) (4) suspension (C-935788-003); Lymphoma study C-935788-009 R788 Sodium tablet
Exposures Achieved at Maximum Tested Dose	Single Dose	R406 (600mg, C-940406-001): Cmax: 3920 ±888 (22.6%) ng/mL AUC _{0-∞} : 36600 ±7760 (21.2%) ng*h/mL R788 (b) (4) suspension (400 mg, C-935788-001): Cmax: 1220 ±317 (26.0%) ng/mL AUC _{0-∞} : 13400 ± 4360 (32.7%) ng*h/mL R788 Sodium tablet (300 mg, C-935788-008): Cmax: 1690 ±762 (45.0%) ng/mL AUC _{0-∞} : 15300 ±5870 (38.4%) ng*h/mL
	Multiple Dose	R406 (b) (4) solution (300mg, C-940406-001) Cmax: 7630 ±2340 (30.8%) ng/mL AUC _{ss} : 106000 ±24900 (23.5%) ng*h/mL R788 (b) (4) suspension (250mg, C-935788-003): Cmax: 2020 ±832 (41.2%) ng/mL AUC _{ss} : 29600 ±11700 (39.5%) ng*h/mL R788 Sodium tablet (200mg BID, Lymphoma study C-935788-009): Cmax: 1754 ±900 (51.3%) ng/mL Estimated AUC _{ss} : 24500 ±11900 (48.5%) ng*h/mL
Range of linear PK	Single Dose: Dose linearity from 100 to 300 mg of R788 Sodium tablet (C-935788-008) Multiple Dosing: Dose linearity after BID dosing of R788 was found at 100, 160, and 250 mg doses of R788 (b) (4) suspension (Linearity was assessed based on cross study calculation, C-935788-004, C-935788-	

	001, and C-935788-003). Dose linearity after BID dosing of R406 was found at 100, and 200 mg doses of R406 (b)(4) solution. Increasing the dose to 300 mg BID of R406, caused higher than dose-proportional increases in C _{max} and AUC ₀₋₂₄ .	
Accumulation at steady state	Based on PK data obtained from single dose tablet study, the accumulation of R406 at steady state is estimated to be 1.69.	
Metabolites	Human mass balance study has not yet been performed. Analysis of plasma samples by LC/MS showed that no observed metabolite represented more than 10% of the parent drug systemic exposure. Direct N-glucuronides of R406 were the predominant metabolites observed in plasma. Activity of these N-glucuronides has not been determined.	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability in human could not be calculated due to lack of IV data. In animals, absolute bioavailability of R788 exceeded 40%.
	T _{max}	Median T _{max} of R406 in human after dosing of R788 sodium tablet (C-935788-008) was 1.5h (range: 1-4 h)
Distribution	V _d /F or V _d	V _d /F estimates from single oral doses of R788 sodium tablet (C-935788-008) at 100, 200mg, and 300 mg were 509 ±210 (41%)L, 384 ±152 (40%)L, 480 ±111(23%)L, respectively.
	% bound	98.2%; linear over the range of of 100 to 4000 ng/mL
Elimination	Route	Primary route of elimination in humans is not presently known. No unmetabolized R406 was observed in urine of patients from study C-935788-004. Major metabolites in urine were direct N-glucuronides.
	Terminal t _{1/2}	The average terminal half-life of R406 after dosing of R788 Na tablet (C-935788-008) is 17.2 h (41%) (range: 8.6 to 44.8 h)
	CL/F or CL	CL/F estimates from single oral doses of R788 Na tablets (C-935788-008) at 100, 200mg, and 300 mg were 341 ±105 (31%)mL/min, 254 ±83 (33%) mL/min, 366 ±126(35%) mL/min, respectively.
Intrinsic Factors	Age	Data are not available
	Sex	Data are not available
	Race	Data are not available

	Hepatic & Renal Impairment	Data are not available
Extrinsic Factors	Drug interactions	In C-935788-001, AUC _{0-∞} after a single 80 mg dose of R788 increased two-fold (3770 to 7770 ng*hr/mL) when Ketoconazole was co-administered. Cmax increased by 39% (328 to 454 ng/mL)
	Food Effects	R788 Sodium tablets co-administered with a high-fat and high-caloric meal increased the Tmax (from 1.39h to 3.22h) and lowered the Cmax (decreased from 605 ng/mL to 363 ng/mL) when compared with R788 tablets taken under fasting condition. No effect on AUC 0-∞.
Expected High Clinical Exposure Scenario	<p>Human volunteers dosed with 250 mg po bid (extensive sampling) achieved a mean Cmax of 2020 (± 832) ng/mL. Lymphoma patients (limited sampling) dosed with 200 mg po bid achieved a mean Cmax of 1754 (± 832) ng/mL.</p> <p>We estimate that a dose of 300 mg po bid would achieve a mean Cmax of 2300 (± 1100) ng/mL.</p>	

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/s/

JANELL E CHEN
11/29/2017

QIANYU DANG
11/29/2017

GIRISH K BENDE
11/29/2017

LARS JOHANNESSEN
11/29/2017

MICHAEL Y LI
11/29/2017

CHRISTINE E GARNETT
11/29/2017

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

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

Memorandum

Date: November 09, 2017

To: Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager,
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Carole Broadnax, R.Ph., PharmD, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for Tavalisse (fostamatinib disodium hexahydrate) tablets, for oral use

NDA: 209299

In response to DHP's consult request dated May 12, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for Tavalisse.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received via a Sharepoint link sent by electronic mail from DHP (Rachel McMullen) on November 1, 2017. OPDP's comments for the draft PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on November 08, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received via a Sharepoint link sent by electronic mail from DHP on November 1, 2017 and our comment is provided below.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
11/09/2017

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

PATIENT LABELING REVIEW

Date: November 8, 2017

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

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

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

From: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD, RPh
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TAVALISSE (fostamatinib disodium hexahydrate)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209299

Applicant: Rigel Pharmaceuticals, Inc.

1 INTRODUCTION

On April 17, 2017, Rigel Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 209299 for TAVALISSE (fostamatinib disodium hexahydrate) tablets. This submission proposes an indication for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to previous treatment.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on May 12, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TAVALISSE (fostamatinib disodium hexahydrate) tablets.

2 MATERIAL REVIEWED

- Draft TAVALISSE (fostamatinib disodium hexahydrate) tablets PPI received on April 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 2, 2017.
- Draft TAVALISSE (fostamatinib disodium hexahydrate) tablets Prescribing Information (PI) received on April 17, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 2, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI we:

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

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
11/08/2017

ROBERT L NGUYEN
11/08/2017

BARBARA A FULLER
11/08/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review: October 19, 2017
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 209299
Product Name and Strength: Tavalisse (fostamatinib) tablet
100 mg, 150 mg
Product Type: Single-Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Rigel Pharmaceuticals
Submission Date: April 17, 2017 and July 19, 2017
OSE RCM #: 2017-757
DMEPA Safety Evaluator: Leeza Rahimi, Pharm.D.
DMEPA Team Leader: Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Rigel Pharmaceuticals submitted a New Drug Application (NDA) 209299 for Tavalisse (fostamatinib), 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. Tavalisse (fostamatinib) tablets will be available in two different strengths of 100 mg and 150 mg.

The Division of Hematology Products (DHP) requested that we review the labels and labeling of the product and evaluate for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the Prescribing Information (PI), carton and container labels for areas of vulnerability in regards to medication error. Our review identified areas in the labels and labeling that can be improved to increase readability and prominence of important information.

We provide our recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the PI, container label and labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information (FPI):

1) Section 2 Dosage and Administration:

- a) Please revise all instances of symbols to their intended meanings. For example, change “≥” to read “greater or equal” to prevent misinterpretation or confusion of the symbol.

b) Section 2.2 Monitoring:

- i. See 1-a.

4.2 RECOMMENDATIONS FOR RIGEL PHARMACEUTICALS

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

A. Container Labels:

- 1) As currently presented the NDC is denoted by a placeholder (00000-000-00). We request that you add the intended numbers to the container labels in accordance with 21 CFR 201.2. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668), nor is using the identical product code for injectable products containing the same concentration of drug but different total volumes. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.
- 2) Revise the symbol “≥” to read to its intended meaning to avoid misinterpretation. For example, revise “≥ 18 years of age” to read “Greater or equal to 18 years of age”.^a

^a Draft Guidance: Container and Carton, April 2013 (lines 242-244, 479)

- 3) Consider reorienting the barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature.^b
- 4) Revise the storage information to be consistent with the recommendation in the Prescribing Information. Revise the information to read: “Store at room temperature, 68°F to 77°F (20°C to 25°C).

^b Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tavalisse (fosamatinib) that Rigel Pharmaceuticals submitted on April 17, 2017, May 22, 2017, and July 19, 2017.

Table 2. Relevant Product Information for Tavalisse	
Initial Approval Date	N/A
Active Ingredient	Fosamatinib
Indication	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.
Route of Administration	Oral
Dosage Form	Tablets
Strength	100 mg, 150 mg
Dose and Frequency	<ul style="list-style-type: none">• 100 mg twice daily. After 4 weeks, increase to 150 mg twice daily, if needed to achieve platelet count greater than or equal to $50 \times 10^9/L$ as necessary to reduce the risk of bleeding.• For adverse reactions, consider dose reduction, interruption of treatment, or discontinuation.
How Supplied	Bottles of 60 count. Professional Samples are available in 30 and 60 count.
Storage	Store at room temperature, (b) (4) Do not remove desiccants.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 19, 2017, we searched DMEPA's previous reviews using the terms, Tavalisse, and Fosamatinib. Our search identified zero labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Tavalisse (fosamatinib) labels and labeling submitted by Rigel Pharmaceuticals on April 17, 2017, May 22, 2017, and July 19, 2017.

- Container label
- Professional Sample Labels
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

Container Labels: 100 mg:



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LEEZA RAHIMI
10/19/2017

HINA S MEHTA
10/20/2017

MEMORANDUM

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

DATE: September 22, 2017

TO: Richard Pazdur, MD
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)

Edward M. Cox, MD, MPH
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products (OAP)

FROM: Amanda Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

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

SUBJECT: Routine inspection of Quintiles Phase One Services,
Overland Park, KS.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study C788-054 (NDA 209299) conducted at Quintiles Phase One Services, Overland Park, KS.

No significant deficiencies were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I found the data from the audited study C788-054 reliable. Thus, I recommend that the data from study C788-054 and other studies of similar design be accepted for further Agency review. Additionally, based on the findings from the current inspection I recommend that the data from study (b) (4) (NDA (b) (4)) be accepted for further Agency review.

Inspected Studies:

NDA 209299

Study Number: C788-054 (Protocol C-935788-054)

Study Title: "An Open-Label, Single-Center, Randomized,
Partial Replicate, 3-Way Crossover Study to
Assess the Bioequivalence of Orange Film-Coated
Patheon and AZN 150 mg Fostamatinib Tablets"

Dates of conduct: 04/28/2016 - 07/01/2016

Following study was not audited during the inspection:



Clinical site: Quintiles Phase One Services
6700 W 115th Street
Overland Park, KS

ORA investigator Lori Gioia (BIMOW-GRP4) inspected Quintiles
Phase One Services, Overland Park, KS from July 18-21, 2017.

The inspection included a thorough examination of study records
(paper-based and electronic), subject records, informed consent
process, protocol compliance, institutional review board
approvals, sponsor and monitor correspondence, test article
accountability and storage, randomization, adverse events, and
case report forms.

At the conclusion of the inspection, investigator Gioia did not
observe any objectionable conditions and did not issue Form FDA
483 to the clinical site.

Conclusion:

After reviewing the inspectional findings, I found the data from
the audited studies to be reliable. Therefore, I recommend that
the data from study C788-054 (NDA 209299) be accepted for
further review. In addition, based on the findings from the

current inspection, I recommend that the data from study (b) (4)
(NDA (b) (4)) should also be accepted for further Agency review.

Studies of similar design conducted between the last inspection
(July 2017) and the end of the current Surveillance Interval
should be accepted for review by the Agency without an
inspection.

Amanda, Ph.D.
Pharmacologist

Final Classification:

NAI- Quintiles Phase One Services
Overland Park, KS
FEI#: 3003854351

cc:
OTS/OSIS/Kassim/Kadavil/Haidar/Turner-Rinehardt/Fenty-
Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au

Draft: AL 09/21/2017
Edit: GB 9/22/2017; AD 09/22/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS-Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/Clinical Sites/Quintiles
Phase One Services, Overland Park, KS/NDA 209299_Tevalisse

OSIS File #: BE 7542

FACTS: 11751187

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/s/

AMANDA E LEWIN
09/22/2017

GOPA BISWAS
09/22/2017

ARINDAM DASGUPTA
09/22/2017

CLINICAL INSPECTION SUMMARY

Date	September 13, 2017
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Hyon-Zu Lee, Pharm.D., Medical Officer Kathy Robie-Suh, M.D., Ph.D. Clinical Team Leader Rachel McMullen, M.P.H., M.H.A., Regulatory Project Manager Division of Hematology Products
NDA	209299
Applicant	Rigel Pharmaceuticals, Inc.
Drug	fostamatinib
NME	Yes
Therapeutic Classification/Status	IgG receptor signaling blocker via splenic tyrosine kinase (SYK) system
Proposed Indication	Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP)
Consultation Request Date	May 12, 2017
Summary Goal Date	November 15, 2017
Action Goal Date	February 16, 2018
PDUFA Date	February 17, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Bussel and Mayer) were selected by the Division of Hematology Products (DHP) for inspection in support of NDA 209299. Rigel Pharmaceuticals, Inc., the sponsor of the study was also inspected. The study data from these clinical sites as reported by the sponsor are considered to be reliable in support of the requested indication.

The preliminary regulatory classification for Dr. Mayer is No Action Indicated (NAI). The final regulatory classification for Dr. Bussel is No Action Indicated (NAI). The preliminary regulatory classification for the inspection of Rigel Pharmaceuticals, Inc. is No Action Indicated (NAI).

2. BACKGROUND

Fostamatinib blocks IgG receptor signaling in both macrophages and B cells via the SYK (spleen tyrosine kinase) kinase system, making it a targeted therapeutic candidate for the treatment of patients with immune thrombocytopenia.

The sponsor submitted NDA 209299 for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who had an insufficient response to a previous treatment. In review of this NDA, CDER/OHOP/DHP requested inspection of two clinical investigators and sponsor for replicate studies, Study C-935788-047 and Study C-935788-048.

Study C-935788-047 and Study C-935788-048

Study C-935788-047 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy of 24 weeks of treatment with fostamatinib versus placebo in achieving a stable platelet count in subjects with persistent/chronic ITP.

The primary objective of this study was to establish the efficacy of fostamatinib disodium (fostamatinib) as compared with placebo in achieving a stable platelet response in subjects with persistent/chronic immune thrombocytopenic purpura (ITP).

Efficacy was measured by platelet counts performed at biweekly study visits, and frequency and severity of bleeding according to the ITP Bleeding Score (IBLS) and World Health Organization (WHO) bleeding scale over the 24-week study period. The primary study endpoint was a stable platelet response by Week 24 defined as having a platelet count of at least 50,000 per microliter on at least four of the last six scheduled visits over Weeks 14 to 24.

Study C-935788-048 was a replicate study, similar to C-935788-047.

Study C-935788-047 enrolled 76 subjects. There were 36 study centers that enrolled at least one subject. The first subject enrolled on July 14, 2014 and the last subject completed on April 21, 2016. The sponsor reported that the study demonstrated statistically significant efficacy for the primary efficacy endpoint.

Study C-935788-048 enrolled 74 study subjects. There were 23 study centers that enrolled at least one study subject. The first subject enrolled on January 9, 2015 and the last subject completed on August 31, 2016. As reported by the sponsor, the study did not achieve statistical significance for the primary efficacy endpoint.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects	Inspection Dates	Classification
James Bussel, M.D. Cornell Medical College 525 East 68th Street, Room Payson-695 New York, NY USA 10065	C-935788-047 Site #63 7 total	June 26 to 30, 2017	NAI
Jiri Mayer, M.D. Fakultni nemocnice Brno Interni hematologicka a onkologicka klinika Jihalavska 20 Brno, Czech Republic 625 00	C-935788-048 Site #428 8 total	September 4 to 7, 2017	Pending: Preliminary NAI
Rigel Pharmaceuticals, Inc. 1180 Veterans Boulevard South San Francisco, CA 94080	Sponsor of: Protocol C-935788-047 Protocol C-935788-048	August 21 to 23, 2017	Pending: Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

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

Clinical Investigator**1. James Bussel, M.D./Study C-935788-047**

The inspection was conducted from July 26 to 30, 2017. A total of seven subjects were screened, and seven subjects were enrolled. There were four study subjects who developed progressive disease, and one additional subject who was lost to follow-up. Two study subjects completed the study. A comprehensive review of seven subjects' records enrolled at this site was conducted. Partial review for various source records was completed for all the enrolled study subjects.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Jiri Mayer, M.D./Study C-935788-048

The inspection was conducted from September 4 to 7, 2017. A total of 9 subjects were screened, and 8 subjects were enrolled. Five subjects discontinued from the study treatment because of the lack of response, and an additional study subject did not want to continue participation in this trial. Two subjects completed the study. An audit of all the subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

Sponsor

3. Rigel Pharmaceuticals, Inc.

This inspection was conducted from August 21 to 23, 2017.

The sponsor inspection included review of the following: clinical site set up, site management and monitoring, financial disclosures, and trial master file.

Monitoring plans and monitoring visit reports were reviewed. Review of the monitoring reports conducted by the contract research organization (CRO) for two clinical sites demonstrated that the sites received adequate periodic monitoring. IRB approvals, clinical site protocol deviations, and serious adverse event reporting were adequate.

A Form FDA 483 was not issued at the end of the inspection.

The sponsor appeared to maintain adequate oversight of the clinical trial.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.

Team Leader, Good Clinical Practice Assessment Branch

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Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.

Branch Chief, Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation

Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
09/13/2017

JANICE K POHLMAN
09/13/2017

KASSA AYALEW
09/14/2017



Inspection Assignment Memorandum

User Fee: Yes, PDUFA

Surveillance: Yes

Directed: No,

Application: Yes

Submission: Premarket Original

Entity: Contract Research Organization (CRO)

Date: 7/20/2017

From: Amanda Lewin, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: Division of Bioresearch Monitoring Operations West (BIMOW)-Division 2

Preannounce: No

Priority: Yes

ORA Due Date: 11/15/2017

Compliance Program: 7348.001 (BE)

Program Assignment Code: 48001A (NDA)

**Operation Code: 12 (Domestic)
31 (Sample Collection)**

Application Number: NDA 209299

Product Name: Tavalisse (Fostamatinib Tablets, 150 mg)

Sponsor: Rigel Pharmaceuticals, Inc., San Francisco, CA

Tel: 650-624-1144; aduliege@rigel.com

Study/Protocol Number: C788-054 (Protocol C-935788-054)

Center Participation: Yes or No

Joint Regulatory Agency Participation: Yes or No

Establishment(s) for inspection	FEI Number	FACTS Number
Quintiles Phase One Services 6700 W 115 th Street, Overland Park, Kansas 66211 POC: Dr. Lisa Vansaghi	3003854351 (b) (4)	11751187
Inspection History (optional)	Previous clinical inspections were conducted at the site in June 2014 and January 2016: Observations noted deviations from investigational plans and changes to research activity prior to IRB approval.	

Note	<p>Please contact the OSIS scientific point of contact (POC) at CDER-OSIS-SCIPOC-BE@fda.hhs.gov prior to the beginning of the inspection to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.</p> <p>Please follow the compliance program with emphasis on the specific instructions in the memorandum.</p> <p>If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov and cc CDER-OSIS-BEQ@fda.hhs.gov immediately.</p> <p>Send the following information to the respective email in the table.</p> <table border="1" data-bbox="492 1304 1292 1923" style="margin-left: auto; margin-right: auto;"> <tr> <td style="text-align: center;">Scientific questions/comments</td> <td style="text-align: center;">Not applicable</td> </tr> <tr> <td style="text-align: center;">Not applicable</td> <td style="text-align: center;">Inspection status updates</td> </tr> <tr> <td colspan="2" style="text-align: center;">Significant deviations found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data</td> </tr> <tr> <td style="text-align: center;">Not applicable</td> <td style="text-align: center;">EIR (when available in OSAR) Form FDA 483 and 483 responses</td> </tr> <tr> <td colspan="2" style="text-align: center;">Inspection findings at end of inspection</td> </tr> <tr> <td style="text-align: center;">Not applicable</td> <td style="text-align: center;">Post Inspection correspondence from establishment</td> </tr> </table>	Scientific questions/comments	Not applicable	Not applicable	Inspection status updates	Significant deviations found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data		Not applicable	EIR (when available in OSAR) Form FDA 483 and 483 responses	Inspection findings at end of inspection		Not applicable	Post Inspection correspondence from establishment
Scientific questions/comments	Not applicable												
Not applicable	Inspection status updates												
Significant deviations found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data													
Not applicable	EIR (when available in OSAR) Form FDA 483 and 483 responses												
Inspection findings at end of inspection													
Not applicable	Post Inspection correspondence from establishment												

If the endorsed EIR and exhibits are paper, send the documents to Angel Johnson, OSIS Project Specialist.

Ms. Angel Johnson
Project Specialist
FDA/CDER/OTS/OSIS
WO22 RM1471
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Important: All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct the inspection of the **clinical portion** of the following study(ies). Background materials are available in ECMS under the ORA folder.

IMPORTANT REMINDERS:

1. Inspections should be scheduled for no more than one week unless otherwise noted.
2. **A 100% audit of the studies is not required unless noted (refer to the DATA AUDIT CHECKLIST section of this memo). If specific audit instructions are not provided, please audit as much as possible during the one week inspection.**
3. If the assignment contains more than 3 studies, instructions to audit specific sections of the study will be included in the DATA AUDIT CHECKLIST section of this memo.
4. Please note that additional studies for the site may be added to the assignment no later than 2 weeks prior to the inspection start date. The additional studies may be added because more significant, complex or recent studies are received by OSIS, or specific study issues are identified after the initial assignment is issued. Addition of these additional studies **SHOULD NOT** extend the inspection duration at the site.

Do not reveal the studies to be inspected, drug names, or the study investigators to the site prior to the start of the inspection. You should provide this information during the inspection opening meeting. Please note that the inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of completed sections A and B of this memo to the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov.

(Refer to DATA AUDIT CHECKLIST in Section B-Clinical Data Audit for additional information.)

NDA 209299

Study #1: C788-054 (Protocol C-935788-054)
Study Title: An Open-Label, Single-Center, Randomized, Partial Replicate, 3-Way Crossover Study To Assess the Bioequivalence of Orange Film-Coated Pathteon And AZN 150 Mg Fostamiatinib Tablets

Clinical Site: Quintiles Phase One Services
Investigator: Lisa Vansaghi
of Subjects: 42

SECTION A – RESERVE SAMPLES

Reserve samples must be collected for Study C788-054. In addition, verify that the lot numbers on the reserve sample containers match those in the study report for the studies mentioned above.

For the reserve samples you will be collecting, take a photograph of the unblinded reserve sample containers (test, reference, and placebo, if applicable) showing the drug name, strength (or concentration), lot number, and expiration date, and exhibit in the EIR.

The recommended quantity of reserve samples (test and reference product) to be collected from each shipment is based on the dosage formulation and is shown below:

Dosage formulation	# of units to collect
Oral solid dosage forms (e.g., tablets, capsules)	30 units each test and reference
Topical creams, ointments, and gels	3 units each test and reference
Inhalers, pumps, and vials for injection	3 units each test and reference
Any dosage form in block design	1 Block (containing Kits of test and reference)

Collect a convenient quantity that has at least the amount specified above. For example, if tablets are kept in bottles of 100, collect one bottle. If tablets are kept in bottles of 10, collect three bottles. Do not open and subsample bottles.

Because these bioequivalence studies are subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the OSIS POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov immediately.
- If the reserve samples were stored at a third party site, (1) collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager; and (2) request the reserve samples to be shipped back to the site so that the samples can be collected during the inspection. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

David Keire, Ph.D.
Director
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist:

- Confirm that informed consent was obtained prior to the study procedures for all subjects enrolled in all studies.
- Audit the study records for all subjects enrolled in Study C788-054.
- Compare the randomization schedule with the Case Report Forms or dosing records and verify that 100% of the subjects received their intended treatment (i.e., test or reference) in each period.
- Compare the study report submitted to FDA with the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.

- Check reports for the subjects audited.
 - Number of subject records reviewed during the inspection: _____
 - Number of subjects screened at the site: _____
 - Number of subjects enrolled at the site: _____
 - Number of subjects completing the study: _____

- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

- Confirm that site personnel followed SOPs during study conduct.

- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.

- Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).

- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

- Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS scientific POC prior to commencement of the inspection. Therefore, **we request that the OSIS scientific POC be contacted at CDER-OSIS-SCIPOC-BE@fda.hhs.gov for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.**

If you issue Form FDA 483, please forward a copy to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov and cc CDER-OSIS-BEQ@fda.hhs.gov, as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

If the endorsed EIR and exhibits are in OSAR (or in another electronic format), send the email notification regarding the availability of the documents in OSAR to CDER-OSIS-BEQ@fda.hhs.gov.

If the endorsed EIR and exhibits are submitted in paper format, send the endorsed EIR and exhibits to the OSIS Project Specialist at the address below.

OSIS Project Specialist: Ms. Angel Johnson
Project Specialist
FDA/CDER/OTS/OSIS
WO22 RM1471
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Tel: 301-796-3374

Email cc:

ORA HQ BIMOW

OSIS/Kassim/Taylor/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov

OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Lewin

OSIS/DGDBE/Cho/Choi/Skelly/Au

Draft: AL 6/30/2017

Edit: GB 6/30/2017

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Quintiles Phase One Services, Overland Park, KS/NDA 209299_Tevalisse

OSIS file #: 7542

FACTS: (11751187)

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

/s/

AMANDA E LEWIN
07/20/2017

GOPA BISWAS
07/20/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209299 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: TAVALISSE™ Established/Proper Name: fostamatinib Dosage Form: tablet Strengths: 100 mg; 150 mg Route(s) of Administration: Oral		
Applicant: Rigel Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: April 15, 2017 Date of Receipt: April 17, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: April 17, 2018		Action Goal Date (if different): NA
Filing Date: June 16, 2017		Date of Filing Meeting: May 30, 2017
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): 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		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)			
Review Classification: <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher			
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division <i>(if OTC product)</i> :				
List referenced IND Number(s): <div style="background-color: #cccccc; width: 100px; height: 20px; margin: 5px 0;"></div> (b) (4) <ul style="list-style-type: none">• IND 074939 (immune (idiopathic) thrombocytopenia)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>	<input type="checkbox"/>	<input type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
<ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</p> <p>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; <u>and</u> (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</p>	<input type="checkbox"/>	<input type="checkbox"/>		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Applicant has Orphan Drug Designation for this indication and therefore they are exempt from PREA.
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Applicant has Orphan Drug Designation for this indication and therefore they are exempt from PREA.
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

8

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSL/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<ul style="list-style-type: none"> • QT-IRT consult submitted 5/24/17 • OSI consult (clinical inspections) submitted 5/15/17 • OSIS (bioequivalence) consult submitted 6/2/17 • OSE consult submitted 5/12/17
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): (b) (4) Clinical EOP2 Meeting: October 8, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 5, 2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div>	<input checked="" type="checkbox"/>			Carcinogenicity SPAs

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 31, 2017

BACKGROUND: DHP has received a new NME (NDA 209299) (fostamatinib) from Rigel Pharmaceuticals. This NME application will be in the PDUFA V “Program”. The applicant has submitted a request for a proprietary name of TAVALISSE and this is being reviewed by DMEPA.

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.”

The applicant has orphan designation for the above indication.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rachel McMullen	Y
	CPMS/TL:	Amy Baird	N
Cross-Discipline Team Leader (CDTL)	Kathy Robie Suh		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy			
Clinical	Reviewer:	Hyon Zu Lee	Y
	TL:	Kathy Robie Suh	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Runyan Jin	Y
	TL:	Qi Liu	Y
• Genomics	Reviewer:		

• Pharmacometrics	Reviewer:	Jee Eun Lee	Y
Biostatistics	Reviewer:	Stella Karuri	N
	TL:	Yuan Li Shen	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brian Cholewa	Y
	TL:	Chris Sheth	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Sherita McLamore Hines Anamitro Banerjee	N Y
	RBPM:	Teshara Bouie	Y
• Drug Substance	Reviewer:	Monica Cooper	Y
• Drug Product	Reviewer:	Mike Adams	Y
• Process	Reviewer:		
• Microbiology	Reviewer:	NA	
• Facility	Reviewer:	Steven Hertz	Y
• Biopharmaceutics	Reviewer:	Kaushal Dave	Y
		Okpo Eradiri	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Ruth Lidshore	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Rachael Conklin	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Leeza Rahimi	Y
	TL:	Hina Mehta	Y
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen	Y
	TL:	Elizabeth Everhart	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orenca	Y
	TL:	Janice Polhman	Y

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	
	TL:	Janice Pohlman	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees	<ul style="list-style-type: none"> DPV <ul style="list-style-type: none"> Lynda McCulley Saharat Patanavanich DEPI: <ul style="list-style-type: none"> Steve Bird Carolyn McCloskey OSE PM: Wana Manitpisitkul 		N
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease.
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable

<p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	NA
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, MD, Office Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): September 15, 2017

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: April 2016

NDA 209299/Tavalisse (fostamatinib)

Applicant: Rigel Pharmaceuticals, Inc.
Receipt Date: April 17, 2017

TASK	21ST CENTURY REVIEW TIMELINE
Applicant Orientation	May 19, 2017
Filing Meeting	May 30, 2017
Filing Date (Day 60)- Communicate review issues Day 74	June 16, 2017 June 30, 2017
Mid-cycle Meeting Mid-cycle Communication (TCON)	September 15, 2017 September 28, 2017
Labeling Meetings	October 5, 11, 19, 25 November 2, 30
Pre-Meeting for LCM Late-cycle Meeting with Applicant	December 4, 2017 January 11, 2018
Primary Reviews Completed	December 15, 2017
Wrap-up Meeting	February 26, 2018
Secondary Reviews Discipline Letters	December 21, 2017 December 21, 2017
Send proposed Labeling/PMC/PMR/REMS	November 15, 2017
Complete Cross Discipline TL Review	February 28, 2018
Compile and Circulate action letter and action package	March 30, 2018
Complete Office Director Review and Sign-off PDUFA Goal Date	April 17, 2018

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
06/29/2017

MARA B MILLER
06/29/2017

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

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

Application: NDA 209299

Application Type: New NDA

Drug Name(s)/Dosage Form(s): TAVALISSE™ (fostamatinib); tablet; 100 mg, 150 mg

Applicant: Rigel Pharmaceuticals, Inc.

Receipt Date: April 17, 2017

Goal Date: April 17, 2018

1. Regulatory History and Applicant's Main Proposals

DHP has received a new NME (NDA 209299) (fostamatinib) from Rigel Pharmaceuticals. This NME application will be in the PDUFA V "Program". The applicant has submitted a request for a proprietary name of TAVALISSE and this is being reviewed by DMEPA.

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."

The applicant has orphan designation for the above indication.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. There should be ½ inch margins on all sides and between columns.
2. Date and page numbers should be removed from the document.
3. Please remove space between the HL heading and the HL limitation statement. Likewise, please remove space between product title and initial U.S. Approval.
4. The numerical identifiers in parenthesis should not be bolded.

Selected Requirements of Prescribing Information

5. At the beginning of HL, the following heading, “HIGHLIGHTS OF PRESCRIBING INFORMATION” must be bolded and should appear in all UPPERCASE letters.
6. Provide a toll-free number for reporting suspected adverse reactions.
7. Patient counseling information in HL: The statement is correct; however, Patient counseling information must be in upper case letters. Please revise the Patient counseling information statement to make this change.
8. Update the heading at the beginning of the TOC to read: FULL PRESCRIBING INFORMATION: CONTENTS*.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 19, 2017. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

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

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
- Comment:**
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
- Comment:** *HL exceeds one-half page.*
- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).
- Comment:**
- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.
- Comment:**
- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.
- Comment:** *Please remove space between the HL heading and the HL limitation statement. Likewise, please remove space between product title and initial U.S. Approval.*
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
- Comment:**
- YES** 7. Headings in HL must be presented in the following order:

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

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

Comment:

Patient Counseling Information Statement in Highlights

- NO** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

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

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

Comment: *The statement is correct; however, Patient counseling information must be in upper case letters. Please revise the Patient counseling information statement to make this change.*

Revision Date in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.
Comment:
- NO** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment: Update the heading at the beginning of the TOC to read: “*FULL PRESCRIBING INFORMATION: CONTENTS.*”
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

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

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

RACHEL S MCMULLEN
06/29/2017

MARA B MILLER
06/29/2017